Part 1. Chapter 1
What is Cephalic Hypersensitivity Syndrome?

1 Why I am proposing the concept of cephalic hypersensitivity syndrome

Why do we need a book about cephalic hypersensitivity syndrome today? There are two reasons. The first is that based on my 40 years of experience as a physician in headache outpatient clinics, I hope that the patients who suffer from chronic headache become aware of cephalic hypersensitivity syndrome as an illness. Many patients who complain of chronic headache come to headache clinics for treatment despite also suffering from a wide range of other indefinite complaints, and their complaints are often complex. It is not uncommon for headache specialists to encounter patients whose complaints they do not fully understand. It pains me when I meet patients who have gone to a headache clinic in good faith, only to be given inappropriate treatment that makes their illness even more complex. As a warning against treatment-by-numbers following the diagnostic guidelines put out by medical associations, I would like to tell patients that it is not a good idea to blindly trust a sign that says "Headache Clinic" based only on a specialist certification.

I also want to send a message to young clinicians telling them to act as scientists. When I asked outstanding junior colleagues for their thoughts on my previous book *Cephalic Hypersensitivity Syndrome is on the Rise*, the response was "Your book does not provide any evidence." For someone like me, who believes that doctors should try to act as scientists, these words were both surprising and shocking. Evidence is not created solely by universities, research institutions, or medical associations. The sort of "evidence" generated by pouring vast sums of money into randomized controlled clinical trials or using statistical models to demonstrate significant differences does not occupy such an important position in the natural sciences. I would hope that young doctors will act like scientists and possess the reliable ability to observe patients' illnesses calmly from a multifaceted, objective perspective, so that when they encounter a phenomenon in clinical practice for the first time, their minds will be open to all sorts of possibilities. This is why I strongly hope my younger colleagues will read this volume.

What makes me so uncomfortable with the label "headache specialist" is the gap between the International Classification of Headache Disorders (ICHD), which

so many specialists believe should be followed, and my clinical experience. This is obviously a table of classification codes for use in research, created for the purpose of easy computer management. Once a doctor is used to this system, conditions that do not fit it neatly are regarded as "exceptions," with the risk that they may not be treated properly even if they are actually curable. One issue is that young doctors who blindly trust the ICHD view illness through the lens of this classification rather than looking at the patient in front of them. Such doctors are unaware that since the adoption of the ICHD, those of us who are primary care practitioners have been at the mercy of every change in name and criterion when the classification has been revised, and this has caused harm.

For example, it has been well known for many years that migraine and tension headache are not easily distinguishable in clinical practice, with many patients suffering from a mixture of the two. Previously, we could use the convenient terms "mixed-type headache" and "transformed headache," which were easy to explain to patients, but each time the ICHD has been revised, the number of categories has increased, from 268 in the ICHD-2 [1] to 302 in the ICHD-3β [2 3], and clinically convenient categories have been eliminated. Many doctors who run headache outpatient clinics tend to believe that migraine and tension headache are treated in different ways. Transformed intractable tension headache is an appropriate example of cephalic hypersensitivity syndrome. Insisting on the ICHD categories may be disadvantageous in some ways in clinical practice. Transformed intractable headache should be treated as cephalic hypersensitivity syndrome.

Recognition of the name "cephalic hypersensitivity syndrome" in medical association guidelines

The name "cephalic hypersensitivity syndrome" did not exist when I first started offering headache outpatient clinics, and it is yet to be established even today. My proposed "cephalic hypersensitivity syndrome" (CHS) shares similarities with the "central sensitivity syndrome" (CSS) [4] proposed by Muhammad Yunus, a specialist in fibromyalgia in the Department of Rheumatology of Illinois University College of Medicine. I will discuss the differences between CHS and Yunus' concept in detail in Chapter 3, but in most cases, my suggested "cephalic hypersensitivity syndrome" is actually chronic illness syndrome. Some medical institutions are now offering clinics for patients with “indefinite complaints syndrome,” but I prefer to use “chronic illness

Main guidelines and results of searches for terms

	① Epilepsy	② Depression	③ Fibromyalgia	④ Chronic headache	⑤ Chronic pain	⑥ Restless legs syndrome	⑦ Dizziness / vertigo
Nō kabinsyō (cephalic hypersensitivity syndrome)	0	0	0	0	0	0	0
Central sensitivity syndrome (CSS)	0	0	p.95	0	0	0	0
Tyūsūsei kansa (central sensitization)	0	0	0	p.85 p.91 p.101 p.201	p.611	0	0
Central sensitization	0	0	p.186	0	0	0	0
Futei syūso (indefinite complaints)	0	0	p.41 p.63 p.80 p.186	p.69	p.611 p.613	0	p.203

* The numbers indicate the page numbers of the guidelines in which the terms are mentioned.

① Japanese Society of Neurology (Editorial supervisor): Clinical Practice Guideline for Epilepsy Management 2010

② Guideline for treatment of major depressive disorder by the Japanese Society of Mood Disorders, 2013

③ Japan College of Fibromyalgia Investigation & National project team by the Ministry of Health, Labour and Welfare (Editor): Fibromyalgia Guideline 2013

④ Japanese Society of Neurology / Japanese Headache Society (Editorial supervisor): Clinical Practice Guideline for Chronic Headache 2013

⑤ Standards of Neurotherapeutics: Chronic pain (ed Japanese Society of Neurological Therapeutics)

⑥ Standards of Neurotherapeutics: Restless legs syndrome (ed Japanese Society of Neurological Therapeutics)

⑦ Standards of Neurotherapeutics: Dizziness and vertigo (ed Japanese Society of Neurological Therapeutics)

syndrome.” Because the terms "indefinite complaints syndrome" and “chronic illness syndrome” generally carry negative connotations, I myself prefer to use the term "cephalic hypersensitivity syndrome" for my own clinics.

The previous table shows the results of searching the guidelines published by various medical associations for the Japanese equivalents of the terms "*nō kabinsyō* (cephalic hypersensitivity syndrome), "central sensitivity syndrome (CSS)," "*tyūsūsei kansa* (central sensitization)," and “central sensitization” "*futei syūso* (indefinite complaints)."[5–11].

The Japanese equivalent of "*nō kabinsyō* (cephalic hypersensitivity syndrome)" was not mentioned in any of the guidelines. The Japanese for "*tyūsūsei kansa* (central sensitization)" was found in guidelines on chronic headache and chronic pain. The English terms "CSS" and "central sensitization" were only used in the guidelines on fibromyalgia. In the fibromyalgia guidelines, it was introduced in the context of overseas treatment and materials on the latest discoveries. Yunus' diagnostic criteria for fibromyalgia were mentioned only very briefly in the guidelines.

The term "*futei syūso* (indefinite complaints)" is used in the guidelines for fibromyalgia, chronic headache, chronic pain, and dizziness / vertigo, but none of these refers to "*futei syūso* (indefinite complaints)" as a condition requiring treatment in itself.

Yunus needed time to formulate the term "central sensitivity syndrome" (CSS). The expressions used in the guidelines issued by medical associations require sufficient consensus to have been achieved in the field concerned. In that sense, the use of "*tyūsūsei kansa* (central sensitization)" in the guidelines issued by the Japanese Headache Society and the Japanese Society of Neurology, and the use of "CSS" and "central sensitization" by the Japan College of Fibromyalgia Investigation, suggest that we may be nearing the day when cephalic hypersensitivity syndrome is recognized.

Cephalic hypersensitivity syndrome represents the aggravation of indefinite complaints to the point at which it impedes everyday activities

The symptoms of indefinite complaints include headache, stiff shoulders,

dizziness / vertigo, back pain, feeling lethargic, inability to sleep, numbness and pain at different points around the body, and fatigue that never seems to go away. These symptoms fluctuate and change, intensifying and subsiding with the fickleness of the weather.

As these complaints are mostly subjective, and objective findings are few, they are rarely regarded under the umbrella of a single condition, and even if full medical examinations and tests are performed, it is difficult to identify findings or causes that may underlie these symptoms. Thus, there is no reliable method of treatment. Anti-anxiety drugs and tranquilizers can be administered to treat the symptoms, but as most patients do not improve, they end up going doctor-shopping. In the process, medical institutions stop taking them seriously, and they become so-called "healthcare refugees," indefinite complaints patients with no medical home. Cephalic hypersensitivity syndrome represents the aggravation of indefinite complaints to the point at which it interferes with work and everyday life.

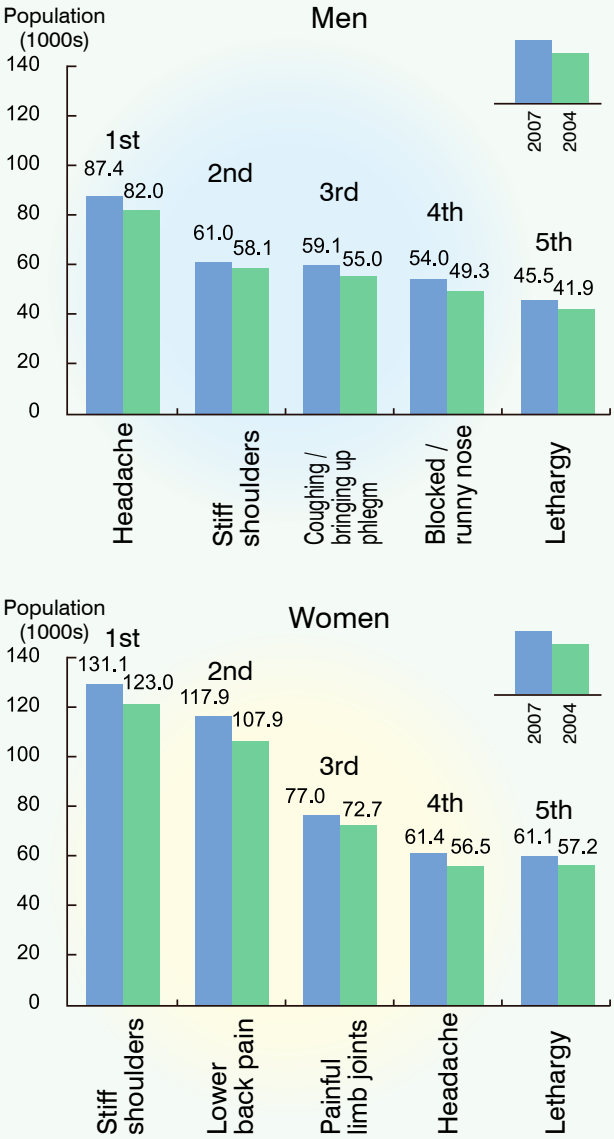
The Ministry of Health, Labour and Welfare is concerned about chronic pain and indefinite complaints

In September 2010, a Ministry of Health, Labour and Welfare (MHLW) study group on chronic pain included the following warnings in its recommendations in the Future Measures to Deal with Chronic Pain [12].

- The effects of chronic pain include greatly reducing the patients' quality of life and making it difficult for them to find work, causing a major burden on society.
- Treatments that have little effectiveness are repeatedly used.
- Patients visit many different medical institutions in search of treatment.
- Many medications of established value for treating chronic pain that are used overseas are not yet covered by health insurance in Japan.
- There is a need for the collection of scientific evidence and the formulation of criteria for treatment indications based on evidence.
- Society as a whole must engage in measures to combat chronic pain.

Reference: The Japanese government is also concerned about the effects of indefinite complaints on the labor force

From 2007 Comprehensive Survey of Living Conditions [13]



Note: People complaining of these symptoms did not include hospitalized patients, but the household population that comprised the denominator did include those admitted to a hospital.

2 The true identity of cephalic hypersensitivity syndrome

Headache, dizziness / vertigo, tinnitus, dry mouth, palpitations, suffocating sensation, insomnia, loss of appetite, nausea, numbness in a limb, chills, pain, sweating, anhidrosis, frequent urination, irritability, fatigue, lethargy, and a wide variety of other symptoms are all in fact symptoms of a breakdown in the balance of the autonomic nerves. Autonomic nerve balance is preserved by various hormones that are also neurotransmitters. If the autonomic nerve balance or hormonal balance breaks down, the homeostasis of the human body is impaired. The autonomic nerves play a major role in cephalic hypersensitivity syndrome; therefore, I will continue to refer to the autonomic nerves throughout this book.

The body's homeostasis is protected by the autonomic nerves and hormones

The autonomic nervous system preserves the body's homeostasis through interaction and coordination with the endocrine and immune systems. There are two types of autonomic nerves, the sympathetic and parasympathetic nerves, which intertwine and combine to control the organs. Depending on whether you are working or resting, or whether it is day or night, they both act with each other on the organs in an antagonistic fashion. The autonomic nerves control the circadian rhythm of daily human activity. The sympathetic nerves govern activity during the day. Sympathetic nerves are also known as the "fight or flight" nerves as they increase blood pressure, raise the pulse rate, expand the airway in the throat, dilate the pupils to make it easier to see, and constrict the blood vessels in the skin to reduce hemorrhage in the event of injury, among other actions. Fight mode is the physical function required for pursuing animals, whereas flight is the response to attack by an enemy as well as to an injury or other painful or frightening stimulus. The parasympathetic nerves govern nocturnal activity by reducing blood pressure and pulse rate, and governing digestion and absorption as well as sleep. These autonomic nerve functions are caused by the action of neurotransmitters / hormones including serotonin, dopamine, noradrenaline, adrenaline, and acetylcholine.

Circadian and seasonal variation in hormones

Hormones that are also neurotransmitters are known to exhibit both circadian and seasonal variation. In Japan, approximately 30,000 people commit suicide each year, but the number varies in different seasons. The rate increases in spring from March to May and in fall in October, but decreases in winter from December to February [14]. This may be connected with the fact that serotonin and dopamine decrease in spring and autumn. An example of monthly hormonal variation is the irritation and anxiety that occur as part of premenstrual syndrome, and the serotonin hypothesis holds that this may be caused by a decrease in serotonin during the luteal phase. In terms of circadian variation, the hormones responsible for diurnal activity are serotonin, dopamine, and noradrenaline, whereas those responsible for nocturnal activity are melatonin, growth hormone, and acetylcholine. Melatonin possesses antioxidant activity that purifies the body during sleep, but this hormone remains poorly understood. It is produced in the brain in the pineal gland from the essential amino acid tryptophan, by way of serotonin. Growth hormone acts to promote body repair and learning, whereas acetylcholine promotes digestion and absorption. The concentrations of serotonin and dopamine are higher during the day and drop at night. Noradrenaline mainly acts during the day and acetylcholine at night, but they possess 24-hour activity as in the case for serotonin and dopamine.

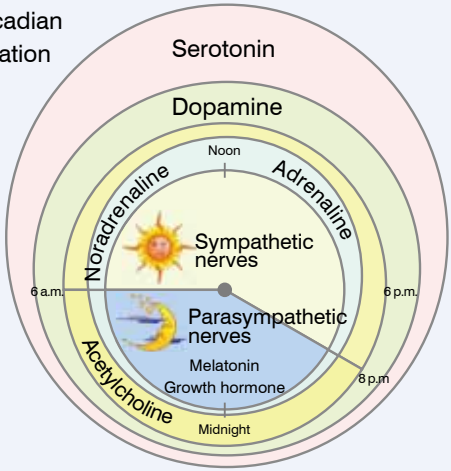
Sympathetic nerves and cephalic hypersensitivity syndrome

As described above, the sympathetic nerves are autonomic nerves that are active during the day for hunting prey. The parasympathetic nerves are autonomic nerves that are active in promoting digestion and absorption during periods of rest and during sleep at night. Both the sympathetic and parasympathetic nerves are involved in cephalic hypersensitivity syndrome, but it is the sympathetic nerves that play the main role, as it is their tension that induces cephalic hypersensitivity syndrome. People who develop cephalic hypersensitivity syndrome have similar personalities. I will describe these in detail later, but they include many people who are scrupulous, hard-working, and caring. This type of personality may be known as headache personality, cephalic hypersensitivity syndrome personality, or sympathetic nerve-type personality. The sympathetic nerves generate the instantaneous strength required for hunting prey. Anger is an action of the sympathetic nerves. When they are activated, the

blood vessels in the cutaneous mucosa constrict, and the face becomes white. The pupils dilate, and the airway expands. Blood pressure and pulse rate both rise, creating instantaneous strength. Chronic tension of the sympathetic nerves generates emotions such as anger, fear, and anxiety. If this sympathetic nerve tension persists, individuals have less endurance, are easily tired, and their ability to digest and absorb food decreases, leading them to lose their appetite. In terms of the white blood cell levels, the number of granulocytes increases, whereas the number of lymphocytes / leukocytes declines. Granulocytes kill bacteria by phagocytosis and with active oxygen. Lymphocytes are an important component of the immune system, the body's resistance mechanism. If stress is continual, the sympathetic nerves become tense, the granulocyte count increases, and the lymphocyte count declines. When the large number of granulocytes reach the end of their lifespan after ten days, they break down, releasing large amounts of active oxygen and damaging the tissues. Lymphocytes have a lifespan ten times longer than that of granulocytes, and when their number declines, the likelihood of developing cancer increases.

Sympathetic nerve tension causes a wide range of complaints, from gastrointestinal symptoms to mood disorders. The sympathetic nervous system and cephalic hypersensitivity syndrome are inseparably linked.

Circadian variation



Hormones that are also neurotransmitters possess 24-hour activity and preserve the body's homeostasis. The hormones required for action are secreted in greater quantities during the day, and those required during rest and sleep are secreted at higher levels during the night.

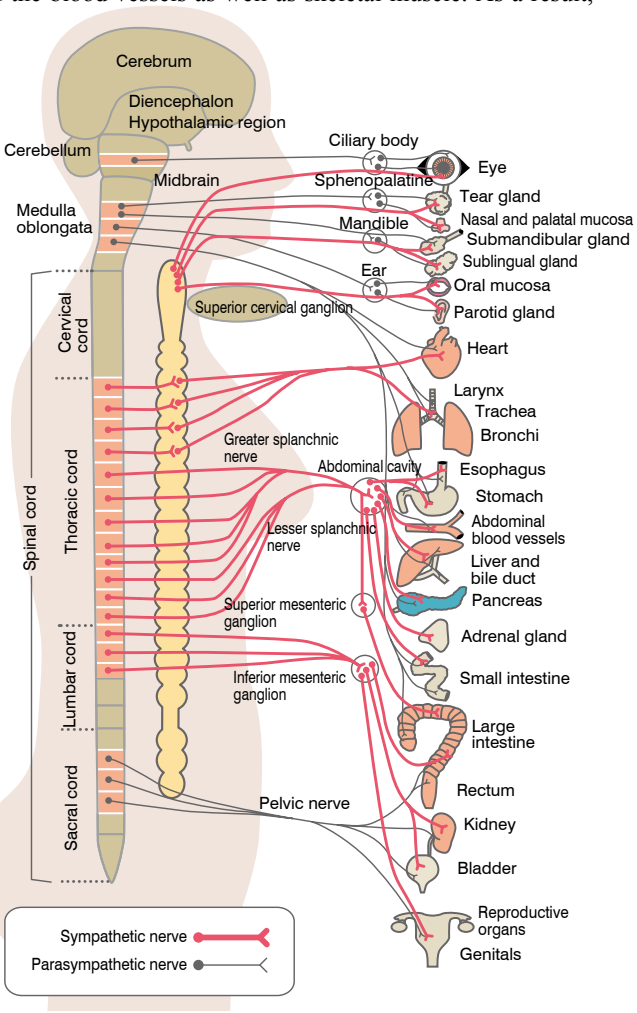
Column

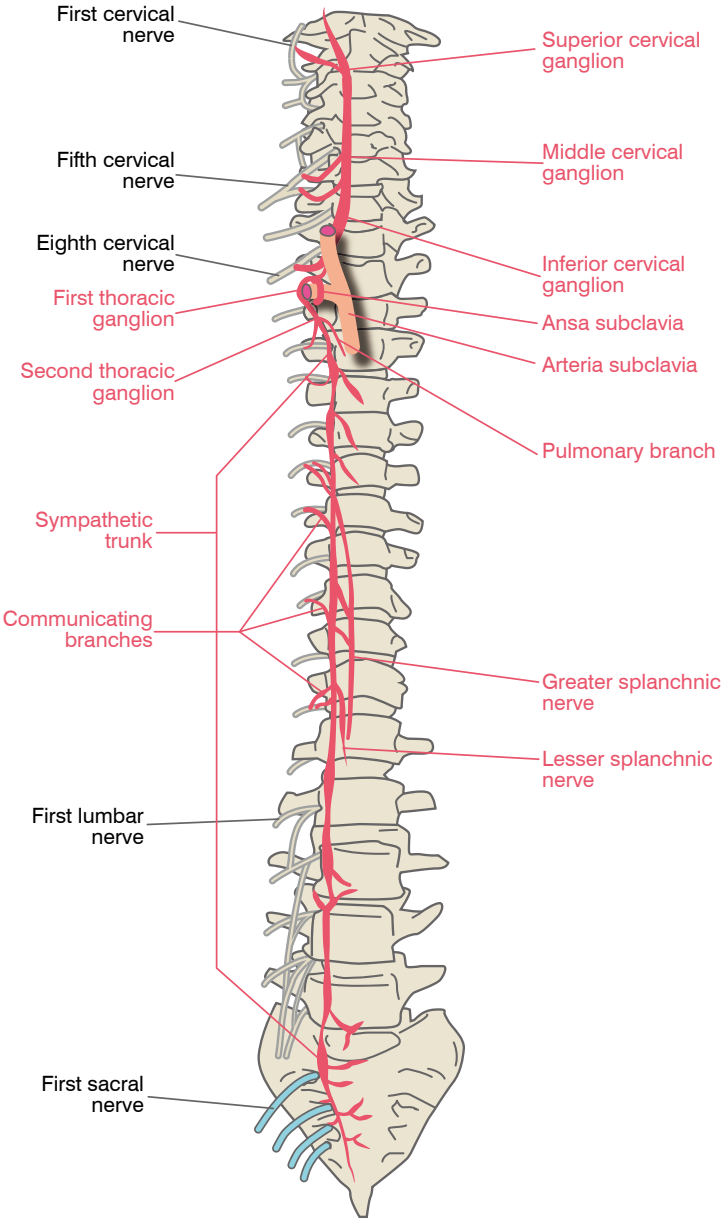
●Melatonin

Melatonin levels rise at night during sleep, when it purifies the body through its antioxidant activity. This activity is believed to be twice as powerful as that of vitamin E and five times that of glutathione, and its anti-aging and anti-cancer properties have attracted attention. The pineal gland, which regulates melatonin secretion, is sensitive to light and dark, and also influences the estrus cycle [15]. Due to its low cost, in the United States, melatonin is a popular over-the-counter product used for adjusting sleep rhythms as well as preventing cancer. As mentioned earlier, melatonin is produced from the essential amino acid tryptophan by way of serotonin. Meat and fish have a high tryptophan content, and in plants, it is plentiful in soybeans and other pulses and in cereal germ. It is an important precursor of growth hormone. Its use as a supplement has famously led to deaths in the United States as a result of impurities in the production process. Ideally, it should be ingested in food as part of a balanced diet.

Anatomical diagram of the visible autonomic nerves

The central autonomic nerves (the central sympathetic and parasympathetic nerves) are mainly located in the hypothalamic region of the diencephalon. The sympathetic trunk extends like a string of beads in front of the spine (on its ventral side). From the sympathetic trunk, the sympathetic nerves are attached to the arterial walls to reach throughout the body, where they act to contract and extend the smooth muscle of the blood vessels as well as skeletal muscle. As a result, they are intimately involved with the movement of both smooth and skeletal muscle.




First cervical nerve
Fifth cervical nerve
Eighth cervical nerve
First thoracic ganglion
Second thoracic ganglion
Sympathetic trunk
Communicating branches
First lumbar nerve
First sacral nerve
Superior cervical ganglion
Middle cervical ganglion
Inferior cervical ganglion
Ansa subclavia
Arteria subclavia
Pulmonary branch
Greater splanchnic nerve
Lesser splanchnic nerve

Column

●The autonomic nerves are visible nerves

Many people believe that the autonomic nerves are a sort of invisible nerve, but actually they are just as visible as any other type. Palmar hyperhidrosis (see note), for example, can be improved by inserting a fine endoscope through a 5-mm incision in the armpit into the chest and cutting the sympathetic nerve from the fourth thoracic vertebra, a surgical procedure that takes just ten minutes.

(Note) Palmar hyperhidrosis is a disorder in which the autonomic nerve balance is disrupted by tension or stress, causing the palms to sweat even though body temperature does not rise. In serious cases, it may impede everyday activities.

Autonomic dysregulation is serotonin dysregulation

To understand cephalic hypersensitivity syndrome in more depth, in addition to a basic knowledge of autonomic nerves, you also need to know more about the causes of autonomic dysregulation. Many of the varied symptoms of autonomic dysregulation are similar to those of serotonin deficiency. Autonomic dysregulation can also be described as dysregulation of serotonin, the "mother of all hormones."

Autonomic dysregulation and serotonin

	Autonomic dysregulation	Serotonin deficiency	Serotonin overdose Serotonin syndrome
Head	Headache	Headache	Headache
Mouth / throat	Dry mouth, taste disturbance Feeling of pressure in the throat	Tongue pain, strange feeling in the throat	
Heart	Palpitations, tachycardia		Tachycardia
Lungs	Suffocating sensation		
Stomach / intestines	Loss of appetite, constipation, diarrhea	Heaviness of the stomach, loss of appetite, constipation, diarrhea	Vomiting, diarrhea
Blood vessels	Constriction, pallor		Hypertension
Limbs	Numbness, chills, pain		
Skin	Cold sweats, hyperhidrosis, anhidrosis		Sweating
Urinary organs Reproductive organs	Frequent urination, feeling that there is still urine in the bladder, sensation of residual urine, irregular menstruation	Frequent urination	
Muscles Joints	Stiffness, muscle pain	Chronic myalgia	Muscle spasms
General bodily symptoms	Easily tired, dizziness / vertigo, mild fever	Easily tired, drop in body temperature	Rise in body temperature, febrile shivering, tremors
Mental symptoms	Difficulty falling asleep, irritability, depressive mood	Difficulty falling asleep, irritability, loss of temper, depressive mood	Irritability, anxiety, excitement

Note: Both too much and too little serotonin cause almost exactly the same symptoms.

Column

●What is the vagus nerve?

The vagus nerve is one that is easy for students to get wrong in exams. Its name comes from a Latin word meaning "wandering," and it lives up to its name by covering a much wider range than any other cranial nerve, innervating organs all the way from the neck to the chest and down past the abdomen. Many people assume that it is an autonomic nerve, but in fact, it is unique in that it combines the characteristics of three different types of nerves: motor, sensory, and parasympathetic. The vagal reflex, which occurs as a result of a shock or other mental or physical stimulus, displays its characteristic nature as a mixed nerve. Not only psychogenetic shock, but also stimuli such as urination or defecation may reduce blood pressure, resulting in unconsciousness.

The most important brain hormones

Over 100 different types of brain hormones that are also important neurotransmitters are thought to exist. Several are essential to human activity. It is impossible to understand the autonomic nervous system without knowing about serotonin, which has been variously described as the "stability hormone," "happiness hormone," and "love hormone." Serotonin and acetylcholine are mainly involved with the parasympathetic nervous system, whereas dopamine and noradrenaline are mainly involved with the sympathetic nervous system.

Serotonin

Serotonin was originally discovered as a substance that constricts blood vessels. It is synthesized in a number of different organs in the body, with 95% of endogenous serotonin found in the digestive tract. It is responsible for actions such as promoting intestinal peristalsis. The small percentage of serotonin found in the spinal cord supports the homeostatic function of everyday activities in humans and other higher animals.

So what does serotonin actually do? It regulates and controls almost all the basic activities of humans and other higher animals, including waking and sleeping, mood and emotion, memory, analgesia, posture maintenance, and autonomic nerve regulation. It seems that some individuals may have higher serotonin levels than others due to their family history.

There are ways of maintaining serotonin at the appropriate level in everyday activities, so there is no need for people with a family history of low serotonin to worry. The first thing to understand is the underlying principle of serotonin. The continuous activity of serotonin and rhythmic body movement interact in tandem with each other. The three main rhythmic movements are walking, chewing, and breathing. Although this may sound simple, human beings today walk far too little. Most food today is soft, meaning that we also chew too little. Excessive stress also means that our breathing is disturbed. From this perspective, the three main rhythmic movements are taken far too lightly in daily life. We have to make an effort to consciously maintain a rhythm when walking, chewing, and breathing. So how can we do this? The answer is simple: walk, choose hard foods, and take time out to regulate your breathing when you can. The northern European habit of sunbathing is good for more than just tanning: exposure to sunlight also increases serotonin and calms our emotional state.

It is also important to avoid reducing serotonin levels. The most important factor that suppresses serotonin secretion is chronic stress. Brooding and worrying about things that are out of your control diminish serotonin. In our stressful society, it is important to be smart by distracting yourself and doing something different to lift your mood.

"Social grooming" is an interesting concept. In animal biology, it refers to monkeys cleaning each other's fur, but in humans in the West, actions such as shaking hands, hugging, and kissing embody the habit of touching at close quarters in everyday encounters. Sadly, such habits are not very familiar in Japan today. Historically, however, grooming was generally practiced in Japanese households. Family members would gather around a small table in a small room to eat together in close proximity. Mothers would take their babies into the bath with them, and fathers would bathe with the older children. The whole family would also often go to the public baths together.

Dopamine

Next in importance after serotonin, is the body-regulating hormone dopamine. The most important action of this hormone is in ensuring that the muscles move smoothly. A lack of dopamine means the muscles no longer move smoothly, and actions become clumsy and awkward. In the facial expression muscles, this reduces facial expressivity, creating a mask-like appearance. Parkinson's disease is a well-known example of dopamine deficiency.

Another action of dopamine is to increase motivation. The type of motivation created by dopamine is the active motivation that seeks out a sense of accomplishment and reward. In contemporary society, however great the action of dopamine, there are not many opportunities for experiencing a sense of achievement and reward. In fact, there are few such opportunities. Under these circumstances, dopamine promotes the search for easy achievements and rewards. As a result, people seek satisfaction from smoking, alcohol, gambling, and sleeping pills, in what is termed "dependency." A lack of dopamine causes clumsy movements and a loss of motivation. On the other hand, too great an increase leads to the bad habit of depending on easily available rewards.

Noradrenaline and adrenaline

Noradrenaline is another important hormone. It reacts immediately in the event of great stress or perceived danger. Noradrenaline acts on the adrenal glands to elicit an adrenaline boost. When a danger is perceived, both noradrenaline and adrenaline come into action to raise blood pressure, increase heart rate, speed up

breathing, and dilate the pupils, playing an important role in risk management by keeping the body in fight mode. However, when these hormones become over-expressed, this leads not to a well-regulated fight mode but to one that is out of control. This state is what is known as "panic." Panic disorder is a runaway state in which noradrenaline is out of control. Serotonin also plays an important role in regulating and controlling noradrenaline. Adrenaline production in the adrenal cortex is induced by acetylcholine, and its action is similar to that of noradrenaline. It can thus be said that these two hormones are "brother hormones."

Column

The relationship between adrenaline and epinephrine

Adrenaline is a hormone that plays an important role in the action of the sympathetic nerves. It is known as adrenaline in most countries worldwide, including Japan, but in the United States, it is called epinephrine. The reason that such an important hormone is known by different names in different places stems from the events in those countries. It was discovered in 1893 by George Oliver in Britain, but its pharmacological properties were first established in 1895 by Polish physiologist Napoleon Cybulski. Both men are credited as its discoverers. It was first successfully purified in 1901 by Jokichi Takamine and Keizo Uenaka, Japanese researchers who were at that time carrying out research in the United States. Four years previously, in 1897, it had been successfully extracted by American scientist John Abel, who named it epinephrine. However, this extract contained many impurities and did not have any physiological activity.

The substance purified by Takamine and his colleagues was developed as a pharmaceutical product under the name of adrenaline, but as Takamine died some ten years earlier than Abel, he was unable to counter Abel's assertion that the results achieved by him and Uenaka had been stolen from Abel's discovery, and his achievements were buried in the historical record. Laboratory notes left by Uenaka were subsequently used to disprove Abel's claim in Europe and Japan, and outside the United States, adrenaline was adopted as the official name [16]. As I am Japanese, I prefer to use adrenaline. Uenaka's laboratory notes are now properly archived in a temple in Hyogo Prefecture. In terms of etymology, the "ad" in adrenaline comes from the Latin for "to" or "toward," and "renaline" from "renal," referring to the kidneys. (The adrenal glands are located next to the kidneys.) The "nor" in noradrenaline comes from "normal," and "noradrenaline" may thus be understood as "normal adrenaline." Noradrenaline acts on the adrenal medulla to produce adrenaline. These two hormones are "brother hormones" that both possess sympathetic nerve activity.

Acetylcholine

Acetylcholine is well known as a parasympathetic nerve neurotransmitter. It also acts in the anterior half of the sympathetic nerves and at the joint between motor nerve synapses and skeletal muscles, and is intimately involved with muscle motor function. Acetylcholine achieved notoriety after the Aum Shinrikyo cult released sarin on the Tokyo subway in 1995. Sarin is such a deadly nerve gas that even Hitler hesitated to use it. It blocks the action of acetylcholine, making muscle activity impossible. Acetylcholine is also involved in memory and learning, and the acetylcholine activator Aricept (donepezil) is therefore a well-known treatment for Alzheimer's disease. Its relationship with muscle means that it is also involved in the muscle rigidity seen in Parkinson's disease.

I hope you will have understood from the preceding explanation just how important serotonin actually is. Serotonin preserves the body's homeostasis, and as a hormone and neurotransmitter, it is essential for the continued smooth running of human existence. Numerous agents have been developed to enhance the action of serotonin. Mood stabilizers, antidepressants, and antipsychotics are all drugs that elevate serotonin levels in a stable fashion. In recent years, selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) have become widely prescribed.
In order to maintain a healthy lifestyle, it is important to eat, exercise, and take breaks, as this helps prevent a deficiency in serotonin, the mother of all hormones.

Column

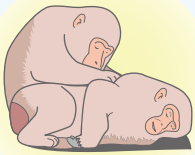
●Drug treatments for Alzheimer's disease

Aricept (donepezil), sold as a treatment for Alzheimer's disease, activates the acetylcholine-activated nerves involved in memory and learning. Pfizer, the world's largest pharmaceutical manufacturer, developed its active ingredient, donepezil, on the basis of the acetylcholine hypothesis, focusing on research that showed clear improvements in cognitive performance in animal models. It was thus approved by the US Food and Drug Administration (FDA) and was sold worldwide before it received approval in Japan. Based on my clinical experience, Memary (memantine), another treatment for Alzheimer's disease that has been developed on the basis of the glutamine hypothesis, may be more effective than Aricept (donepezil). We still have much to discover about acetylcholine.

How lifestyle can increase serotonin levels

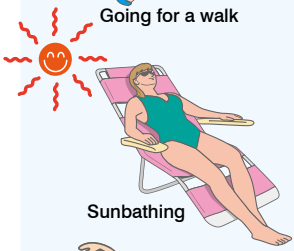
—the happiness hormone

Going for a walk

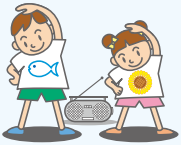


Social grooming

Shaking hands / hugging



Sunbathing



Rhythmic breathing

Bathing as a family

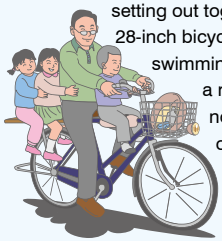
Chewing thoroughly / eating as a family

Serotonin deficiency leads to

Losing one's temper
Emotional instability
Insomnia
Constipation
Loss of memory
etc.

The author's fond memories

Me in front of my father and my two sisters perched on a washboard strapped to the luggage rack; all four of us are setting out together on a 28-inch bicycle to go swimming in the sea—a rare event nowadays. One of my cherished memories.



Cephalic hypersensitivity syndrome is caused by the dysregulation of the hormone-nerve system

The central nervous system and the autonomic and other nerves that link the center with the periphery are not wired separately from each other at all. The easiest way to illustrate this is to picture the space above the ceiling in a building, filled with electric wires and gas pipes. If the rain gets in, some of the pipes may corrode and the electric wires short out. Something similar can happen to our bodies' nervous system. As living organisms, we possess the learning ability required to adapt, also known as synaptic plasticity (see page 246), and this is far more complicated and troublesome than electric wiring. Nerve degeneration or disruption results in wires becoming crossed, resulting in the wrong signals being transmitted and the brain remembering mistaken information. In most cases, repair functions come into play before that happens, but if even one of the functions of the nervous system is seriously impaired, a chain reaction of disruption occurs that cannot easily be repaired. This is the underlying cause of the diverse array of symptoms of various grades seen in cephalic hypersensitivity syndrome, and the reason that it is difficult to treat with drugs alone when it becomes intractable.

Stress has a major effect on the autonomic nervous system as well as on brain hormones. Chronic stress impairs the maintenance of homeostasis of the body by the autonomic nerves and hormones. This results in the development of chronic illness syndrome and of cephalic hypersensitivity syndrome that interferes with work and everyday life. What may be only minor stress to start with leads to nerve degeneration if it is experienced repeatedly. The method of treatment and choice of drug will vary depending on the type of stress, but in principle, it will consist of lifestyle changes, improvements in thinking, and night therapy, with cognitive behavioral therapy to ensure that these become habitual, as shown in my treatment algorithm (see Page 64).

The brain hormones serotonin, dopamine, noradrenaline, and acetylcholine form nervous systems activated by these substances in their roles as neurotransmitters, which are known as the serotonergic, dopaminergic, noradrenergic, and acetylcholinergic nervous systems. The branching

points of these various nervous systems, nerve nuclei, are arranged in a row in the diencephalon (thalamus and hypothalamic region), midbrain, pons, and medulla oblongata, just like an electric circuit board, through which nerves run to various parts of the body. The wires that enter the brain all have their own respective destinations, and their actions vary depending on the characteristics of that part of the brain. The following description is a little technical, so general readers may prefer to skip over it and go straight on to Page 47.

Serotonergic nervous system

Nine nerve nuclei, numbers B1–B9, are located from the midbrain to the medulla oblongata. The pathway that involves the median raphe nucleus that runs between the midbrain and the pons is connected as far as the hippocampus in the brain and handles memory information processing, whereas the pathway that involves the dorsal raphe nucleus is connected with areas such as the cerebral cortex and the hypothalamic region and deals with activities such as sleep and waking, body temperature regulation, and eating that are basic to our lives. The pathway that involves the raphe nuclei of the medulla oblongata is connected with the sympathetic ganglion and emits signals that excite the sympathetic nerves. The pathway that involves the nucleus raphe magnus is connected to the posterior horn of the spinal cord, where pain-transmitting Aδ fibers and C fibers are located, and inhibits the transmission of pain signals to the brain.

Dopaminergic nervous system

Eight nerve nuclei, numbers A8–A15, are located mainly from the diencephalon to the midbrain. Of the pathway that involves the ventral tegmentum, the pathway that involves the cerebral limbic system is activated by emotions, among other stimuli, whereas the pathway that involves the mesolimbic system and the frontal lobe is activated by stimuli such as stress and anxiety. The feeling of ease as pain subsides, and the stress and anxiety felt as it intensifies, are all actions of the nervous system. Although much remains unknown, in Parkinson's disease, the pathway that involves the substantia nigra pars compacta and that is associated with extrapyramidal movement degenerates and is unable to supply the necessary dopamine, whereas in

restless legs syndrome, abnormalities of the pathway that involves the posterior diencephalon have been reported.

Noradrenergic nervous system

Seven nerve nuclei, numbers A1–A7, are located mainly from the pons to the medulla oblongata, caudal to the location of the dopamine nerve nuclei. Some pathways that involve the locus ceruleus, branching in the thalamus, hypothalamic region, septum, hippocampus, and amygdala to connect to the entire cerebral cortex and others, also involve the cerebellum and the spinal cord. The noradrenergic nervous system is activated by the stress response and activates corticotropin-releasing hormone, cortisol secretion, and the sympathetic nerves. This action creates a state of tension, with racing heart, dilated pupils, constricted blood vessels, and breaking out in a cold sweat. The areas within the brain that are connected with the noradrenergic nervous system are close to those connected with the serotonergic nervous system, which acts to control and dampen it.

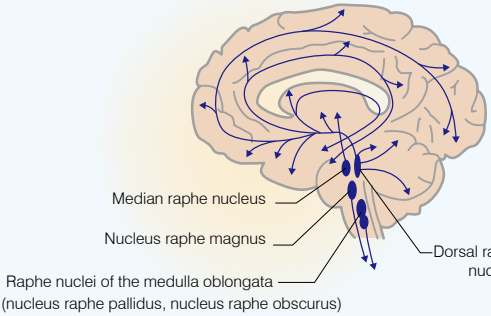
Acetylcholinergic nervous system

Acetylcholine was discovered in the 20th century as an intercellular messenger. As well as acting as a neurotransmitter in the motor, sympathetic, and parasympathetic nerves, it also performs functions in the form of non-neuronal acetylcholine in the immune system, blood vessels, digestive tract, upper airway, and placenta. The acetylcholinergic nerve nuclei in the brain are located in the sites classified as Ch1–Ch8. Acetylcholine is used in the preganglionic fibers of both the sympathetic and parasympathetic nervous systems. In the sympathetic nervous system, acetylcholine is used in the preganglionic fibers and noradrenaline in the postganglionic fibers.

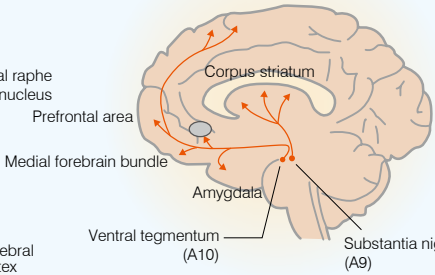
The Ch1–Ch4 nerve nuclei are located in the basal forebrain beneath the basal ganglia, and the nucleus basalis of Meynert (Ch4) in particular plays an important role in memory, waking, cognition, and thought. It has previously attracted attention because neurons in this location form one of the first groups of cells to die in the process of Alzheimer's disease, but neuron death occurs over a wide area in Alzheimer's, and a direct association with the acetylcholinergic nervous system has not

been shown [17]. Ch5 and Ch6 are located in the midbrain-pons region and are closely associated with waking. Together with the noradrenergic and serotonergic nervous systems, this system regulates the excitement of the sensory relay nucleus of the thalamus.

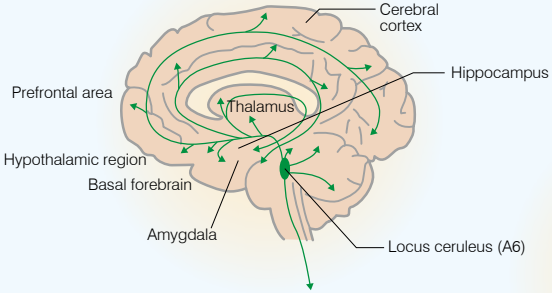
Serotonergic nervous system

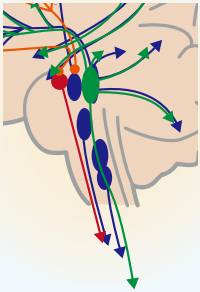


Dopaminergic nervous system

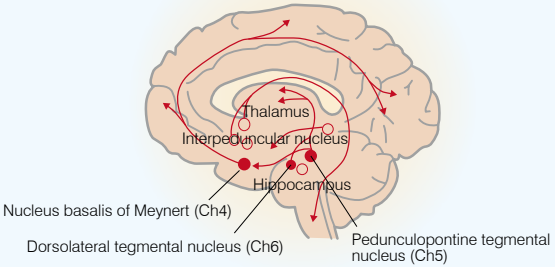


Noradrenergic nervous system

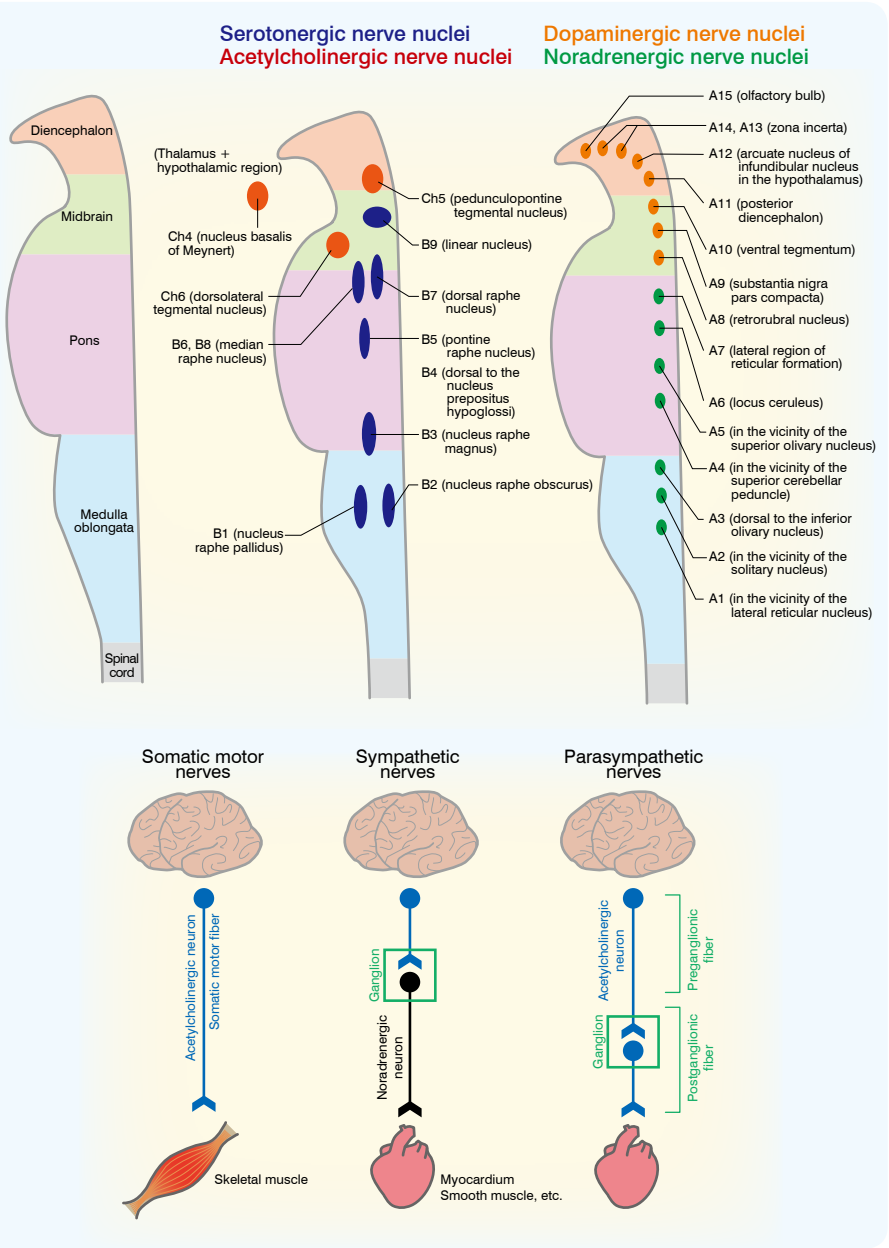




Acetylcholinergic nervous system



The descending inhibitory system involves mainly the serotonergic, noradrenergic, and acetylcholinergic nervous systems

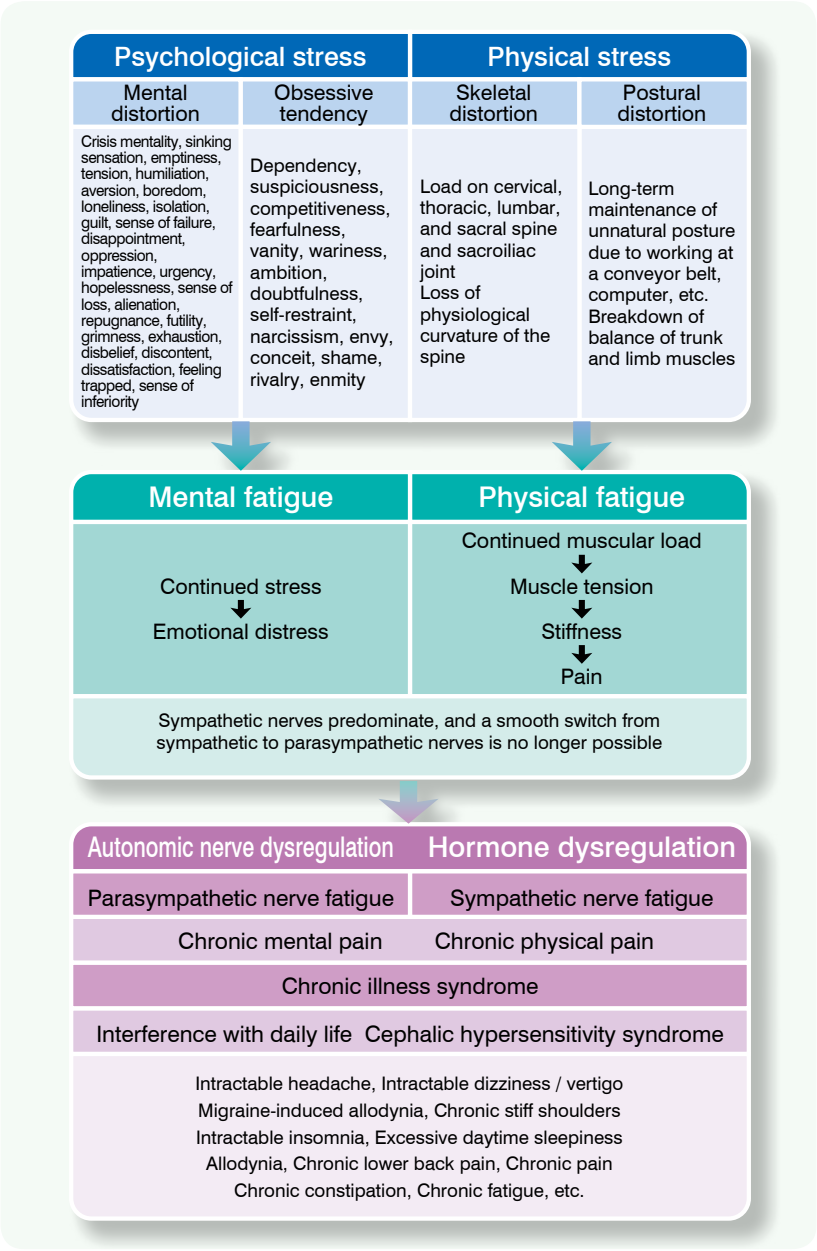

Serotonergic nerve nuclei
Acetylcholinergic nerve nuclei
Dopaminergic nerve nuclei
Noradrenergic nerve nuclei
Diencephalon
Midbrain
Pons
Medulla oblongata
Spinal cord
(Thalamus + hypothalamic region)
Ch4 (nucleus basalis of Meynert)
Ch6 (dorsolateral tegmental nucleus)
B6, B8 (median raphe nucleus)
B1 (nucleus raphe pallidus)
Ch5 (pedunculopontine tegmental nucleus)
B9 (linear nucleus)
B7 (dorsal raphe nucleus)
B5 (pontine raphe nucleus)
B4 (dorsal to the nucleus prepositus hypoglossi)
B3 (nucleus raphe magnus)
B2 (nucleus raphe obscurus)
A15 (olfactory bulb)
A14, A13 (zona incerta)
A12 (arcuate nucleus of infundibular nucleus in the hypothalamus)
A11 (posterior diencephalon)
A10 (ventral tegmentum)
A9 (substantia nigra pars compacta)
A8 (retrorubral nucleus)
A7 (lateral region of reticular formation)
A6 (locus ceruleus)
A5 (in the vicinity of the superior olivary nucleus)
A4 (in the vicinity of the superior cerebellar peduncle)
A3 (dorsal to the inferior olivary nucleus)
A2 (in the vicinity of the solitary nucleus)
A1 (in the vicinity of the lateral reticular nucleus)
Somatic motor nerves
Sympathetic nerves
Parasympathetic nerves
Acetylcholinergic neuron
Somatic motor fiber
Skeletal muscle
Ganglion
Noradrenergic neuron
Myocardium
Smooth muscle, etc.
Acetylcholinergic neuron
Preganglionic fiber
Ganglion
Postganglionic fiber

3 Why does cephalic hypersensitivity syndrome develop?

When the ancestors to us *Homo sapiens* first started to walk on two legs, their brains underwent dramatic development. However, bipedalism made the skeleton susceptible to distortion and the muscles vulnerable to stiffening. Similarly, as the functions of the "mind" developed to a new level, this generated mental distortions and fixations. Cephalic hypersensitivity syndrome is a disease to which we are fated by our human nature.

I hope the foregoing explanation will have given you an understanding of how chronic stress gives rise to cephalic hypersensitivity syndrome. However, in most cases, low-key stress is an everyday experience that is resolved and forgotten. Most people experience headache, stiff shoulders, back pain, fatigue, and similar symptoms on an everyday basis, and no one is ever entirely free from worries about relationships with others. So why does cephalic hypersensitivity syndrome develop?

Take a look at the illustration. Maintaining a poor posture causes physical fatigue. If psychological stress is not resolved but accumulates, the result is mental fatigue. I will explain this in more detail later, but fatigue is a danger signal in basic biological activity that says "unless you take time to recover now, something bad will happen," and indicates that disruption of the autonomic nerves is already occurring. People who know how to relax their bodies and who are good at taking breaks will not go on to develop cephalic hypersensitivity syndrome. The problem is those people who are not good at this. For such people, both their lifestyle and personality type make them vulnerable to developing cephalic hypersensitivity syndrome. The important point here is that body and mind cannot be separated, but are closely related to each other. Stiff shoulders, back pain, and other physical symptoms lead to emotional distress and depression, and psychological stress generates stiffness and pain in the body.


Psychological stress
Physical stress
Mental distortion
Obsessive tendency
Skeletal distortion
Postural distortion
Crisis mentality, sinking sensation, emptiness, tension, humiliation, aversion, boredom, loneliness, isolation, guilt, sense of failure, disappointment, oppression, impatience, urgency, hopelessness, sense of loss, alienation, repugnance, futility, grimness, exhaustion, disbelief, discontent, dissatisfaction, feeling trapped, sense of inferiority
Dependency, suspiciousness, competitiveness, fearfulness, vanity, wariness, ambition, doubtfulness, self-restraint, narcissism, envy, conceit, shame, rivalry, enmity
Load on cervical, thoracic, lumbar, and sacral spine and sacroiliac joint
Loss of physiological curvature of the spine
Long-term maintenance of unnatural posture due to working at a conveyor belt, computer, etc.
Breakdown of balance of trunk and limb muscles
Mental fatigue
Physical fatigue
Continued stress
Emotional distress
Continued muscular load
Muscle tension
Stiffness
Pain
Sympathetic nerves predominate, and a smooth switch from sympathetic to parasympathetic nerves is no longer possible
Autonomic nerve dysregulation
Hormone dysregulation
Parasympathetic nerve fatigue
Sympathetic nerve fatigue
Chronic mental pain
Chronic physical pain
Chronic illness syndrome
Interference with daily life
Cephalic hypersensitivity syndrome
Intractable headache, Intractable dizziness / vertigo
Migraine-induced allodynia, Chronic stiff shoulders
Intractable insomnia, Excessive daytime sleepiness
Allodynia, Chronic lower back pain, Chronic pain
Chronic constipation, Chronic fatigue, etc.

Ailments such as stiffness, pain, anxiety, and insomnia appear on an everyday basis, and at this point, many people visit a medical institution or take medication purchased at a pharmacy. Medication may take away the pain temporarily, but once the balance of the autonomic nervous system has been disrupted, painkillers will not return it to its normal state. Pain is another of the body's danger signals, and to suppress it with drugs and carry on doing too much will eventually disturb the brain hormones and the various nervous systems, particularly those that transmit pain, until they continue to transmit rogue signals. The brain attempts to learn and adapt to these abnormal signals. As a result, the signals sent from the body and those sent from the brain become mixed up and confused, creating a condition in which sensation, movement, and the psychological state are disturbed in a complex manner. This is the true nature of the diverse manifestations of chronic illness syndrome. Although its pathology varies according to differences in the symptoms that constitute the original cause, in all cases, it is a form of cephalic hypersensitivity syndrome.

I will now go on to explain the sort of person and type of lifestyle that make it more likely that cephalic hypersensitivity syndrome will develop.

What sort of person is likely to develop cephalic hypersensitivity syndrome?

Personality-based factors

Not everyone who suffers from symptoms such as headache, dizziness / vertigo, stiff shoulders, and back pain will develop cephalic hypersensitivity syndrome. I believe that a susceptible personality type underlies this condition. Many patients with chronic illness syndrome, manifested as symptoms such as headache and dizziness / vertigo, are earnest and scrupulous, with relatively inflexible personalities. Asked to perform a task, they are the type who do it properly without cutting corners. Many people of this type are not very adaptable and tend to allow stress to build up internally. They also tend to have decided preferences and to have a caring personality. Vulnerable to stress and liable to allow it to build up, they are easily tired and often feel anxious, eventually becoming depressed. People like this are vulnerable to developing cephalic hypersensitivity syndrome.

Lifestyle-based factors

Lifestyle issues that make people more susceptible to cephalic hypersensitivity syndrome include going to bed at late hours and getting little sleep, as well as irregular eating habits and lack of exercise. Chronic constipation is a frequent problem.

Many older people feel that six hours of sleep is sufficient, but if they are active, then they actually require seven. People in middle age who are working require between seven and eight hours of sleep. Continued lack of sleep gradually leads to cumulative fatigue. The problem is one of self-control and should not be blamed on the environment. In exceptional cases, factors such as the time spent commuting or the time when family members come home may make it impossible to get sufficient sleep. In this case, the family should work together to arrange matters and find the extra hour somewhere.

Irregular eating habits and chronic lack of exercise are also major problems. People who do not eat breakfast and those who eat late at night are susceptible to developing cephalic hypersensitivity syndrome. Many of those with this condition are not accustomed to walking. Few people who boast of the amount of daily exercise they perform or report that they start each morning with *rajio taisō*, the group calisthenics broadcast on Japanese national radio, develop cephalic hypersensitivity syndrome. Many of those who suffer from it dislike exercising. As I explained in detail in the section on serotonin (see Page 35), walking is an ideal rhythmic movement that increases the level of the brain hormone serotonin. People who commute by car to and from desk jobs not only do not walk enough, but also do not have sufficient exposure to natural sunlight. Without exposure to sunlight, serotonin levels fall. A low-serotonin lifestyle also diminishes melatonin levels. A drop in melatonin results in poor sleep, and when this is added to eating at irregular hours and a dislike for exercise, chronic constipation is the inevitable result. The only way to break out of this vicious cycle is self-control. People with poor health who are troubled by chronic illness syndrome should first take a good look at their own lifestyle.

Laboratory test results are not the be-all and end-all

Doctors check the results of blood tests and other laboratory tests against "reference values," and based on this, they tell patients that certain values may need monitoring or that treatment may be required. These reference values for tests do not indicate a clear boundary between "abnormal" and "normal." They provide a range of values, results within which can be regarded as normal. This means that doctors may not describe a test result as indicating a disease even if it is somewhat outside the reference values.

In April 2014, the Japan Society of Ningen Dock ("*ningen* dock" is a Japanese-English term meaning "human dock" that refers to regular in-depth health checkups, like putting a ship into dry dock) published a draft of new standards for laboratory test reference values based on its own research. The reference values currently used by many hospitals are those issued by specialist medical associations, and there are some differences between the two sets of values. However, for patients with cephalic hypersensitivity syndrome who react sharply to falling outside reference values, this small difference takes on massive significance. Even when it is explained to them that laboratory test results are only reference values and should not be treated as the be-all and end-all, people with the type of personality predisposed to cephalic hypersensitivity syndrome find this difficult to understand. If symptoms can be kept under observation without immediate treatment because the Japan Society of Ningen Dock reference values cover a wider range, this helps to reduce stress on the part of patients.

Problems with the reference values for laboratory test results formulated by medical associations

When discussing how these reference values are set, the role of the specialist medical associations, which operate the certification system for specialist doctors, cannot be overlooked. The way in which it has become standard for doctors to use reference values for laboratory test data when explaining symptoms is an issue not unrelated to cephalic hypersensitivity syndrome.

Numerical values on which patients focus their entire attention include those for blood pressure, liver function, blood sugar, and cholesterol. For all of these, the Japan Society of Ningen Dock reference values accept a wider range of levels

as normal. For example, compared with the diagnostic reference level for LDL bad cholesterol of 140 mg/dl or over indicated by the Japan Atherosclerosis Society, the new Japan Society of Ningen Dock values cover a much broader range, with the upper limit for men of 178 mg/dl, and the upper limits for women stratified by age as 152 mg/dl at age 33–44, 183 mg/dl at age 45–64, and 190 mg/dl at age 65–80, offering much greater leeway [18]. For over a decade, I have been explaining to patients that it is illogical to use a single reference value for laboratory test results, such as levels of cholesterol and creatinine, for which clear gender and age differences are evident in clinical practice, and have given them a document setting out their own personal guidelines. I would like to make the following proposal.

- Use the Japan Society of Ningen Dock reference values for healthy individuals, those with mild symptoms, and those who have yet to develop symptoms.
- Use the stricter reference values formulated by specialist medical associations for individuals who have already developed a disease.

The reference values put forward by specialist medical associations are the fruits of over a decade of observational studies. The Japan Diabetes Society uses numerical values that have been empirically and statistically analyzed from trends in the laboratory test results and symptoms of large numbers of patients. The Japan Atherosclerosis Society and the Japanese Circulation Society also use numerical values that have been empirically and statistically analyzed from the changes in laboratory test results and symptoms of patients with disorders such as ischemic heart disease, myocardial infarction, and cerebral infarction.

The reference values proposed by the Japanese Society of Ningen Dock have been calculated from the laboratory test results of healthy individuals extracted from among all those who have undergone health checkups, including both patients currently undergoing treatment and healthy people who are not receiving any treatment. According to the Society's website, its reference values have been calculated on the basis of the standard deviations from the numerical values for 10,000–15,000 healthy individuals extracted from the data for 1.5 million individuals who underwent "*ningen* dock" health checkups in 2011. The reference values formulated by specialist medical associations indicate that

patients with results that are persistently greater than these numbers are at higher risk of developing disease, not the immediate presence of an abnormality. The Japanese Society of Ningen Dock reference values simply indicate the numerical values regarded as healthy. Both sets of values are thus correct, and are valuable as references.

Iatrogenic cephalic hypersensitivity syndrome from over-medication

Over-medication: Anticholesterol drugs

Although non-specialists may find this difficult to understand, in fact the reference values for laboratory tests vary in several different ways. Test result forms show the so-called "normal limits," but it is wrong to assume that all laboratory test results are measured by the same method. There are three different types of reference values: (1) values that indicate a diagnosis (diagnostic thresholds), (2) values that indicate whether treatment must be started (treatment thresholds), and (3) values that indicate targets for disease prevention in daily life (preventive medical thresholds). These values, which have been statistically calculated depending on who has carried out the survey and what sort of people have been surveyed, must be interpreted in different ways.

The argument between the Japan Atherosclerosis Society and the Japan Society for Lipid Nutrition on the guidelines for the use of statins, a type of medication for lowering cholesterol, is still fresh in my memory. The Japan Atherosclerosis Society put forward laboratory test results as guidelines for statin use that took as their evidence the results of the Nippon Data large-scale study carried out by a Ministry of Health, Labour and Welfare study group and the Japanese Society of Cardiovascular Disease Prevention. The Japan Society for Lipid Nutrition, on the other hand, not only carried out a review of the literature that covered more than just medical publications, including nutritional studies of Japanese, but also pointed out that the Nippon Data study was inadequate; on this basis, they claimed that the values calculated from that imperfect study were too low. Their point was that if medication were to be prescribed on the basis of the Japan Atherosclerosis Society criteria, it would be taken by people who do not actually need it, potentially causing them to develop drug-induced illnesses [19]. Disappointingly, this huge controversy between these two societies appeared to have surprisingly little impact on

doctors actually engaged in clinical treatment. The revised reference values published by the Japanese Society of Ningen Dock have given fresh life to this controversy. It is not my intention to criticize only the Japan Atherosclerosis Society: the problem is one common to many medical associations that base themselves on the specialist certification system.

One very interesting fact is that the list of supporting members who donate money to the Japan Atherosclerosis Society and the Japanese Society of Cardiovascular Disease Prevention, which support the Nippon Data study, includes a large number of pharmaceutical companies. The Japanese Society of Ningen Dock, on the other hand, publishes its policy on conflicts of interest as a medical association (how it deals with studies funded by corporate money). Its partner in studies in which the Society is involved is the National Federation of Health Insurance Societies (Kenporen), a federation of organizations that need to pay out money if their members become ill. When it comes to a conflict between groups that sell medication to sick people and those that are required to pay for their treatment, it is obvious that the latter will be far more concerned with prevention than the former.

In my experience, some of the people who come to me complaining of fatigue and headache have been taking statins for several years. They have unthinkingly continued to use them even though their cholesterol levels have dropped to the point at which they are only just above the level of hypocholesterolemia. When I tell such patients to stop taking their medication, their symptoms of fatigue and headache mysteriously improve.

What I would like to repeat again here is that there is no need to view laboratory test results, which have such a shady background, as the be-all and end-all, or to make people sick who would not otherwise have become ill. Patients should protect themselves by understanding the hidden socioeconomic factors that underlie the reference values proposed by specialist medical associations supported by drug companies, rather than trusting blindly in doctors' explanations of laboratory test results.

Overmedication: Antihypertensive drugs

Mr. K, aged 42, had inherited a small company from his father and was hard-pressed to cope with carrying on the business. After a few years, he found that he was not sleeping well and was constantly tired, meaning that his thinking was slow and his work efficiency dropped. Encouraged by his wife, who was worried about him, he reluctantly went to the doctor.

Hospital A:

He first underwent the normal run of laboratory tests. His blood pressure was higher than the reference value, and his blood sugar and uric acid were also a little high. His doctor explained medication for blood pressure, blood sugar, and uric acid by saying "Your blood pressure is very high. If we don't do something now, you could have a brain hemorrhage, so I'll prescribe medication to bring these values down to normal levels." Mr. K thought that his insomnia and tiredness must be due to conditions such as hypertension and diabetes, and he started taking the medication that same day. Not only did his insomnia and fatigue fail to improve, he also became concerned about his blood pressure. Anxious about what would happen if his health broke down, he started measuring it daily. Despite the fact that his blood pressure declined to the point at which it was rather too low (possibly due to the medication) and his blood sugar was also normal, he was still unable to sleep. His health became worse and worse. His wife was apprehensive about many other things, and his anxiety intensified.

After the prescription ran out, he went to Hospital B:

He was questioned closely by a nurse about his recent lifestyle, history of foreign travel, and habits. He was then examined by a doctor, who said "You seem to be working very hard. Do you find it hard to sleep because you're worried about your work?" Mr. K explained how worried he was about his insomnia and how easily tired he was, upon which the doctor told him "You're tired because you work too much. The first thing you need to do is to review both what you do at work and your lifestyle. I'll also run some tests to rule out the possibility of other illnesses." These showed that Mr. K's blood pressure was higher than the reference value, and his blood sugar and uric acid were also a little high. The doctor's response was to say, "Your numbers are a bit high, but that's probably because you drink a lot of beer because you can't sleep. I'll prescribe you some

medication to make you less tense. So you don't actually get sick, eat a low-salt diet and go to bed early." He was told to measure his blood pressure every morning immediately after waking up, and was given a diary in which to record his blood pressure as well as a pamphlet explaining the relationship between sleep and hormones. On reading this, his wife said, "The company depends on your being in good health. I'll do my bit, if you go to bed early." Mr. K reassessed his work practices, went home early, and took time to go for walks in the park with his wife on weekends. His sleeping patterns gradually improved, and he no longer felt so tired. His blood pressure and blood sugar also returned to normal levels.

Overmedication: Antidepressants

I have already explained how a lifestyle with a rhythm that promotes the appropriate secretion of serotonin helps prevent cephalic hypersensitivity syndrome. I hope you understand that our contemporary way of life easily gives rise to serotonin deficiency. If a medical condition develops as a result of a lack of serotonin, this can be treated by taking medication to increase serotonin levels. I explained earlier that many antidepressants and anti-anxiety drugs act to increase serotonin, but overmedication and resultant new illness is a matter of concern.

As I will explain in detail later, my proposed "night therapy" (chronomodulated therapy) involves taking a low dose of medication just once, at 8 p.m. For this night therapy to be effective, my patients must taper off the doses of the drugs they have been prescribed long-term by other doctors, such as phenothiazine anti-anxiety drugs (commonly known as "tranquilizers"), or antipsychotic drugs prescribed by psychiatrists. For some medications, coming off them suddenly may cause side effects, and such drugs should not be discontinued without careful consideration. I carefully ask patients about all the drugs they are taking and obtain their consent to reduce the dose gradually. Many doctors will not do this out of a feeling that it would be impolite to the previous doctor or the patient's primary care physician. It is a difficult decision for anyone.

Cases of mild serotonin syndrome as a side effect of antidepressants and anti-anxiety drugs that increase serotonin levels are not uncommon. Serotonin syndrome results from overmedication. If patients are prescribed too much

medication that increases serotonin, the hormone level becomes too high, causing palpitations, shortness of breath, mild fever, sweating, and irritability. Rather than alleviating anxiety, increased serotonin also aggravates it, and patients become over-excited. Overdosing on medication causes side effects, and it can be poisonous. (For more details on serotonin syndrome induced by serotonin overdose, see the table on autonomic dysregulation and serotonin on Page 33.)

Summary – how to maintain a balanced relationship with medications

Many etymologies for the term *kanjinkaname* ("the essential point," written with the Japanese characters for "liver," "kidney," and "essential") have been suggested, but the fact that the liver is the most important organ in the body has long been a basic health precept. With the current ascendency of Western medicine, this has been forgotten, and symptomatic treatment has become the mainstream. Antihypertensive drugs for high blood pressure, statins to reduce high cholesterol, painkillers for headache, and the justification given for all these is to prevent the patient from developing a cerebral infarction, cerebral hemorrhage, or other serious condition.

When filling prescriptions, many pharmacists provide patients with a written explanation and a sticker to put in their *okusuri techō* (a booklet for recording all the medications taken by an individual). The *okusuri techō* system was introduced after the sorivudine incident (see note) in 1993 and the Great Hanshin-Awaji Earthquake of 1995. However, despite reports of scandals related to adverse drug reactions, large numbers of patients are still taking so many different types of medications that they are unable to remember them all themselves, or unthinkingly continue to use medications with no idea of their pharmacological actions or side effects. The extragovernmental body of the Ministry of Health, Labour and Welfare, the Pharmaceuticals and Medical Devices Agency (PMDA), undertakes the collection and dissemination of side effects as a third-party organization. However, the number of potential drug combinations is infinite, and given the additional factor of constitutional predispositions of individual patients, predicting side effects is far from easy.

Patients assume that if a doctor gives them medication, then it must be safe.

But, in many cases, the package insert states that the mechanism of action is still unknown. Because human experiments are not permitted, it is frequently the case that results are taken from recreations of human pathological conditions in rats and other animal models. Once inside the body, medication is often metabolized by enzymes and excreted via the liver and kidneys. It is only to be expected that some drug metabolites may block the actions of other drugs, or conversely enhance them. If the liver is weakened by disease, taking multiple drugs may damage it further. Poor liver and kidney function or functional impairment may form an undercurrent to the development of cephalic hypersensitivity syndrome.

I am not saying that all medication is bad. However, unthinkingly taking several different drugs at once for a long period will not restore anyone to health. What I want to get across is that it is possible to have too much of a good thing. Even if the symptoms of a disease can be temporarily suppressed with medication, eliminating the underlying cause is a far more difficult task. In particular, chronic, transformed disorders such as cephalic hypersensitivity syndrome cannot be cured without addressing their lifestyle-related causes. Overmedication is a factor that should not be overlooked.

(Note) Patients being treated with both sorivudine, a medication for treating herpes zoster infection, and the chemotherapy agent fluorouracil developed leukopenia, thrombocytopenia, and other severe blood disorders, and a number of them died.

4 Diagnosis of cephalic hypersensitivity syndrome

As mentioned above, there is an urgent need to improve the system of preliminary examinations to prevent cephalic hypersensitivity syndrome and other iatrogenic disorders. Japan has a severe shortage of doctors, and the establishment of a system for preliminary examinations prior to examination by a doctor should be a priority. My American psychiatrist friend would have a nurse, pharmacist, or health information manager perform full preliminary examinations of patients before he carried out his own consultation. Information can be gathered at this stage on detailed symptoms, disease history, and medication history. It also helps with the early identification of the side effects of medication. He told me that he would see only 20 patients a day, all by appointment, and was free every afternoon, an incomparable situation compared with the Japanese practice of a two-hour wait for a three-minute consultation, and I remember thinking that we lived in completely different worlds. In my hospital, I subsequently put together preliminary examination teams headed by experienced nurses, setting up my own Japanese-style system for preliminary examinations. I like the way in which this system enables efficient, effective medical treatment for both patients and doctors to become more widely known.

Cephalic hypersensitivity syndrome is a disorder that can be diagnosed if an experienced doctor carries out a specialist medical interview after a full preliminary examination. Clues leading to the diagnosis can be unearthed during both detailed medical interviews about current symptoms and those covering the past.

For example, I remember carrying out a medical interview with a patient who was suffering from intractable dizziness. This patient had been constantly complaining for many years of malaise due to dizziness that interfered with daily life. However, a more in-depth medical interview revealed other symptoms including lack of appetite, not sleeping well at night, and feeling heavy-headed on waking. Probing back further into the past, I was able to elicit descriptions of other symptoms, including the facts that the patient had been troubled by stiff shoulders some years previously and had suffered from headaches as a student over a decade before. When I asked about family members, I obtained the

information that both parents and siblings also suffered from headaches. This showed that the patient was suffering from migraine-associated vertigo.
Among the various manifestations of cephalic hypersensitivity syndrome, chronic migraine is the most frequent illness. If migraine is treated as cephalic hypersensitivity syndrome, intractable dizziness will improve.

Cephalic hypersensitivity syndrome is often an underlying cause of insomnia when this is due to parasomnia. Inability to sleep well all night because of twitching or restless legs, then feeling so sleepy during the day that it interferes with work or everyday activities, is a form of chronic insomnia that cannot be cured with sleeping pills. If such patients are treated for restless legs, their daytime sleepiness disappears, along with its interference in their daily lives. Cephalic hypersensitivity syndrome can be diagnosed comparatively easily from the test results, diagnosis, and effectiveness or otherwise of medication prescribed at medical institutions where patients have previously been treated.

The table shows my cephalic hypersensitivity syndrome assessment scoring system, which I have devised on the basis of my own experience. It is helpful if this can be filled in during the preliminary examination. I will describe medical interviews for disorders that tend to progress to cephalic hypersensitivity syndrome in Chapter 2.

Oota Cephalic Hypersensitivity Syndrome Score

Write a circle in the box next to each item that applies to you.

	Worries that cannot be discussed with anyone else		Always gloomy		Eat irregularly, unbalanced diet
	Stressed about personal relationships		Stressed about work or school results		Numbness and pain around the body
	Seeing several different doctors		Always tired		Lack of exercise, dislike exercise
	Don't get enough sleep		Always constipated		Taking several different types of medication
			Subtotal 5 points × ( ) = /60 points		
	Scrupulous		Serious		Fastidious
	Lacking in flexibility		Perfectionist		Strong preferences
	Go to bed late, at around midnight		Wake up several times during the night		Sleep talking
	Bruxism		Vivid altered dreams, nightmares		Snoring, apnea
	Dry mouth, night sweating		Palpitations, suffocating sensation		Feet feel cold, burning, or tickly
	Problems with waking too early in the morning		Difficulty getting up in the morning		Headache
	Stiff shoulders		Dizziness / vertigo		Tinnitus, difficulty in hearing low-pitched sounds
	Sensitive to light, sounds, and smells		Dizziness on standing		Blurred vision, seeing stars
	Eyes are easily tired		Poor posture		Lower back trouble
	Bad menstrual pain		No strength in hands		Numbness in some parts of the arms and legs
	Work mainly on a computer		Work mainly standing up		Spend long periods working or studying
	Work night shifts		No appetite		Abdominal pain
	Diarrhea		Heavy smoker, drink alcohol before going to bed		Often drink coffee
	Don't eat breakfast				
			Subtotal 1 point × ( ) = /40 points		
			Total ( ) points Assessment		

10≤ Total score <30: Mild, 30≤ Total score <70: Moderate, 70≤ Total score: Severe

Kosuke Oota

5 Treatment of cephalic hypersensitivity syndrome

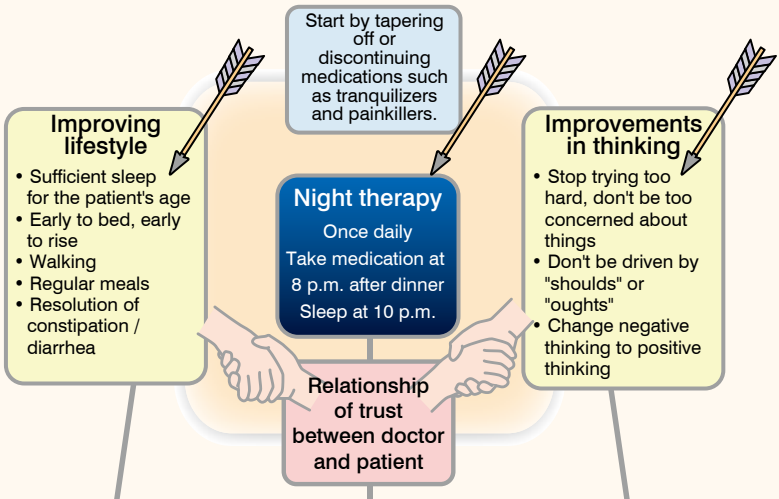
Illustration of my treatment algorithm

An algorithm is a procedure for solving a problem, expressed as a formula. For me, the treatment algorithm for cephalic hypersensitivity syndrome provides the blueprint for treatment. It is like a theoretical equation corresponding to a convincing deduction. Its fundamental principle is simple. That is the nature of formulae: even the equation expressing Einstein's highly complicated theory of relativity is in itself extremely simple. However, the existence of a fundamental principle in nature does not mean that it can be derived by just anyone. Furthermore, even if a formula can be derived, that does not mean that a solution can be found. Einstein was unable to solve the formulae he had himself derived. Even after his death, mathematicians and physicists who were considered geniuses pooled their collective wisdom to establish their reliability. Numerous astronomical phenomena supporting Einstein's formulae are still being discovered, whereas no phenomenon disproving them has yet been found. This in itself is the evidence provided by natural history. It is my hope that more and more cases verifying my treatment algorithm for cephalic hypersensitivity syndrome will be published, and I look forward to the day when my treatment algorithm is accepted.

The "three arrows" supporting the cephalic hypersensitivity syndrome treatment algorithm

The illustration shows the treatment algorithm for cephalic hypersensitivity syndrome. The first arrow supporting treatment comprises improving lifestyle, the second improving thinking, and the third night therapy. Their foundation is a relationship of trust built up between doctor and patient. It is only when each one of these arrows is in practice that treatment will be effective. If even one is missing, good results are impossible to obtain. And for all of them, it is the effort put in by the patient himself or herself that is vital. As I have stressed repeatedly, cephalic hypersensitivity syndrome cannot be cured solely by prescribing and taking medication. In addition to the relationship of trust between the patient and the doctor who provides emotional support, and to the cooperation of family, friends, and colleagues, patients themselves must face

Treatment algorithm: Three arrows



Hormones undergo circadian variation. For this reason, if the rhythm of daily life is disturbed, the immediate consequence is loss of appetite, constipation, and disturbed sleep, leading to tiredness. For the treatment of cephalic hypersensitivity syndrome, sufficient sleep for the patient's age, an appropriate amount of exercise, and regular meals are required.

Night therapy is a form of chronomodulated therapy. Human hormones are affected by the sun (day and night) and moon (the ebb and flow of the tides). The temporal undulations produced by the sun and moon are what cause circadian variation in hormones. Chronomodulated therapy makes skillful use of the fact that the action of medication is related to hormonal circadian variation.

In specialist terminology, this is cognitive behavioral therapy, popularly known as counseling. In order to transform the thinking of people who are scrupulous and earnest and who tend to have strong preferences, making them more flexible and positive, it is important for a doctor to be both persuasive and a skilled conversationalist as well as experienced in order to enter into the patient's mind.

Kosuke Oota

up to their illness, and their own engagement with their treatment is the single most important factor.

The first arrow: Improving lifestyle
Taking back your own health for yourself

Improving lifestyle = Improving thinking = Night therapy

Many people who suffer from cephalic hypersensitivity syndrome have a poor rhythm of daily life and are harboring stress. The central pillar of prevention is to establish a basic rhythm of daily life, that is, to live according to the sun. The significance of a way of life that honors the sun, the god of heaven, should not be played down. People whose personalities render them susceptible to developing cephalic hypersensitivity syndrome should make a particular effort to coordinate their rhythm of daily life with the sun.

The rhythm of human daily life does not start with morning; it starts with sleep. That means going to sleep at the right time and waking up at the right time. Although this sounds very simple, in today's round-the-clock society, it is very hard to put into practice, and many people with cephalic hypersensitivity syndrome have disturbed sleep rhythms. Many also have irregular bowels and suffer from problems such as constipation or over-firm bowel movements or repeated constipation and diarrhea. The treatment of cephalic hypersensitivity syndrome requires improvement in both the rhythm of daily life and bowel regularity.

Working for long periods in the same posture may also cause cephalic hypersensitivity syndrome. Bodily stiffness starts from long-term static muscle load. If this is left unaddressed, this stiffness increases and gradually exacerbates until it turns into chronic pain. It can be prevented by improving everyday habits and the workplace environment. The sort of stretches generally used to alleviate stiff shoulders or back pain are sufficient. At work, you can take a minute now and

then to roll your eyes, roll your head around on your neck, rotate your shoulders, and stretch your back. Almost no one who takes part in *rajio taisō* early-morning group calisthenics has cephalic hypersensitivity syndrome. If someone enjoys exercise but fails to perform enough, they can correct this themselves through their own efforts. The difficulty is people who dislike exercise and therefore do not do any. This is why exercise is better than any medicine.

1. Walking: Walking or slow jogging is basic for maintaining general physical function

Walking not only tones the legs and lower back, but is a whole-body movement that also involves the muscles of the abdomen, upper back, and arms. It prevents and alleviates the back pain and stiff shoulders that result from constantly maintaining a single posture, whether sitting or standing. Between 30 and 40 minutes of daily walking or jogging has a beneficial effect on the lungs, heart, and digestive organs. It increases the secretion of serotonin and other hormones, acting to adjust the hormone balance and thus improving appetite, sleeping, and bowel regularity as well as stabilizing mood. As in one case, so in all: there are no drawbacks. For this reason, I always emphasize walking in particular when advising patients to improve their lifestyle in the treatment of cephalic hypersensitivity syndrome. Those who believe me and start walking usually get better. Those who don't try and walk, regardless of how often they are told, tend not to improve.

Cephalic hypersensitivity syndrome is a disease that occurs through a compensatory mechanism in the brain, stemming from the acquisition of bipedalism by humans. One characteristic of human beings that sets us apart from other animals is our ability to continue to walk for long periods. The homeostasis of the human body has evolved over millennia with walking and running as being key to existence. The present era constitutes no more than an instant compared with this process, which took tens of thousands of years. The rising incidence of cephalic hypersensitivity syndrome and other lifestyle-related diseases is the result of the imbalance between the mechanisms of the human organism, which have evolved over many millennia, and our contemporary lifestyle. The mechanism whereby walking cures cephalic hypersensitivity

syndrome is completely logical when viewed through the lens of the human evolutionary process.

2. Sleeping: The body is regenerated by good-quality sleep

Going to sleep at the right time and getting the necessary amount of sleep for your age should be taken as standard, but in our stress-driven society, these things that should be regarded as perfectly normal can be difficult or impossible. When the human body enters deep sleep, it is bathed in growth hormone and melatonin, which repair damaged cells, revive weakened ones, modulate digestion and absorption, and organize memory learning in preparation for the following day. In the later stage of sleep, levels of serotonin and cortisol secretion rise, and these peak on awakening at dawn. It is hormonal action that leads to waking refreshed in the morning.

3. Diet: Eat a balanced diet and chew well to increase serotonin levels

Being able to eat at mealtimes can also no longer be taken for granted. An increasing number of people think nothing of not eating breakfast or eating supper at 10 p.m., and just as with sleep, fail to exercise their individual responsibility and do not even attempt to remedy a disturbed rhythm of everyday life. What is needed is to ensure (as I will describe later) that no mineral deficiency is present, eat a balanced diet in moderation (*hara hachi-bu*, eating until you feel 80% full), and eat at times that fit the sun's rhythm.

As contemporary inhabitants of a stress-driven society, many people have brains that are deficient in serotonin, the mother of all hormones. Chewing thoroughly during meals ("mastication") is a simple, effective method of increasing serotonin levels. Mastication has been described as the single most rhythmic movement in everyday life. Rhythmic movement acts to increase brain hormones. Chewing every mouthful 30 times and taking 30 minutes to eat each meal also enhances the action of salivary amylase, which aids in digestion and absorption. Mastication tends to be overlooked as an everyday activity, but in fact it acts to adjust the balance of serotonin and other hormones.

4. Regular bowels: Resolving constipation clears toxins from the body

Poor bowel function is one result of an irregular lifestyle. A healthy individual whose autonomic nervous system is a thing of beauty has a smooth, large bowel movement every morning. Yet women with chronic illness syndrome who come to my hospital with beautifully manicured nails nonchalantly admit that they pass a bowel movement once a week. Many people with chronic illness syndrome have little awareness of the importance of bowel regularity. Chronic constipation creates a condition in which toxins are retained within the body, and as such is the origin of many health problems. The health or otherwise of the intestinal environment also affects immune function. In recent years, it has also been shown to play a role in alleviating stress by way of serotonin. Detoxification refers to the purging of toxins from the body, and resolving chronic constipation is by its very nature detoxifying, and is an important prerequisite for maintaining a healthy intestinal environment. I will say more about the association between chronic constipation and chronic illness syndrome, and how to deal with it, in Chapter 2.

5. Breathing: Regular breathing calms the mind

No one feels that they have a problem with unconscious breathing. However, although we may not notice, breathing is actually disturbed to a surprising extent in everyday life. Regulating breathing is very important. Rhythmic breathing is known to act to promote the secretion of serotonin and other hormones. Sitting up straight on a chair and breathing in deeply and exhaling slowly and slightly longer than usual for just one minute once a day is sufficient to regulate breathing.

6. Minerals: Too much sodium causes cell damage

Minerals play an important role in maintaining the body's homeostasis. Sodium, potassium, calcium, magnesium, iron, zinc, and other minerals in the form of ions support cells and the proper action of enzymes in the body. The traditional Japanese diet rarely leads to mineral deficiency, but an over-dependence on processed foods and supplements may cause the balance to break down. Particular caution is required in the intake of minerals having an inverse relationship in terms of intracellular and extracellular concentrations, specifically sodium and potassium, as well as calcium and magnesium. Our contemporary diet contains

too much sodium, and over-consumption rather than deficiency is also a concern for calcium due to the high rate of consumption of dairy products and the wide availability of fortified foods. The minerals that are more likely to be lacking from our contemporary unbalanced diet are potassium and magnesium, and it is important to consciously eat foods that are high in these. Both are found in raw vegetables, pulses, and sea vegetables. It is important to eat these ingredients in their natural form.

As I will describe in more detail in Chapter 3, I believe that disequilibrium of the intracellular fluid balance is related to cephalic hypersensitivity syndrome. In simple terms, the cells become swollen. It is therefore essential to each patient to learn how to reduce his or her salt intake, and I also prescribe diuretics such as Lasix (furosemide). This can help alleviate symptoms associated with lymphatic fluid, dizziness / vertigo in particular, in cephalic hypersensitivity syndrome.

Column

Gerson therapy purifies both body and mind

Chronic illness syndrome is the price that is paid for continuing to lead an unbalanced lifestyle for many years. If the sufferer is unlucky, the symptoms become chronic and the condition intractable. You may have heard of Gerson therapy. Max Gerson (1881–1959) cured his own migraine by means of diet, which he then applied to the treatment of conditions including tuberculosis, chronic inflammatory diseases, chronic degenerative diseases, and cancer; in his later years, he developed this as a dietary therapy for cancer. His ideas can be summed up as dietary therapy to maximize the body's natural capacity for healing, and it depends fundamentally on the theory of healing of chronic inflammatory and degenerative diseases.

This theoretical framework is derived from the numerous clinical cases treated by Gerson himself as well as from the related literature. It was first published in the 1950s, but 60 years later, its mechanism has yet to be fully explained. Nevertheless, some people have actually overcome cancer and extended their lifespan thanks to Gerson therapy. This simple method is based on a program of eliminating salt, restricting animal protein and fat, and drinking large quantities of organic fruit and vegetable juice (mainly carrot and apple), combined with supplements including linseed oil, and solutions of potassium and iodine, as well as detoxification with coffee enemas. Although the principle is simple, those who are used to eating highly flavored processed foods find it extremely difficult to obtain sufficient organic vegetables in season, drink at least two liters of fresh juice daily (special juice made by using a press-style juicer made by a company called Norwalk), use absolutely no salt or ingredients containing salt, and eat absolutely no animal protein or fat other than linseed oil for the first six weeks, as well as undergoing five coffee enemas (using one liter of enema solution containing organic coffee prepared according to a specified procedure). The fact that fifty people nevertheless managed to persevere with this therapy and recovered is persuasive evidence of

the involvement of some sort of scientific mechanism for this method in their recovery.

In his writings, Gerson focused on the intracellular / extracellular concentration gradient of Na^+ and K^+, stating that the intracellular concentration of K^+ decreases in chronic and degenerative conditions, Na^+ accumulates, and thyroid and liver function worsen as symptoms progress. He suggested that these systems must be restored to their normal function, and that this could be done by Gerson therapy and coffee enemas [20].

I also find Gerson therapy valuable from another perspective. The Gerson diet involves eating large quantities of tomatoes, potatoes, and other vegetables. These are foods that are high in γ-aminobutyric acid (GABA), which acts to calm the sympathetic nervous system; although germinated brown rice is perhaps the best known source of GABA in Japan, tomatoes and potatoes also have a high GABA content. I believe that the Gerson diet is effective for treating cephalic hypersensitivity syndrome in terms of its action in calming the excitation of the sympathetic nerves.

I believe that not only cephalic hypersensitivity syndrome but many other chronic disorders develop as the result of simple mechanisms that have many points in common. Yunus, Gerson, and I are thus all actually talking about the same mechanism. Severe cephalic hypersensitivity syndrome is associated with nerve degeneration and also has significant iatrogenic aspects. Given that medication cannot be increased indefinitely, the use of Gerson therapy as well should improve its therapeutic effect. However, the nature of dietary therapy means that the understanding and support of family and friends are essential. It is thus extremely important to work on improving lifestyle habits in terms of diet, exercise, and sleep under normal circumstances.

The second arrow: Improving thinking

The only person who can change you is yourself

Improving lifestyle = **Improving thinking** = Night therapy

In many cases, the majority of the mental stress that exacerbates cephalic hypersensitivity syndrome is caused by personal relationships, whether with family members, in the workplace, or elsewhere. Unfortunately, changing this environment is no easy matter. As the saying goes, leopards don't change their spots, and transforming your own personality or the things you were born with is not a simple task. On the other hand, changing the way we think is one of the few things we can do for ourselves to reduce mental stress. I would like to propose three strategies for mental stress reduction.

① Have the courage to change the way you think.
② Make use of counseling or another form of psychotherapy.
③ Undergo cognitive behavioral therapy from a familiar medical professional.

Some medical institutions, such as those with clinics specializing in psychosomatic medicine and psychiatry clinics, have counselors or clinical psychologists on staff, but it is rare for patients with headache, dizziness / vertigo, and other obviously physical symptoms to undergo initial examination in a clinical department that includes a counselor. In addition, compared with the number of counselors who handle problems such as children who refuse to go to school, there are few in Japan who specialize in treating patients with physical symptoms. In these circumstances, there are cases where those patients with cephalic hypersensitivity syndrome should be referred to a department of psychosomatic medicine or psychiatry.

It would also be good if doctors and nurses in all clinical departments were knowledgeable about cognitive behavioral therapy, but unfortunately,

Japanese medical education does not allow for this, as its importance is only just starting to be recognized.

Cognitive behavioral therapy is defined as "structured psychotherapy with the aim of curing psychological disorders by correcting cognitive bias due to the effects of the form of people's mood or behavior and how they think about and perceive things, and helping with problem-solving." It was developed as a therapeutic method in the 1970s by Beck in the United States as a form of psychotherapy for depression. Theoretically, it is based on information processing models and cognitive models, and in Japan, it is a comparatively new form of treatment that started to attract attention in the late 1980s. It presupposes a good relationship between practitioner and patient, with the therapist engaging to help the patient discover answers for himself or herself[21]. Recently, third-generation cognitive behavioral therapy has been developed that also incorporates techniques such as meditation, although the basic framework whereby it is patients themselves that overturn their negative thinking remains unchanged. Psychotherapists can also carry out this therapy if they have been trained to do so, but as it has strong medical elements, I feel that it is more effective when studied and carried out by a medical professional.

From this general survey, it can be seen that of the three strategies for curing the chronic illness syndrome of cephalic hypersensitivity syndrome, at this point, the most realistic and effective is (1) Have the courage to change the way you think. What I recommend is "magic mirror therapy," "rubber band snapping therapy," and "simple breathing."

Magic mirror therapy consists of standing face-on to a mirror and talking to it directly in a loud voice. You talk to your face in the mirror because you are the one changing the way you think. What you choose to talk about is up to you. In many cases, people look for the causes of mental suffering outside themselves. Within the family, it may be your mother-in-law or father-in-law. Or it could be your husband or your brothers and sisters. At school, it

could be older students or those of your own age. In the workplace, it could be a superior or your colleagues. However, the true cause of your pain is not anything outside you. It comes from the feelings such as anger, jealousy, and resentment in your own heart. If you hate someone or something, try saying "I like him/her/it." It is not enough just to think it: you have to say it out loud yourself, and hear it with your own ears. Doing this creates new pathways in the brain. "Rubber band snapping therapy" is a way of overturning your thinking. It puts a stop to the state of constantly turning over things you dislike or that are painful or anxious inside your head.

The final recommendation, "simple breathing," is similar to meditation. Since ancient times, people have always suffered from mental worry and suffering. Temples and churches have always provided places of healing. Sadly, in Japan, temples have become dedicated to funerals and memorial services and no longer fulfill their original function. In an attempt to heal their mental worries and suffering, people look for distractions and end up eating, drinking, talking, and going on short trips. If these do not improve things, they go to a hospital. However, like temples, although medical institutions today may have wonderful buildings and facilities, they are losing their ability to heal people.

Meditation is an age-old technique for seeking salvation for oneself. One recently developed method of meditation is known as "mindfulness." Meditation purifies the mind when it is contaminated with negative emotions such as anger, resentment, jealousy, and anxiety. Meditation and mindfulness are ways to restore a mind contaminated with negative energy to its former state. Clearing out a mind that has been colonized by intense negative energy is no easy task. It requires daily effort. Before embarking on more advanced techniques such as meditative breathing and chanting, it is a good idea to start off with a simple method that can be used immediately. Whether you are feeling desperate or sad, just a minute or two is sufficient: sit down firmly on a chair, close your eyes, place your hands gently on your stomach, and keep breathing deeply in and out.

Focus entirely on your breathing, without thinking about anything else. Even this by itself is effective.

Tips for magic mirror therapy

Take back your mind in its true colors with
The Magic Mirror

Ms. Minus

The Should and Ought traps

That's what I should be like, this is what ought to happen. Perfectionism

The No Good trap

Only ever seeing my own faults, being convinced that I'm no good as a person

The Dislike trap

Grow to dislike myself
Dislike an increasing number of other people

Turn your thinking around

Ms. Plus

Learn to like yourself
Learn to like others

Try praising yourself

Look for the good things about yourself

Call your name in front of the mirror and shout "I'm wonderful."

Call the name of someone you dislike and shout "I like you."

The Magic Mirror turns your dislike of yourself and others into affection.

The magic mirror transforms you into a straightforward, optimistic person.

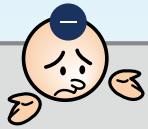
When you fall into the No Good or Dislike traps, when you feel that you hate yourself, or when you can't accept other people, face the "you" you see in the mirror and talk to him or her in a loud voice.

Bring your stress at work, insomnia, depression, and negative thoughts to the Magic Mirror!

Kosuke Oota

Tips for rubber band therapy

Snap away negative thoughts with the Rubber Band!



Mr. Minus

The Should and Ought trap

That's what I should be like, this is what ought to happen. Perfectionism

The No Good trap

Only ever seeing my own faults, being convinced that I'm no good as a person

The Dislike trap

Grow to dislike myself
Dislike an increasing number of other people

Turn your thinking around

Mr. Plus

Learn to like yourself Learn to like others

Talk to yourself.

What's the reasoning behind your assumption of "should" and "ought"?

Different things can be acceptable. Why not think a bit more flexibly,

Try praising yourself

Look for the good things about yourself

If you still feel negative...

Snap the rubber band! Switch to being positive.

All sorts of thoughts float into the human mind, one after another. It's an endless process. These are called "automatic thoughts."Automatic thoughts suffocate your mind. Distorted automatic thinking makes you feel terrible. Every time you notice it, banish it with your rubber band.

When you fall into the No Good or Ought trap, or when a negative thought comes to the surface, say "STOP!" and snap the rubber band on your wrist.
If you feel discouraged: STOP! and snap the band
If you feel down or depressed: STOP! and snap the band

Whether you're healthy, an insomniac, or depressed, use the rubber band snap!

Kosuke Oota

Tips for my own version of cognitive behavioral therapy: The trick to changing your thinking

Shōrinji Temple, where Hyakuzō Kurata wrote his collection of essays *Ai to ninshiki to no shuppatsu* ("The beginning of love and understanding"), stands on the mountain behind my high school. The phrase received at this temple from the Zen master Buddhist priest Eizan Tatsuta, "What is your original face before your parents were born?" is a famous *kōan* (Zen riddle) meaning "Reflect on your true reality." This *kōan* is the starting point for my own version of cognitive behavioral therapy.

My own style of cognitive behavioral therapy starts with gaining the patient's trust, something that is also emphasized by Yunus. Many patients with cephalic hypersensitivity syndrome have already had the experience of going from one medical institution to another and being prescribed various different drugs, none of which have worked, and now they must be told that their condition cannot be cured simply by taking medication but requires that they make an effort to regularize the rhythm of their daily life. To encourage such a behavioral transformation, they must first be willing to trust what I say. During my initial examination, I make a great effort to praise them sincerely. I tell women that they are particularly pretty, whether they are in their 20s or their 80s, and for men I tell them how handsome they are. This is far from mere flattery. They have come to consult me with all their pain and suffering, and after a little gossiping they will give me a smile. Watching changes of expression is an important part of any examination. It is also important to ask about matters such as daily life, family, and financial circumstances during casual conversation. Matters that may be difficult to ask about directly are easier to discuss as part of a general chat with both laughter and tears. Patients who have come in with a gloomy expression on their face leave with a bright smile. I regard this change as building a therapeutic relationship, and this is important.

As the saying goes, you can "become a slave of habit." I always explain the meaning of this expression to patients with cephalic hypersensitivity syndrome. "You have created this condition for yourself, so no doctor, however skilled, can cure it without you making an effort too."

I also tell them that medication only plays a small role in getting back to your

original self, so they need to face up to the challenge of taking themselves back through their own effort.

I have put together my own explanatory pamphlet for use by patients and their families. In it, I recommend magic mirror therapy and rubber band snapping therapy to help treat cephalic hypersensitivity syndrome. I call the three tendencies to fall into negative thinking the "Should and Ought trap," the "No-Good trap," and the "Dislike trap," and give practical instructions, explaining that the secret of transforming these into positive thinking include talking to yourself and gently praising yourself. Rubber band snapping therapy is a way of stopping the automatic thoughts that arise incessantly, which I devised after seeing the scars left by perfectly executed wrist-cutting. Snapping a rubber band leaves a red line on the white skin of the wrist, similar to the scar left by wrist-cutting. This is caused by a biological reaction in the skin known as "dermography," and the snapping noise of the rubber band, the pain, and the red line on the skin seem to produce a perception that resembles that of wrist-cutting. This method is well-regarded, and seems to act to turn feelings around in a "snap."

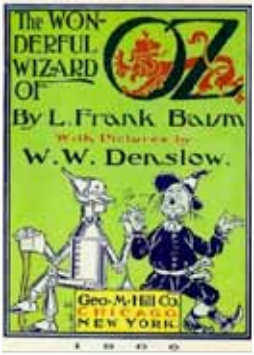
Drug therapy works well when combined with these various Oota-style cognitive behavioral techniques.

Column

People like masks

Most people live lives that fall into the "Should or Ought" trap. In the attempt to avoid behaving in a socially "unacceptable" manner, they bind themselves into lives constrained by what they "should" or "ought to" do. This may well involve a life of deceit.

If one always gave away one's true nature without pretense, it would be difficult to live in the community. The constraints imposed by a shame-focused morality cause increasing mental suffering, and people eventually come to hate this aspect of themselves. Traditionally, festivals offered the opportunity for release. Masks and dressing up played a crucial role in such festivals. By dancing wearing a mask, people became uninhibited enough to release themselves from "should" and "ought." Isn't this a way of recovering your true self? Even people who are serious can dance a traditional comic dance once they are wearing the right costume. The Mask, an American comedy movie released in 1994, is interesting for its depiction of a person released from the constraints of "should" and "ought."



*Book cover illustration taken from *The Wizard of Oz* http://ja.wikipedia.org/wiki/

Read fairy stories however old you are:

Fairy stories, folk tales, and other stories are a gold mine for cognitive behavioral therapy. They are both simpler and more effective than specific therapies that are hard to practice.

The third arrow: Night therapy

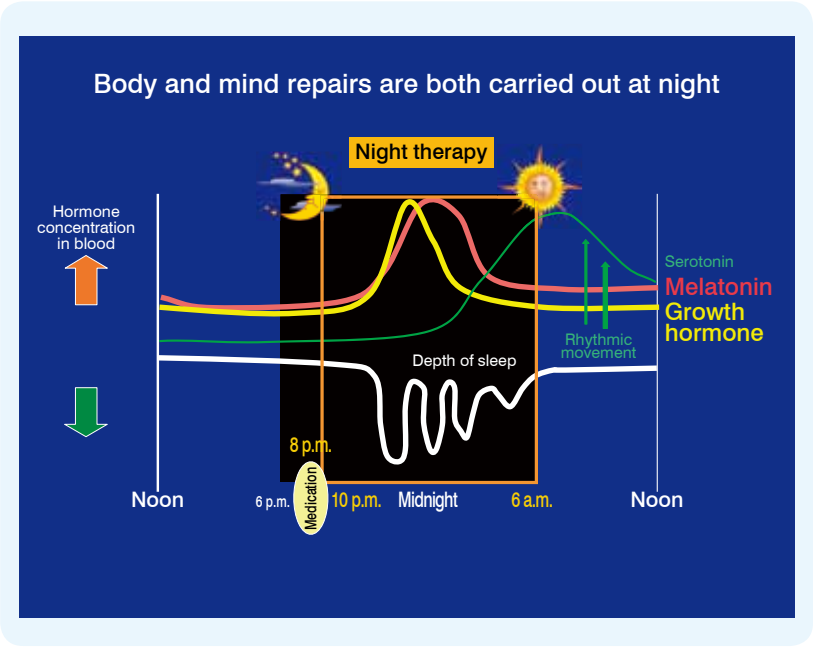
Small doses of medication are effective if taken at night

Improving lifestyle = Improving thinking = **Night therapy**

"Will this really work?"

Many patients who have gone from hospital to hospital and been prescribed numerous different medications without getting better are somewhat doubtful about night therapy. It is a hard job to convince them to stop taking oral tranquilizers and painkillers and take only the medication I prescribe. My prescription is for a combination of low-dose medications, taken only once a day. Night therapy is a solution worked out on the basis of my own experience. I will leave its validation for scientists to carry out later, but because patients do get well under this regime, some sort of biological or scientific mechanism must actually exist. I focus on the presence of circadian variation in the secretion of many types of endocrine hormones. In particular, I infer that there must be some sort of interaction between pharmacokinetics and the circadian variation seen in growth hormone and Na^+ channels.

I have named this therapeutic technique "night therapy," but as far as I have been able to tell from a computer search, no one else has tried to give a name to this sort of chronomodulated therapy. However, chronomodulation studies are underway on the association between the dosage of highly toxic anti-cancer drugs and circadian variation[22][23]. From the patient's viewpoint, they would prefer to take as low a dose of medication as possible as few times as possible to cure their condition. I hope that more doctors will become aware of the effectiveness of night therapy.



Growth hormone and melatonin secretion peak during deep sleep under the direction of the body clock. Growth hormone, as its name suggests, possesses functions related to the body's growth and repair mechanisms. Melatonin is known as the "sleep hormone," and like growth hormone, its secretion peaks during sleep.

These two hormones cooperate in the organization of learning and memory in the hippocampus. They also repair damaged tissues and aid recovery from mental and physical fatigue. At the same time, they also improve resistance and immunity and maintain and repair the body's homeostasis.

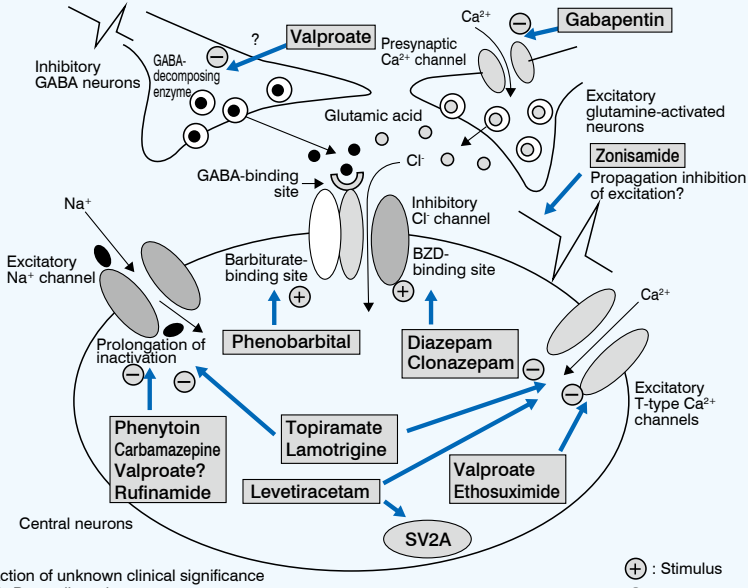
Bathe in the morning sunlight. Reset the body clock each morning. Early to bed, early to rise. This should be taken for granted, but I want you to understand just how very important it is.

Chronopharmacology: Drug action is also subject to circadian variation

Medication works better if it is taken in small doses before going to bed. I discovered this fact during my long years of clinical experience. I have also experienced chronomodulated therapy as the clinical application of chronopharmacology in epilepsy treatment. When instructed to take medication three times a day after food, patients would tell me that "I get sleepy during the day, which stops me from working. It interferes with daily life." So I would tell them to stop taking it at lunchtime, and instead take it in the morning and evening and before going to bed. When I did this, they would tell me they were sleeping well and suffering from fewer episodes. Aleviatin (phenytoin) and Tegretol (carbamazepine) both reach blood drug concentrations in the therapeutic range and decrease attacks at a higher rate when administered in the evening rather than during the day. The anticancer agent cisplatin is famous for its intense side effects, including gastrointestinal symptoms, renal dysfunction, and bone marrow suppression, but patients administered it at 5 p.m. experience significantly less nausea and renal toxicity than do patients given it at 5 a.m. Conversely, adverse reactions to Adriacin (doxorubicin hydrochloride) are more intense when it is administered in the evening. Ovarian cancer patients treated with Adriacin (doxorubicin hydrochloride) at 6 a.m. and cisplatin at 5 p.m. experience significantly fewer adverse reactions compared with those who did not receive the drugs at specific times, and survived for significantly longer [24]. Chronomodulated therapy with anticancer agents is in the process of gaining recognition. I anticipate that the day is at hand when the chronopharmacology of the night therapy I use to treat cephalic hypersensitivity syndrome will be explained.

6 Drug treatment for cephalic hypersensitivity syndrome

The pathophysiology of cephalic hypersensitivity syndrome overlaps in many respects with that of epilepsy. This is also evident in the fact that migraine and epilepsy have many points in common in terms of both their symptoms and the drugs used to treat them. As explained in detail in Chapters 2 and 3, the mechanism whereby conditions such as migraine and dizziness / vertigo develop into intractable cephalic hypersensitivity syndrome causes a similar hyperexcitability of the brain as that seen in epilepsy. This can be explained by the abnormal firing of voltage-dependent Na^+ channels. Ca^{2+}-channel abnormalities and the involvement of neurotransmitters such as glutamate and GABA have also been demonstrated. Antiepileptic drugs that block the action of these substances are therefore also effective in the treatment of cephalic hypersensitivity syndrome.



From Hirotoshi Echizen. Manual of Therapeutic Agents 2014, page 29. Illustration of the pharmacological action of epilepsy. Igaku Shoin, 2014.

Cephalic hypersensitivity syndrome may also be caused by an imbalance of the autonomic nerves or an abnormality in serotonin or other brain hormones as a result of the disturbance of the rhythm of everyday life by mental and physical stress. Antidepressants that supplement the deficiency of brain hormones are effective for this type. Interestingly, antiepileptics and antidepressants are both recommended in cases of chronic headache, chronic pain, and fibromyalgia (see Page 244). Of course, fine adjustment is necessary in each individual case, as I shall show later in my description of coded prescriptions, but based on the pathophysiological mechanism of cephalic hypersensitivity syndrome, the core of my drug treatment is antiepileptics and antidepressants.

Pain may occur as a result of a range of different mechanisms, and conventional analgesics may be unable to alleviate it sufficiently. Such intractable pain can be treated more effectively by antidepressants and antiepileptics than by drugs developed for the purpose of pain relief, although most of the former are not approved as painkillers. Other classes of drug, including vasodilators, muscle relaxants, antiarrhythmics, and sympathetic nerve inhibitors also possess pain-relieving actions, but these too are not approved for use as painkillers under the Japanese health insurance system. However, overseas, many of them have been approved as analgesics. To remove this inconsistency, the Ministry of Health, Labour and Welfare has issued an official notification on the off-label use of ethical pharmaceuticals (a so-called “application based on public knowledge”), and has investigated how to deal with this. However, if medications that do not meet this condition are prescribed off-label, the government prohibition on mixed billing applies. There are some conditions that cannot be dealt with solely using the treatments currently covered by health insurance, and there are calls for the prohibition on mixed billing to be abolished.

Here, I will describe the long-standing antiepileptic Tegretol (carbamazepine); the comparatively new antiepileptic Topina (topiramate), which has already been approved overseas for the prevention of migraine; and the long-standing tricyclic antidepressant Tryptanol (amitriptyline), which has recently finally received approval for the treatment of chronic pain and intractable migraine.

Antiepileptics

Tegretol (carbamazepine) was first synthesized by Walter Schindler *et al*. in Switzerland in 1957, and was developed in 1960 by Geigy. It was initially marketed as a drug to treat trigeminal neuralgia rather than as an antiepileptic, but was approved for the treatment of epilepsy and seizures in the United Kingdom in 1965 and in the United States in 1974. It was brought to market in Japan in 1965 as a psychoactive epilepsy treatment and as a treatment for trigeminal neuralgia. In the 1970s, Haruhiko Takesaki and Masanori Hanaoka in Japan reported that it also has an antimanic effect, and in 1990, its indications were expanded to include mania, mania in manic depression, and agitation in schizophrenia. As an analgesic, it is also used off-label as a supplementary medication for complex regional pain syndrome in addition to trigeminal neuralgia.

Topina (topiramate) is a comparatively new antiepileptic that was discovered by Bruce Maryanoff and Joseph Gardocki of McNeil Pharmaceutical in 1979. Since its approval in the United Kingdom in 1995 as a concomitant therapy for adult partial seizures, it has been approved in many European nations and the United States and is now widely used in clinical practice. In the United States, it was approved by the FDA in 1996 and is also currently approved for the prevention of migraine. In Japan, it was approved as an antiepileptic for use as concomitant therapy for partial seizures (including secondary generalized seizures) in epilepsy patients who do not respond adequately to other antiepileptics. It has yet to be approved for the prevention of migraines under health insurance in Japan, despite its approval for this purpose in Europe and the United States around 2004.

Antidepressants

Tricyclic antidepressants [such as Tryptanol (amitriptyline), Noritren (nortriptyline), and Tofranil (imipramine)] are a widely recognized choice worldwide for the treatment of chronic pain, including migraine. However, in Japan, although they were recognized at a very early stage by some specialists as supplementary medications for use in pain clinics and palliative care, they are not generally well known. The reason is a mystery.

Tryptanol (amitriptyline) was developed around 1960 at the dawn of the development of antidepressants, alongside the tricyclic antidepressants Tofranil (imipramine) and Noritren (nortriptyline). Tofranil (imipramine) was developed by Geigy in Switzerland and psychiatrist Roland Kuhn and his colleagues in 1957, followed by Tryptanol (amitriptyline), which was developed in 1959 by Merck in the United States. Noritren (nortriptyline), a metabolite of Tryptanol (amitriptyline), was developed by Lundbeck in Denmark in 1961. In Japan, Tofranil (imipramine) was approved as an antidepressant in 1957, Tryptanol (amitriptyline) in 1961, and Noritren (nortriptyline) in 1971. In 1963, Tryptanol (amitriptyline) was found to have an analgesic effect that is separate from its antidepressant action. Since its approval as an antidepressant by the United States FDA in 1961, as of 2014, its off-label use has been accepted for conditions including chronic pain in adults and the prevention of migraine. The same is true of Noritren (nortriptyline).

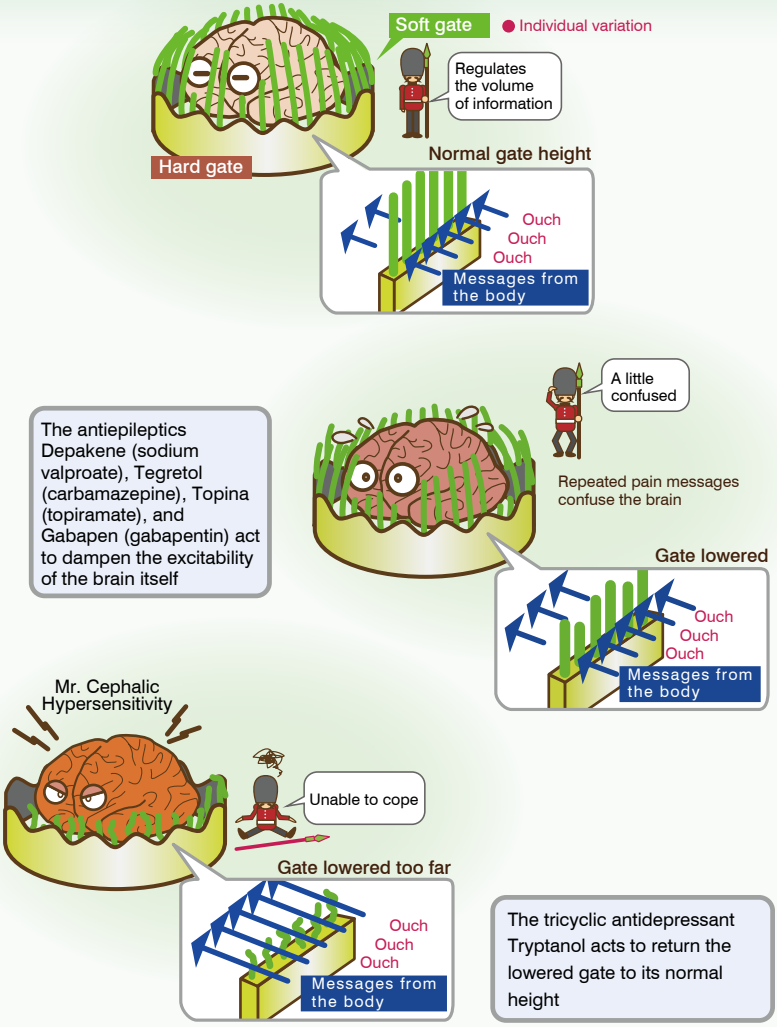
In Japan, a notification was issued in 2009 approving the prescription of Tryptanol (amitriptyline) to be covered by health insurance for depression and depressive state in patients with chronic pain in addition to its existing approval as an antidepressant, and in 2012, a similar notification was issued with respect to its prescription for migraine and tension headache. Similarly, another notification was issued in 2012 approving the prescription of Tofranil (imipramine) for peripheral neuropathic pain. At this point, the approval of Tryptanol (amitriptyline) and Noritren (nortriptyline) for the reimbursement under health insurance of their prescription for neuropathic pain was deferred, but in a 2014 evaluation, Tryptanol was accepted as "meeting the criteria for clinical necessity." Noritren (nortriptyline) is a medication that is easy to use in clinical practice, but its approval has been delayed.

Column

Central sensitization and cephalic hypersensitivity syndrome

The brain has the ability to regulate and control the messages about pain coming from the body. This is because in the event of a wound, sprain, fracture, or other injury, the brain is flooded with a large amount of information. If it were to accept all these pain messages, it would be unable to cope. It therefore acquired the ability to control the volume of pain-related messages. If this capacity for control fails to function normally, the excessive pain-related messages that arrive repeatedly act to chronically stimulate the brain. Initially, the brain becomes tired, but it gradually becomes excited and hypersensitive. The hypersensitive brain is no longer capable of making the correct judgments about the pain-related messages coming from the body. As a result, it overreacts to pain, eventually mistaking contact for pain or suffering from the illusion that an absent pain is actually present. This is how cephalic hypersensitivity syndrome develops from central sensitization. Antidepressants and antiepileptics act to dampen this type of cephalic hypersensitivity syndrome. The "gate" concept shown in the illustration is not the same as the gate control theory (see note) proposed by Ronald Melzack *et al*. in 1965.

(Note) Gate control theory: The theory that there is a balance gate between excitatory input and inhibitory input in the cells that propagate nociceptive messages to the center, which governs the intensity with which pain is perceived. This is currently being revised in light of the discovery of the existence of descending inhibitory regulation from the higher brain centers[25].



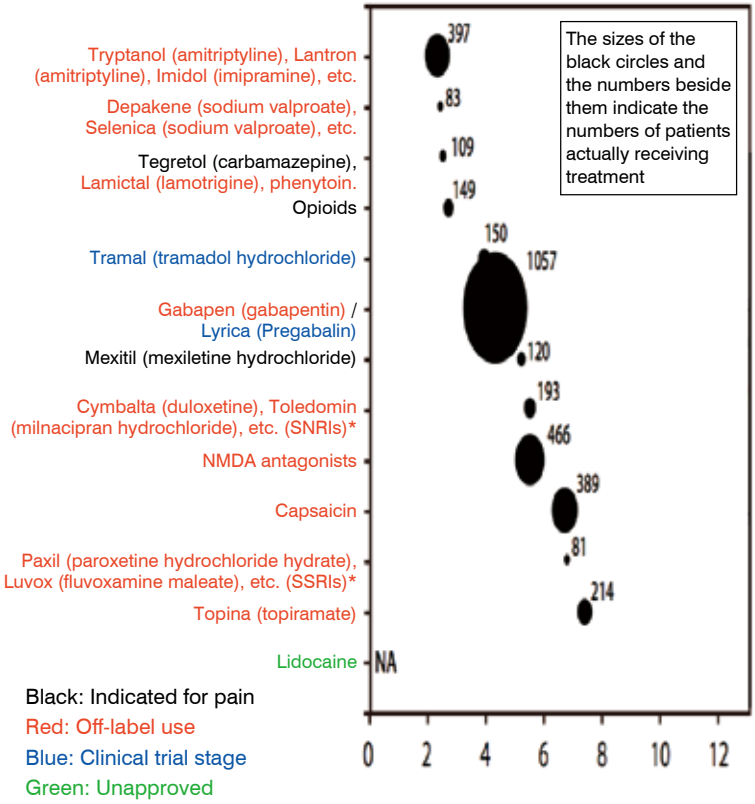
The gate controlling the amount of pain

Finnerup's proposed concept: Drugs should be safer and better priced

The recommendations issued by the Ministry of Health, Labour and Welfare's study group on chronic pain quoted a 2005 paper by Nanna Finnerup that had been published in *Pain*, a globally respected medical journal [12]. That paper made no mention of the anti-inflammatory analgesics such as Loxonin (loxoprofen sodium hydrate) that are generally used in Japan to treat chronic pain. The majority of the analgesics described there are the same ones used to treat cephalic hypersensitivity syndrome. The illustration shows the Japanese brand names of the drugs concerned. Tryptanol (amitriptyline), Depakene (sodium valproate), Tegretol (carbamazepine), and Lamictal (lamotrigine) are all medications with a low number needed to treat (NNT; see note) and an analgesic action equivalent to that of morphine and other opioids. The middle class includes Gabapen (gabapentin) and Toledomin (milnacipran hydrochloride). These are the actual medications I use to treat cephalic hypersensitivity syndrome. As an aside, from the specialist viewpoint, the black circle representing Lyrica (pregabalin) stands out for its size. At that point, Lyrica (pregabalin) was still only in the clinical trial stage, but it was approved as an analgesic by the Ministry of Health, Labour and Welfare soon after. Its high price belies the fact that its therapeutic efficacy is not particularly outstanding compared with Tryptanol (amitriptyline), Depakene (sodium valproate), and Tegretol (carbamazepine). This is revealing about the close connections between the Ministry of Health, Labour and Welfare and pharmaceutical manufacturers.

(Note) NNT is an index used in drug development.
It indicates how many patients must be treated in order to achieve the desired effect in a single individual.

Drugs for treating chronic pain



Adapted from part of Figure 1 in N.B Finnerup et al. Algorithm for neuropathic pain treatment: An evidence-based proposal. Pain 118(3), pp. 289–305, 2005.

* SNRIs: Serotonin-noradrenaline reuptake inhibitors
SSRIs: Selective serotonin reuptake inhibitors

References

Standards of NeuroTherapeutics: Chronic pain (ed Japanese Society of Neurological Therapeutics)

The drugs used for the medical treatment of chronic pain are the tricyclic antidepressants Noritren (nortriptyline) and Tryptanol (amitriptyline), the SNRIs Cymbalta (duloxetine) and Toledomine (milnacipran hydrochloride), the calcium channel blockers Gabapen (gabapentin) and Lyrica (Pregabalin), and the antiepileptics Tegretol (carbamazepine), Depakene/Selenica (sodium valproate), Lamictal (lamotrigine), Topina (topiramate), and Excegran (zonisamide) [9].

Choice of adjuvant analgesics at the National Cancer Center Hospital

• Step 1
Rivotril (clonazepam) (off-label use)
• Step 2
Amoxan (amoxipine) (off-label use)
or Noritren (nortriptyline) (off-label use)
• Step 3
Mexitil (mexiletine) (off-label use)
or xylocaine (lidocaine) (off-label use)
• Step 4
Ketalar (ketamine) (off-label use)

Kingdom of effective drugs

The key drugs that I prescribe to treat cephalic hypersensitivity syndrome are tricyclic antidepressants, antiepileptics, and some antipsychotics. Combined, they can be compared to a royal family with six family members, as I shall describe below.

Many patients with chronic illness syndrome or chronic pain improve when treated with a carefully thought-out combination of low doses of antiepileptics and antidepressants. My first-choice drugs for the treatment of cephalic hypersensitivity syndrome include Tryptanol (amitriptyline) / Noritren (nortriptyline), Depakene/ Selenica (sodium valproate), Tegretol (carbamazepine), Lamictal (lamotrigine), Rivotril (clonazepam), and Topina (topiramate).

For more than a decade, I have also used the antipsychotic Risperdal (risperidone), and have also recently started to prescribe Abilify (aripiprazole) on occasion. Abilify (aripiprazole) is the drug that has propelled the Shikoku-based pharmaceutical manufacturer Otsuka onto the global stage, but Risperdal (risperidone) has a more stable action.

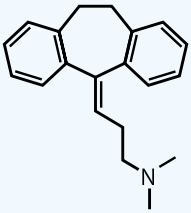
The kings: Tryptanol (amitriptyline) / Noritren (nortriptyline)

Among the drugs I use for treating cephalic hypersensitivity syndrome, the kings are the tricyclic antidepressants Tryptanol (amitriptyline), Noritren (nortriptyline), and Tofranil (imipramine).

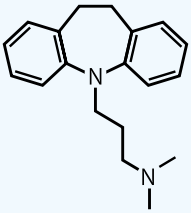
Many years ago, I noticed that the structure of tricyclic antidepressants was very similar to that of Tegretol (carbamazepine), and I realized that there must be some sort of special relationship between them. I later found out that Tofranil (imipramine) and Tegretol (carbamazepine) were developed by the same scientist. Tegretol (carbamazepine) was developed in 1960 by Walter Schindler and his colleagues and Geigy, the same researcher who also developed Tofranil (imipramine). I also found it strange that although Tofranil (imipramine), Tryptanol (amitriptyline), and Noritren (nortriptyline) have almost identical pharmacological actions, the action of Tryptanol (amitriptyline) stands out as being quite different. This became understandable when I heard that in the race

Tricyclic antidepressants

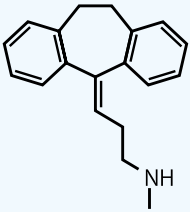
Inhibit the reuptake of noradrenaline and serotonin



Tryptanol
Amitriptyline
Merck (USA)
1959



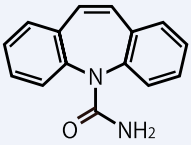
Tofranil
Imipramine
Geigy (Switzerland)
1957



Noritren
Nortriptyline
Lundbeck (Denmark)
1961

Antiepileptic

Blocks Na^+ channels in cerebral and peripheral neurons



Tegretol
Carbamazepine
Geigy (Switzerland)
1960

to develop this class of drugs, it was the US pharmaceutical manufacturer Merck that developed Tryptanol (amitriptyline) and put the greatest effort into being the first to bring a tricyclic antidepressant to market. Even today, the mechanisms of action of these drugs remain poorly understood, but it is my conjecture that by the time Schindler had developed Tofranil (imipramine), he had already had the idea for Tegretol (carbamazepine). This is a simple idea, that drugs with a similar structure can be expected to have a similar effect. Tryptanol (amitriptyline), Noritren (nortriptyline), Tofranil (imipramine), and Tegretol (carbamazepine) have similar structures and mechanisms of action, but Tegretol (carbamazepine) cannot be ranked among the kings because of its side effects.

The Queen: Depakene (sodium valproate)

Depakene (sodium valproate) is the drug that is used most often to treat cephalic hypersensitivity syndrome. It was originally used as a solvent for research. In the late 19th century, it was widely used as a solvent to dissolve lipophilic reagents. In the 20th century, the antiepileptic properties of valproic acid were discovered when it was used as a solvent to dissolve substances contained in medicinal plants in studies of their antipsychotic properties, and 80 years later, in 1967, it was first approved in France as an antiepileptic drug.

It was also the focus of attention in Japan from an early stage. Initially, it was Kyowa Hakko that was active in developing valproic acid, and the company began marketing Depakene (sodium valproate) tablets in 1975. Pharmaceutical manufacturers had not expected that it would sell as a medication to treat childhood epilepsy. However, it was well received in clinical settings, and its use increased dramatically. However, the widespread use of mood stabilizers by psychiatrists also started at around this time, and reports of the side effects of sodium valproate in damaging mitochondria also began to appear. This mechanism still remains unclear.

Subsequently, Valerin (sodium valproate) was developed by Dainippon Sumitomo Pharma and became widely used as it resolved the hygroscopic nature of Depakene (sodium valproate), one of the latter's disadvantages. Depakene (sodium valproate) slow-release tablets were later developed to improve both its hygroscopic nature and its short half-life (8–15 hours). These Depakene-R (sodium valproate) tablets, with the "R" in the name standing for "Retard," are those that I currently use. The Depakene-R (sodium valproate) tablets sold by Kyowa Hakko are excellent, achieving results that are even better than those advertised, and I therefore use them frequently. However, some patients complained that the medication that I had prescribed was visible in their stools and were worried that it might not be working. I consulted the manufacturers, who told me that the active ingredient in Depakene, sodium valproate, was embedded in a sponge-like matrix structure in capsules covered with an ethylcellulose membrane, and that it was almost all released within 10 hours; it was only the capsules with the matrix

structure that were insoluble and were therefore not digested or absorbed, but rather were excreted in the feces. I was satisfied with this explanation and am still prescribing Depakene-R (sodium valproate) today.

Depakene-R (sodium valproate) is now an easy-to-use medication for which the previous problems of hygroscopic nature, solubility in water, and gastrointestinal disturbance have now been solved. As a result, the slow-release tablets, which are almost completely absorbed and are medicinally effective, are now the only version available. Depakene (sodium valproate) also has the advantages that because it was originally a solvent, it is extremely cheap, so much so that it was even used as a soap and does not harm the human body. Gentle and effective, it is the queen of drugs.

A further advantage is evident when Depakene (sodium valproate) is used in combination with Lamictal (lamotrigine). Depakene (sodium valproate) undergoes glucuronidation in the liver and is excreted in urine. As Lamictal (lamotrigine) is also metabolized via the same pathway, the glucuronic acid that would metabolize it is already being used by Depakene (sodium valproate), and as a result its metabolism and excretion are delayed and its effectiveness is multiplied. This means that a lower dose of Lamictal (lamotrigine) can be used to obtain the same effect when it is administered in combination with Depakene (sodium valproate). Yet another advantage is that Depakene (sodium valproate) is reliable in preventing migraine, which is common among patients with cephalic hypersensitivity syndrome, and is frequently used as a medication for this purpose. Depakene (sodium valproate), which is so much cheaper than the very expensive triptan preparations used to treat migraine once it develops, is an unsung hero that reduces the amount used of the latter.

The Crown Prince: Rivotril (clonazepam)

In 1969, Gastaut reported the efficacy and safety of Rivotril (clonazepam) for the treatment of epilepsy. This provided the impetus for its development as an antiepileptic in Japan, and Rivotril (clonazepam) was approved in 1980, whereas Landsen (clonazepam), another clonazepam formulation, was approved in 1981. The story behind the name "Landsen" is interesting: it was intended to mind the *randoseru* satchels (their name in turn derived from the Dutch *ransel*) used by elementary school students, in order to possibly market it for pediatric epilepsy. The use of Rivotril (clonazepam) as an epilepsy medication declined during this period, but it started to be used to treat depression, anxiety disorder, abnormal skin sensations, pain, tinnitus, and REM sleep behavior disorder. It is particularly effective against anxiety disorder, beating Paxil (paroxetine hydrochloride hydrate) and other SSRIs, and its effect as a mood stabilizer that flattens out the rollercoaster of emotions has now become well known. I long ago bade farewell to my old comrades Cercine (diazepam) and Benzalin (nitrazepam) in order to prescribe Rivotril (clonazepam). The reasons that Rivotril (clonazepam) is so popular include its broad therapeutic range, good balance, and easily discernible effect. Structurally, it very closely resembles the basic structure of nitrazepam, such as Cercine (diazepam) and Benzalin (nitrazepam), with only the addition of a halogen base to this basic structure. One of the fascinating things about pharmacology and drug discovery is that such a small change makes such a great difference in the medicinal effect.

If we try and disentangle the question of why Rivotril (clonazepam) is effective against cephalic hypersensitivity syndrome in pharmacological terms, we find references stating that it suppresses seizure discharges of the brainwaves due to stimulation of the hypothalamus from the amygdala. This GABA receptor-mediated action is well balanced in terms of antianxiety, sleep, and emotional regulation, and naturally resulted in its replacing Cercine (diazepam), which had been known as an "all-purpose medication." Despite the fact that it was approved as an antiepileptic, Rivotril (clonazepam) has thus now become accepted as a prize pupil among anti-anxiety drugs. Its nature as an antiepileptic means that it can be prescribed for 90 days at a stretch, making it a great value as it can be

prescribed long-term at low cost. This makes it especially useful for patients with symptoms that require long-term administration, such as restless legs syndrome and twitching legs.

The Crown Princess: Risperdal (risperidone)

Risperdal (risperidone) is like a lady-in-waiting who supports her husband from the shadows. I used to prescribe Contomin (chlorpromazine), but have not used it since Risperdal (risperidone) became available. Recently, I have also been using Abilify (aripiprazole), a Japanese-manufactured drug in the same series that has proved popular in Japan. Risperdal (risperidone) is a well-balanced drug that is easy to use in small doses. I only prescribe it at a dose of 0.5 mg/day.

Risperdal (risperidone) was successfully synthesized as a novel pharmaceutical with a benzisoxazole skeleton, a different structure from that of conventional antipsychotics, by Janssen Pharmaceutical in Belgium in 1984. It is known as a serotonin-dopamine antagonist because of its pharmacological action.

Risperdal (risperidone) is effective against both the positive and negative symptoms of schizophrenia and works well for patients who complain of intense anxiety, frustration, and confusion. It can be a good idea to prescribe it at a low dose for patients with an intractable chronic illness syndrome. It is highly compatible with other drugs used to treat cephalic hypersensitivity syndrome, and there are few concerns about its interactions. There are no serious contraindications due to its interactions with either Tryptanol (amitriptyline), the king of drugs, or Depakene (sodium valproate), the queen, and in low doses, it agrees very well with its parents-in-law. This is why it can be compared to a "crown princess." Medications that are not compatible with Risperdal (risperidone) because of their actions include Tegretol (carbamazepine) and BI Sifrol (pramipexole hydrochloride).

Column

●Lyrica (pregabalin) is overprescribed

Lyrica (pregabalin) was originally marketed in 2010 as a treatment for post-herpetic neuralgia, one of the best-known forms of intractable pain, because of its action as a "calcium channel $\alpha 2\delta$ ligand". It has recently come to be used to treat cancer pain, an important form of neuropathic pain. Interestingly, Lyrica (pregabalin) is also increasingly being prescribed to treat back pain, stiff shoulders, and other types of chronic pain. No doubt the doctors who prescribe it have their own reasons for doing so, but there are many other much cheaper drugs than Lyrica (pregabalin) that are internationally recognized treatments for neuropathic pain, including the tricyclic antidepressants Tryptanol (amitriptyline) and Noritren (nortriptyline) and the antiepileptics Depakene/Selenica (sodium valproate). I believe it is more appropriate for patients first to try these drugs, which are inexpensive and have almost the same effect, and then to prescribe Lyrica (pregabalin) as the second choice (see page 110).

The courtiers in supportive roles

There are six courtiers that look after the royal family of drugs used to treat cephalic hypersensitivity syndrome: Tegretol (carbamazepine), Lamictal (lamotrigine), Topina (topiramate), E Keppra (levetiracetam), Mystan (clobazam), and Gabapen (gabapentin). These medications have slightly different mechanisms of action and have their own specific roles and areas to defend. If the drugs in the royal family are insufficiently effective, they can be used as well in different combinations, depending on the patient's condition.

Tegretol (carbamazepine): Inexpensive but somewhat difficult to use

Tegretol (carbamazepine) was first marketed in 1962 as an analgesic for trigeminal neuralgia, and was first sold as an antiepileptic drug in the United States in 1974. I have made good use of this medication for almost 30 years. As I mentioned earlier, Tegretol (carbamazepine) is a drug that was synthesized by Walter Schindler after he had developed the tricyclic antidepressant Tofranil (imipramine). Structurally, it closely resembles tricyclic antidepressants, and thus, the mood-stabilizing properties of Tegretol (carbamazepine) have also been the subject of attention. This mood-stabilizing action resembles those of Depakene (sodium valproate) and Lamictal (lamotrigine), but as Tegretol (carbamazepine) is more effective in suppressing neurogenic pain, there were high hopes that it might also suppress emotional and impulsive excitability. Despite its nature as an extremely useful and convenient drug, it produces problematic side effects including skin symptoms, leukopenia due to bone marrow suppression, and anemia.

I once prescribed Tegretol (carbamazepine) to a man who was complaining of intense pain from shingles. Unhappily, he developed the serious side effect of mucocutaneous syndrome (Stevens-Johnson syndrome). This did not respond to medication, and the outcome was fatal. I and the head nurse used to visit his grave together every year, but no matter what excuses might be made, the responsibility for his death lay squarely with the doctor who prescribed the drug. A study of the risk of drug eruption due to Tegretol (carbamazepine) found that individuals of

Han Chinese ethnicity who carry the HLA-B1502 gene have a risk of developing drug eruption due to Tegretol (carbamazepine) that is 2500 times higher than usual. At that time, no detailed risk data were available for Japanese individuals, but it has recently been shown that the great majority of patients who develop serious drug eruptions carry the HLA-A3101 gene. This gene is present in 10% of the Japanese population, and the risks posed by Tegretol (carbamazepine) are correspondingly high. Since my patient's death, I have prescribed Tegretol (carbamazepine) far less often. Zebinix (eslicarbazepine acetate), which has fewer side effects than Tegretol (carbamazepine), is now available overseas, but has yet to be approved for use in Japan.

If the choice is made to use Tegretol (carbamazepine), the best method of prescription is to gradually increase the dose over one or two months, watching out for skin eruptions. A high rate of skin eruptions is seen in one in ten patients treated with Tegretol (carbamazepine), Lamictal (lamotrigine), and Topina (topiramate), the latter two of which I shall discuss below. In most cases, the eruption appears within two months. Only in rare cases does it progress to mucocutaneous syndrome.

Lamictal (lamotrigine): Somewhat difficult to use

Lamictal (lamotrigine) is an alternative antiepileptic to Tegretol (carbamazepine). Although its mechanism of action is similar to that of Tegretol (carbamazepine), it also has some differences. It was first synthesized in the United Kingdom in the 1960s as an antiepileptic with a triazine skeleton and the properties of a folate agonist. As Lamictal (lamotrigine) was developed to treat childhood epilepsy, it is sold in the form of chewable, dispersible tablets that can be chewed or dissolved in water. Since its approval in Ireland in 1990 as an adjunct treatment for adult epilepsy, it has come to be used worldwide. Similar to other antiepileptic drugs, in Japan, it was approved in 2011 as a mood stabilizer (for tranquilizing and sedation, neurological gastroenteritis, sleep disorder, autonomic dysregulation, and similar uses). Since then, its action in improving depression has become the focus of attention. Its statement of efficacy includes many good things, but these efficacies greatly depend on the individual who takes it, and it is not a universal panacea. The difficulty lies in its side effects, as one in ten patients develop skin eruptions, and 0.4% go on to develop mucocutaneous syndrome (Stevens-Johnson syndrome), almost the same rate as for Tegretol

(carbamazepine) and a frighteningly high figure. Doctors must be deliberate about prescribing it. Lamictal (lamotrigine) should also be started on a low dose, which can be slowly increased over one to two months, enabling skin eruptions to be detected early. It is then possible to prevent mucocutaneous syndrome by discontinuing the prescription. To treat cephalic hypersensitivity syndrome, I use 5-mg tablets for children and 25-mg tablets for adults. In many cases, I also give patients Depakene (sodium valproate). The additional use of Depakene (sodium valproate) doubles the blood concentration of Lamictal (lamotrigine), meaning that it is effective at a low dose.

As an aside, Lamictal (lamotrigine) also elevates the function of GABA, which means that it acts to improve memory. GABA function may be difficult for most people to understand, but it is found in brown rice, particularly germinated brown rice, and is known to enhance and augment long-term memory. As a "Food for Specified Health Uses," it is sold in the form of various supplements. Lamictal (lamotrigine) improves GABA function through its action as an NMDA (see note) receptor antagonist in the same way as Memary (memantine), another NMDA receptor antagonist marketed since 2011 by Daiichi Sankyo for the treatment of Alzheimer's disease. Although not in the near future, it may be possible to use Lamictal (lamotrigine) as an Alzheimer's disease treatment.

(Note) NMDA: ***N***-methyl-D-aspartate

Topina (topiramate): Difficult to use

Topina (topiramate) is an antiepileptic with a sulfamate structure on a fructopyranose skeleton that was discovered in 1979 in the United States. It is attracting attention as an antiepileptic for its powerful Na^+-channel and Ca^{2+}-channel blocking properties as well as its elevation of GABA function. After its approval in the United Kingdom in 1995, it was approved by the United States FDA in 2006 and in Japan in 2007 as an antiepileptic. It has similar compatibility problems as those of Lamictal (lamotrigine), working in some patients but not in others, and is well tolerated in some but poorly tolerated in others. It is unpredictable, but in some people, it is extremely effective. It also has similar side effects as those of Lamictal (lamotrigine). Long-term administration may result in serious side effects, with kidney or urinary stones developing in 2.3%

of patients and hypohidrosis and associated fever in 0.3%. It also shares the side effects of other antiepileptics, with incidences of liver dysfunction, potassium and sodium electrolyte imbalance, and weight loss of more than 10%. I know of no antiepileptic drug other than Topina (topiramate) that causes side effects in over 10% of patients. It is only natural that doctors hesitate to prescribe it. However, globally, its share of the epilepsy drug market is second only to that of E Keppra (levetiracetam). A close investigation reveals that it is being used for dieting. Used inexpertly for this purpose, its side effects may have extremely costly consequences. Although obvious, it bears repeating that dieting should be attempted by means of lifestyle adjustments such as diet and exercise.

Although Topina (topiramate) is not approved for the treatment of migraine in Japan, I have treated a woman in her 60s who improved dramatically through its use. The patient was a pharmacist with in-depth knowledge of migraine medication, and had already attended several different headache clinics over the years. She had tried all the latest migraine medications at that point, including Triptans (serotonin, 5-HT1B/1D agonists), Depakene (sodium valproate), Gabapen (gabapentin), and Inderal (propranolol). However, for some reason, she had never tried taking Topina (topiramate). I explained to her that Topina (topiramate) is an extremely particular medication, one that works dramatically well in some people but only produces side effects in others. After she started taking it, she came back to report joyfully that it had liberated her from the headache from which she had suffered for many years.

E Keppra (levetiracetam): Easy to use

Although I have had little experience with using this drug to treat migraine, participation in a clinical trial gave me the impression that this is an excellent medication that acts rapidly against epileptic attacks with few side effects.

E Keppra (levetiracetam) is an unusual type of drug with a mechanism of action that differs from those of conventional antiepileptics in that it binds specifically to synapse vesicle protein 2A in the brain. It was discovered in Belgium in the 1980s. Since its approval in the United States in 1999 to treat adult epilepsy, it has come to be used worldwide. In Japan, it is a relative newcomer, having been approved in 2010. One of its features is that because it does not bind to GABA

receptors, benzodiazepine receptors, glutamate receptors, or ion channels, it is easy to use in combination therapy or as an additional prescription. On the other hand, it has a high incidence of side effects, with 53% of patients developing nasopharyngitis and 35% feeling drowsy. As it is a relatively new drug, little post-marketing surveillance data have yet been gathered, and the incidence of serious side effects is still unknown, but it currently has the most sales worldwide of any antiepileptic. This may be due to both its rapid action and the fact that its action and effect are reliably maintained. However, with respect to side effects, my own clinical trial and experience of its use have not necessarily given me the impression that they are far more common than with other antiepileptics. The name "E Keppra" means the sun god of epilepsy. I have seen patients with intractable migraine who have responded dramatically to half a 250-mg tablet of E Keppra (levetiracetam).

Mystan (clobazam): Easy to use

Mystan (clobazam) is a benzodiazepine antiepileptic that binds selectively to benzodiazepine receptors and is believed to enhance the action of GABA neurons. Clobazam, its main constituent, was first synthesized in Italy in 1966. It was originally approved in Germany and France as an anti-anxiety drug in 1975, but in 1978 it was shown to be effective against intractable epilepsy and was also marketed as an antiepileptic beginning in 1984. Since then, it has come to be used worldwide as an antiepileptic, and was approved in Japan in 2000. Today, it is prescribed as adjuvant medication when the first-choice antiepileptic is not sufficiently effective. Its most common side effects are drowsiness, unsteadiness, and dizziness / vertigo, and these sleep-inducing effects can be useful when I prescribe it as part of my night therapy. Although it does not have any common serious side effects, it has the disadvantage that patients develop tolerance after around six months, and its effectiveness diminishes, as well as not being very compatible with Depakene (sodium valproate), the queen. The name "Mystan" is derived from the German *meist* ("most"), referring to the fact that it is effective against the majority of epileptic attacks. I often add Mystan (clobazam) 5 mg to add something else to night therapy.

Gabapen (gabapentin): Innocuous

Gabapen (gabapentin) is an antiepileptic that was first synthesized in Germany

in 1973. It was approved as adjuvant medication for adult epilepsy in the United Kingdom and United States in 1993, and has subsequently come to be widely used worldwide, with childhood epilepsy also having been approved as an additional indication. In Japan, it was approved in 2006 as adjuvant medication for epilepsy patients who do not respond sufficiently to other antiepileptic drugs, and its indications were expanded to include childhood epilepsy in 2011.

It possesses no activity with respect to GABA or benzodiazepine receptors, and does not bind to voltage-dependent Na^+ channels. Although its mechanism of activity has yet to be definitively identified, it is believed to involve the blocking of voltage-dependent Ca^{2+} channels, increased GABA within the brain, and GABA transporter activation. As it causes few interactions with other antiepileptics, it is used as adjuvant medication. Its main side effects are drowsiness and dizziness / vertigo, and it is thus a drug suited to my night therapy. Recently, it has also started to be used off-label for restless legs syndrome and the alleviation of chronic pain. No common serious side effects have been reported, but it should be used with caution in patients with diminished renal function and older people. It is an appealing drug with a broad area of defense, and one that is easy to use.

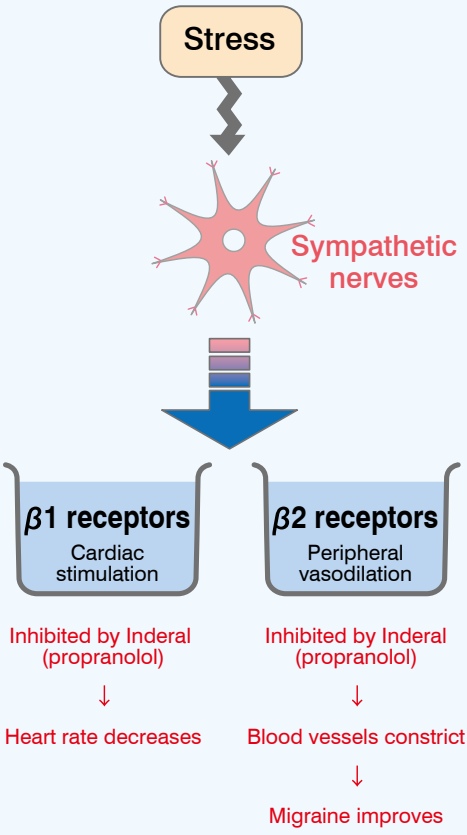
Cercine (diazepam): Pleasant awakening

The coded prescriptions that I formerly used consisted of Tegretol (carbamazepine), Tryptanol (amitriptyline), and Cercine (diazepam). In the intervening years, I have switched from Tegretol (carbamazepine) to Depakene (sodium valproate), from Tryptanol (amitriptyline) to Noritren (nortriptyline), and from Cercine (diazepam) to Rivotril (clonazepam), but Cercine (diazepam) is an enduring favorite that I still sometimes use now and again. Launched on the market in 1965, Cercine (diazepam) is classified as a benzodiazepine anti-anxiety drug. It has a long half-life (the time during which it is active) of over 20 hours, meaning that both drug resistance and drug dependence are low. Any drowsiness it causes as a side effect is only mild, giving it the advantage that it can be taken during the day. The newer drugs Wypax (lorazepam) and Depas (etizolam) have shorter half-lives compared with that of Cercine (diazepam) and cause more intense drowsiness as a side effect. Those patients who use Depas (etizolam) as sleep-inducing medication are actually utilizing this side effect.

Despite its long half-life, Cercine (diazepam) does not continue to act for an entire day. In general, it works for around half a day. The reason for my continued affection for Cercine (diazepam) is that it offers the present of a particularly pleasant awakening, and is an easily used antidote to stress.

Inderal (propranolol): Effective reasons

Inderal (propranolol) was approved as a treatment for migraine in 2013. Unlike antidepressants and antiepileptics, it is a β-blocker that inhibits the excitation of the sympathetic nerves. There are around 20 different varieties of β-blockers currently on the market, which are classified according to the type of β receptor and their mode of action. Among these, Inderal (propranolol hydrochloride), which blocks the β1 and β2 receptors, is particularly effective for the treatment of cephalic hypersensitivity syndrome. Inderal (propranolol) is fat soluble and can migrate to the central nervous system, meaning that there is a high risk of it causing symptoms such as nightmares, depression, and impotence. Although it is short-acting, long-term prescription is inadvisable. The αβ-blocker Arotinolol Hydrochloride (arotinolol hydrochloride), a treatment for essential tremor, is water soluble and does not migrate to the central nervous system. The characteristics of β-blockers vary in terms of the time of onset of action and the duration for which this action is sustained, but Inderal (propranolol) is short-acting and easy to use as needed. The mechanism of action of β-blockers is profound, and they are effective treatments for cephalic hypersensitivity syndrome when the homeostatic balance of the sympathetic nervous system breaks down.


Stress
Sympathetic nerves
β1 receptors
Cardiac stimulation
β2 receptors
Peripheral vasodilation
Inhibited by Inderal (propranolol)
↓
Heart rate decreases
Inhibited by Inderal (propranolol)
↓
Blood vessels constrict
↓
Migraine improves

Column

Ergotamine deserves a rethink in view of its low cost

One drug, ergotamine, is difficult to use but still deserves a rethink in view of its low cost. Ergotamine has a similar chemical structure to those of important neurotransmitters such as serotonin and dopamine and displays a wide range of neurological actions. As a result, its use has entailed problems due to its powerful vasoconstrictive action as well as drug dependency. Interaction with anhydrous caffeine has been shown to enhance its effect, and for a time, it was mainly prescribed in compounded form. However, recently, dihydroergotamine mesylate, formed by altering the chemical structure of ergotamine by dehydration and methylation, has become more popular. Ergotamine formulations have been replaced by triptans, a family of generic new drugs, but these cost fifty to sixty times as much as ergotamine. Some headache specialists claim that their efficacy is worth the increased price, but in practice, some patients at my clinics tell me that however good the medication may be, they are unable to pay for it. Ergotamine formulations are a helpful alternative for such patients. Although they cannot replace triptans, when used wisely for patients with the type of migraine that occurs during sleep, they can reduce pain on waking, rendering assistance with triptan unnecessary. Given the inconvenience of the fact that a triptan cannot be also taken on the same day if ergotamine does not work, and the difficulties of dosage and timing of taking the drug, it is unsurprising that many doctors hesitate to prescribe it.

The diagnostic criteria for ergotamine-overuse headache in the 2nd Edition of the International Headache Classification comprise regular use of the maximum dose for ten days in a month over at least three months. Cleamine S (ergotamine tartrate) is a combination tablet containing caffeine, and I therefore avoid prescribing it to be taken before going to sleep, but very few patients have complained to me

about side effects. Its low cost is its greatest attraction, so with their agreement and understanding, I prescribe it for patients suffering from migraine during sleep who are unable to take triptans because of their high cost.

Comparison of headache drug prices

Ergotamines

Brand name	Generic name	Drug price (yen)	Generic
Dihydergot tablets 1 mg	Dihydroergotamine mesylate	15	6
Cleamine S 0.5 mg	Ergotamine tartrate / anhydrous caffeine combination tablets	8	

Triptans

Brand name	Generic name	Drug price (yen)	Generic
Imigran tablets 50	Sumatriptan succinate	816	406
Imigran nasal spray 20	Sumatriptan	1,073	–
Imigran kit subcutaneous injection 3 mg	Sumatriptan succinate	3,525	–
Zomig tablets 2.5 mg	Zolmitriptan	961	–
Zomig RM tablets 2.5 mg			
Relpax tablets 20 mg	Eletriptan hydrobromide	926	–
Maxalt tablets 10 mg	Rizatriptan benzoate	946	–
Maxalt RPD tablets 10 mg			–
Amerge tablets 2.5 mg	Naratriptan hydrochloride	919	–

Other analgesics

Brand name	Generic name	Drug price (yen)	Generic
Tryptanol tablets 10 mg Noritren tablets 10 mg	Amitriptyline hydrochloride Nortriptyline hydrochloride	10 6	–
Tegretol tablets 100 mg Depakene tablets 100 mg	Carbamazepine Valproate	8 10	6 9
Neurotropin tablets 4 units	An extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus	32	–
Loxonin tablets 60 mg	Loxoprofen sodium hydrate	18	8
Celecox tablets 100 mg	Celecoxib	69	–
Lyrica capsules 25 mg	Pregabalin	77	–

Source/reference: http://www.e-pharma.jp/

My coded prescriptions

The coded prescriptions I issue in my everyday treatment of cephalic hypersensitivity syndrome are in principle made up as powders. Tryptanol (amitriptyline) is ground into powder. Because some drugs such as Depakene (sodium valproate) are hygroscopic (absorb water), I limit their prescription to four weeks at a time. One aspect of patients with cephalic hypersensitivity syndrome is that they have experienced the overuse of medication. Despite the fact that they are taking multiple drugs, they tend to overreact to the prescription of antiepileptics in particular. If necessary, I may conceal the content of a prescription from a patient, although I will explain it to their family members. The advantage of powdered medication is that the patient is unable to change the type of medication they take without asking, although they can be asked to adjust the dose themselves.

Try A: Depakene (sodium valproate) 200 mg, Noritren (nortriptyline) 10 mg

Try B: Depakene (sodium valproate) 100 mg, Noritren (nortriptyline) 5 mg

Try Aa: Depakene (sodium valproate) 200 mg, Noritren (nortriptyline)10 mg, Cercine (diazepam) 5 mg or Rivotril (clonazepam) 0.5 mg

Try Bb: Depakene (sodiumvalproate) 100 mg, Noritren (nortriptyline) 5 mg, Cercine (diazepam) 2.5 mg or Rivotril (clonazepam) 0.25 mg

Try SS: Depakene (sodiumvalproate) 200 mg, Noritren (nortriptyline)10 mg, Rivotril (clonazepam) 0.5 mg, BI Sifrol (pramipexole hydrochloride) 0.125 mg

Try S: Depakene (sodium valproate) 100 mg, Noritren (nortriptyline) 5 mg, Rivotril (clonazepam) 0.25 mg, BI Sifrol (pramipexole hydrochloride) 0.125 mg

I also issue prescriptions coded Try Aa^{+}, Try Bb^{+}, Try A^{+}, and Try B^{+}. The plus sign refers to additional medication. The additional drugs I mainly use include Inderal (propranolol) 5–10 mg (for short-term use), Cercine (diazepam) 2–5 mg, Mystan (clobazam) 5–10 mg, Topina (topiramate) 12.5–50 mg, Lamictal (lamotrigine) 5–100 mg, Tegretol (carbamazepine) 100–200 mg, risperidone 0.25–1 mg, and Gabapen (gabapentin) 200–300 mg.

The next illustration shows the explanatory leaflet that I give to patients.

Medication for cephalic hypersensitivity syndrome

Kosuke Oota

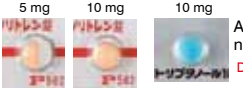
Headache, dizziness / vertigo, stiff shoulders, numbness in the limbs, restless legs, insomnia, chronic pain, dysmenorrhea, backache unrelated to problems in the lumbar spine, chronic fatigue of unknown origin, etc.

Although this medication is also used for epilepsy, the dose I prescribe is so low that all it does is relieve pain.

First-choice treatment medication

Noritren (nortriptyline), Tryptanol (amitriptyline)

5 mg 10 mg 10 mg

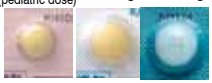


Act to dampen nerves causing pain

Dose: 5–20 mg/day

Depakene / Selenica (sodium valproate)

100 mg (pediatric dose) 200 mg R200 mg

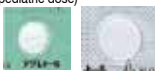


Act to dampen nerves causing pain

Dose: 100–800 mg/day

Tegretol (carbamazepine) Lamictal (lamotrigine)

100 mg (pediatric dose) 200 mg



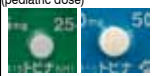
Dose: 50–200 mg/day

5 mg 25 mg

Dose: 5–100 mg/day
(in combination with valproate)
25–200 mg/day
(not in combination with valproate)

Topina (topiramate)

25 mg (pediatric dose) 50 mg

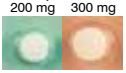


Act to dampen nerves causing pain

Dose: 12.5–100 mg/day

Gabapen (gabapentin)

200 mg 300 mg



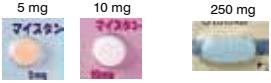
Dose: 200–300 mg/day

Regnite (gabapentin enacarbil)

300 mg

Mystan (clobazam) E Keppra tablets (levetiracetam)

5 mg 10 mg 250 mg

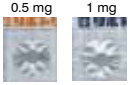


Act to dampen nerves causing pain

Dose: 5–20 mg/day Dose: 125–500 mg/day

Rivotril / Landsen (clonazepam)

0.5 mg 1 mg

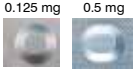


Acts to dampen nerves causing pain

Dose: 0.25–1 mg/day

BI Sifrol (pramipexole)

0.125 mg 0.5 mg



Enhances the action of dopamine, improves symptoms

Dose: 0.125–0.5 mg/day

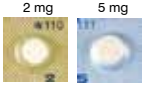
Inderal (propranolol)

10 mg

β-blocker. First-choice medication for migraine with high blood pressure. To be taken with caution by patients with heart failure or asthma symptoms. Dose: 5–20 mg/day

Cercine (diazepam)

2 mg 5 mg

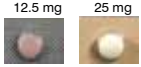


Acts to relieve depressed mood, and also has a muscle-relaxing effect

Dose: 2–10 mg/day

SNRI Toledomin (milnacipran hydrochloride)

12.5 mg 25 mg



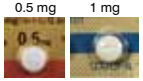
Acts to relieve depressed mood and dampen nerves causing pain

Dose: 12.5–50 mg/day

Second-choice treatment medication

Risperdal (risperidone)

0.5 mg 1 mg



Acts to regulate mental disturbances and calm down feelings

Dose: 0.25–1.5 mg/day

Wintermin (chlorpromazine phenolphthalinate)

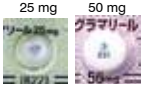
12.5 mg 25 mg

Acts to regulate mental imbalances and disturbances

Dose: 12.5–25 mg/day

Gramalil (tiapride hydrochloride)

25 mg 50 mg



Acts to regulate mental disturbances and calm down feelings

Dose: 25–50 mg/day

Tramal capsules (tramadol hydrochloride)

25 mg

Acts to dampen nerves causing pain. Used in the treatment of many different types of pain, including cancer pain. Must be used with care when combined with other drugs.

Dose: 25 mg/day Prescribed with caution

*Laxatives may also be prescribed.

Magmit (magnesium oxide) 330 mg

Softens stools

Pursennid (sennoside) 12 mg

Makes intestinal movements more active

The three main symptoms of migraine

Headache Stiff shoulders Dizziness

Kosuke Oota

Although this medication is also used for epilepsy, the dose I prescribe is so low that all it does is relieve pain.

Prophylactic medication

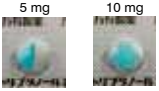
Noritren (nortriptyline)

5 mg 10 mg

Act to dampen nerves causing pain

Tryptanol (amitriptyline)

5 mg 10 mg



Dose: 5–20 mg/day

Depakene/Selenica (sodium valproate)

Act to dampen hypersensitivity causing pain

100 mg (pediatric dose) 200 mg R200 mg R400 mg

Dose: 100–800 mg/day

Rivotril (clonazepam)

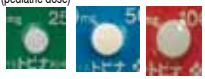
0.5 mg 1 mg 2 mg

Acts to dampen nerves causing pain

Dose: 0.5–2 mg/day

Topina (topiramate)

25 mg (pediatric dose) 50 mg 100 mg



Act to dampen nerves causing pain

Dose: 12.5–100 mg/day

Vasolan (verapamil hydrochloride)

40 mg

Calcium antagonist. Prevents migraine caused by abnormal constriction of blood

Dose: 40–120 mg/day

Migsis (lomerizine hydrochloride)

5 mg

Dose: 10 mg/day

Inderal (propranolol)

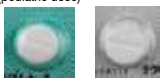
10 mg

β-blocker. First-choice medication for migraine with high blood pressure. To be taken with caution by patients with heart failure or asthma symptoms. Contraindicated with Maxalt tablets (rizatriptan).

Dose: 5–20 mg/day

Tegretol (carbamazepine)

100 mg (pediatric dose) 200 mg



Dose: 50–200 mg/day

Mystan (clobazam)

5 mg 10 mg

Dose: 5–20 mg/day

Lamictal (lamotrigine)

5 mg 25 mg 100 mg

Acts to dampen nerves causing pain

Dose: 5–100 mg/day (in combination with valproate)
25–200 mg/day (not in combination with valproate)

Gabapen (gabapentin)

200 mg 300 mg

Dose: 200–300 mg

*Laxatives may also be prescribed.

Magmit (magnesium oxide) 330 mg

Softens stools

Pursennid (sennoside) 12 mg

Makes intestinal movements more active

Medication to be taken only as needed

Cleamine combination tablets S 0.5 (ergotamine/pyrine/caffeine)

Up to 3 tablets daily

Sumatriptan tablets 50 mg (sumatriptan)

Up to 4 tablets daily

Zomig RM tablets 2.5 mg (zolmitriptan)

Up to 4 tablets daily

Imigran Kit subcutaneous injection 3 mg (sumatriptan)

Up to twice daily

Relpax tablets 20 mg (eletriptan)

Up to 2 tablets daily
*Few side effects

Amerge tablets 2.5 mg (naratriptan)

Up to 2 tablets daily

Maxalt RPD tablets 10 mg (rizatriptan)

Up to 2 tablets daily

Imigran nasal spray 20 mg (sumatriptan)

Up to twice daily

Note: This medication may not be used by individuals to whom any of the following apply:

You must inform the doctor if you are pregnant or breastfeeding, or if you are undergoing treatment for arrhythmia, myocardial infarction, heart failure, cerebrovascular disturbance, peripheral vascular disturbance, or epilepsy. If any of these applies to you, these medications, including Imigran subcutaneous injection and nasal spray, must either be used with caution or not prescribed at all. Their side effects may include chest pain and tightness of the chest within an hour of their use. They also cause drowsiness, so please do not drive after taking them.

7 Prognosis for treatment: Types of prognosis and future issues

For the first 30 years, I offered outpatient clinics under the title "Headache, Dizziness / Vertigo Clinic." My fellow doctors were very suspicious of my reasons for treating headache, dizziness / vertigo together in a single clinic. Now I am finally able to use a single treatment algorithm to treat patients on the basis of the concept of cephalic hypersensitivity syndrome, but in those days, it was difficult for me to explain that it was based on what I knew from clinical experience: I was seeing a surprisingly large number of patients who were experiencing both headache and dizziness / vertigo, and when they were treated for headache, their dizziness / vertigo also improved. In this book, I will discuss the prognosis for treatment based on my experience in the eight years since I changed the name of my clinics to "Cephalic Hypersensitivity Syndrome Clinic."

The prognosis for the treatment of cephalic hypersensitivity syndrome can be broadly divided into two, depending on whether or not it is based on migraine. For patients with migraine who mainly complain of dizziness / vertigo, numbness in the limbs, and allodynia, the prognosis is good, and their symptoms improve almost completely. This is easier to understand if migraine is understood as a marginal condition of epilepsy. My coded prescriptions for cephalic hypersensitivity syndrome that are based around antiepileptic drugs work remarkably well. The earnest personalities of many migraine sufferers also make them cooperative toward treatment and likely to work hard on changing their lifestyle habits, both of which lead to good results. The prognosis is also comparatively good for patients who do not have migraine but who nevertheless suffer from restless legs, twitching legs, and REM sleep disturbance. Not only is medication effective, but patients also often come to see a doctor because family members are concerned about them, making it easier to obtain their cooperation with treatment. However, for those whose symptoms include insomnia, excessive sleepiness, fibromyalgia, chronic fatigue syndrome, and severe menopausal syndrome, the prognosis is not as good. It not only takes longer for symptoms to improve for this type of patient, but the rate of improvement is also poor, and recurrence is more likely. If strong elements of cephalic hypersensitivity syndrome are present, some of their symptoms may improve, but if this is not the case, they are difficult to treat solely by using the cephalic hypersensitivity syndrome treatment algorithm. Unlike

those patients for whom cephalic hypersensitivity syndrome is the underlying condition, difficulties in creating a suitable therapeutic environment, including the patient's own personality, are not uncommon.

What I would like to reemphasize here is that the prognosis for cephalic hypersensitivity syndrome is associated not only with the effectiveness of medication but also with improvements in lifestyle and thinking. This is based on my own impressions gained in the course of my clinical experience. Statistical analysis is required to assess what factors contribute to the prognosis of cephalic hypersensitivity syndrome and its actual degree of improvement. I have therefore started to carry out research focusing on the association between factors that affect the improvement rate, such as the presence or absence of migraine as a basic factor, and prognosis, with the aim of verifying their validity. Going forward, I conjecture that my treatment algorithm for cephalic hypersensitivity syndrome may be effective for some of those patients who suffer from chronic illness syndromes, and I am exploring the construction of a system to help with diagnosis and treatment. I believe that Bayesian estimation may offer an appropriate way of searching for causes from observed phenomena.

Evidence for cephalic hypersensitivity syndrome: Inquiring into the truth of natural science

People who do things "by the book," who never question what they read in textbooks, may be concerned about the evidence supporting my diagnosis and treatment of cephalic hypersensitivity syndrome. I shall go into this in more detail in Chapter 3, but my proposed concept of "cephalic hypersensitivity syndrome" is an umbrella term for various different chronic illness syndromes experienced by patients, and its treatment is based on reliable deductions derived from my experience over many years. Evidence must be founded on scientific principles. One commonly used method of obtaining evidence is to carry out a randomized controlled trial. This enables evidence to be verified statistically. So what is statistical evidence? The format often seen in scientific papers is that in a comparison between A and B, there is a significant difference between them. What happens if the difference is only slight? One statistical method that is frequently used is to increase the survey population. The statistical analysis used in large-scale clinical trials may seem highly reliable at first glance, but the flip

side of this is that if the population is not enormously large, it may not be possible to find a "significant" difference between A and B.

The common element to cephalic hypersensitivity syndrome: low-tone hearing loss

The presence or tendency towards low-tone hearing loss is clinical evidence of cephalic hypersensitivity syndrome. Irrespective of a patient's subjective complaints, audiometry reveals mild hearing loss above 25 dB in the range of 125 Hz to 500 Hz. Generally, hearing loss as a result of old age should be taken into account in the audiometry. In my clinical experience, the presence or tendency towards low-tone hearing loss is apparent among younger patients, i.e., from teenage years to fifties. While general hearing loss is seen in older patients, a tendency for low-tone hearing loss is also evident, compared to the normal audiograms of individuals of the same age. I am currently collecting data to clarify the details of this evidence in my clinic. I am convinced that audiometry will prove to be useful as a clinical biomarker of cephalic hypersensitivity syndrome. (See page 156 for an example audiogram.)

The theories of Yunus and Finnerup

A question raised by both Yunus and Finnerup is whether it is really necessary to spend similarly large amounts of money and time on carrying out clinical trials of the use of drugs that already exist for conditions for which they should theoretically be indicated as it is for the development of new drugs. If they are highly effective and cause almost no side effects, this in itself is perfectly good evidence, whether in one patient or many.

In Part 2, I set out the case histories of 42 patients whom I have treated. These patients surely constitute evidence themselves. Patients do not view recovering from an illness solely in terms of improved laboratory test results for a particular disorder; it is also important to them that issues they have faced in daily life are resolved. I would like those doctors who do things "by the book" to try my treatment for cephalic hypersensitivity syndrome in their own clinical practice rather than rejecting it out of hand as lacking evidence, and then we could have a discussion. I am not someone who rejects evidence-based medicine. However, neither do I trust it blindly. I believe that deciding which evidence to trust in accordance with a hierarchy is the sort of evidence-based medicine that is actually useful to patients.

Column

●Astrophysics theory

Our civilization today originally developed on the basis of inferences and hypotheses reached by observing natural phenomena. I am interested in astrophysics, and scientists such as Galileo, Kepler, Newton, and Einstein put together inferences and hypotheses from a great mass of observational data. In biology, Darwin's law (inference/hypothesis) is famous. Newton derived his law of universal gravitation from Kepler's law. Einstein's theory (inference/hypothesis) of relativity is still not completely understood by the world's mathematicians and physicists, but provided major clues to our understanding of how the universe is put together.

The existence of planets outside the solar system (exoplanets) has long been an open question. Michael Mayor, who made the first definitive discovery of an exoplanet, observed significant fluctuations in the star 51 Pegasi, and inferred that these fluctuations might be caused by a planet orbiting it close at hand. Mayor's conjecture was confirmed by the Kepler space telescope, which had been launched to search for exoplanets. Since then, exoplanets have been discovered on almost a daily basis, with the existence of 1600 so far confirmed. There are over 4000 stars that might have exoplanets. The presence of water and air on some exoplanets has already been inferred, and the day cannot be far off when the existence of extraterrestrial life is no longer conjecture but based on evidence.

Kepler and Galileo from the perspective of cephalic hypersensitivity syndrome

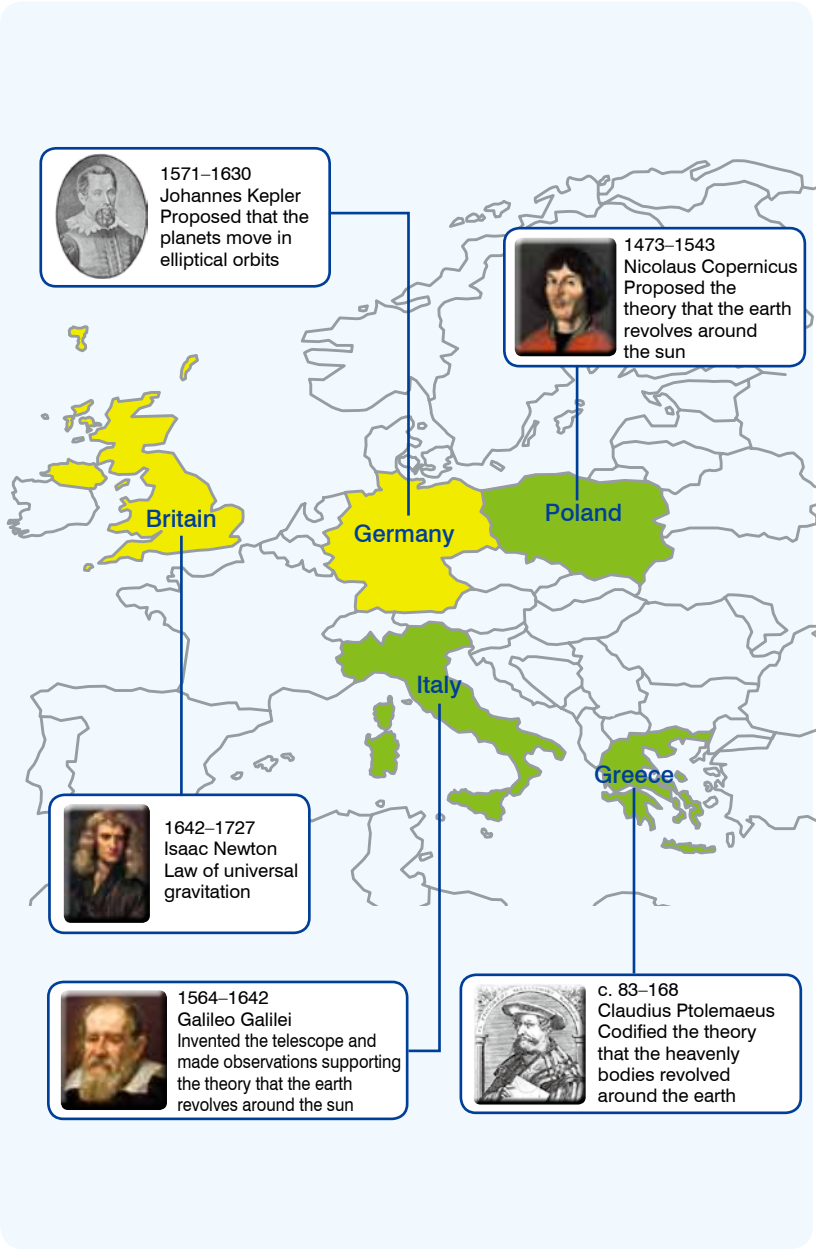
You are probably wondering what on earth the connection could be between Kepler and Galileo and cephalic hypersensitivity syndrome. Start by looking at the illustration. In the 2nd century, Ptolemaeus codified the preexisting cosmology in which the sun and moon revolved around the earth. This cosmology continued to be accepted for the next thousand years until it was overturned by Copernicus. The model he proposed, in which the Earth moved rather than the sun, was supported by Galileo, and in the same era Kepler proposed that the orbits of the planets were not circular, as previously thought, but elliptical. Although Copernicus had proposed that the earth revolved around the sun, because he had assumed circular orbits, he was unable to explain the inconsistencies in the results of his observations. His proposal of a heliocentric universe is known as the "Copernican revolution." I believe that Kepler's conjecture that the orbits were not circular but elliptical, which resolved the inconsistencies in observations, was also a major revolution equal to that of Copernicus. The laws that Kepler discovered led to the family tree of modern science, from Newton's formulation of the law of universal gravitation and eventually to Einstein's theory of relativity, and then to contemporary quantum theory.

When I was reflecting on the idea of cephalic hypersensitivity syndrome, I came across Yunus' paper and knew intuitively that his ideas were the same as mine. As a clinician, I had been making inferences from the patients to whom I had prescribed drugs on the basis of pathology and pharmacology. In other words, clinical observation came first, followed by theory. As more and more observational data are gathered, a common hypothesis gradually became apparent. This hypothesis was further strengthened by the following data, but this was my own personal observation, after which I started searching for a more universal law, a unified theory. When I was reading up on pharmacology, I read Finnerup's paper, and again felt intuitively the commonalities between the two, despite their different specializations and nationalities. However, I do not think that there could have been any communication between Yunus and Finnerup. I can discern the unified theory of cephalic hypersensitivity syndrome running like a common thread through their propositions, but as far as I am aware, neither of them has ever quoted the other's paper. This is

despite the fact that around 400 years ago, Galileo and Kepler were exchanging correspondence with each other across national boundaries.

Over and over again, I want to tell the young doctors who will come after me about the "scientific attitude" towards clinical practice. Observing patients is the primary starting point, not guidelines and pharmaceutical manufacturer's manuals. When you come across phenomena that cannot be accounted for by existing laws or theories, do not regard such patients as "anomalous," as the required attitude is that this may be the opportunity to discover some sort of new truth. My proposed cephalic hypersensitivity syndrome is derived from my repeated experience of this.

Not everyone can be a Newton or an Einstein. Even Newton's accomplishments were based on those of the geniuses Galileo and Kepler who preceded him, and in any era, there will be barriers posed by political, religious, or interpersonal pressure. However, the truth of natural science will always overcome these. I am confident that the concept of cephalic hypersensitivity syndrome can become a unified theory. The rest I will leave to my assistants who will take over from me.


1571–1630
Johannes Kepler
Proposed that the planets move in elliptical orbits
1473–1543
Nicolaus Copernicus
Proposed the theory that the earth revolves around the sun
Britain
Germany
Poland
Italy
Greece
1642–1727
Isaac Newton
Law of universal gravitation
1564–1642
Galileo Galilei
Invented the telescope and made observations supporting the theory that the earth revolves around the sun
c. 83–168
Claudius Ptolemaeus
Codified the theory that the heavenly bodies revolved around the earth

Chapter 1

Quoted Sources

(1) The International Classification of Headache Disorders, 2nd Edition, Revised and Enlarged Japanese Version. Translated by the Japanese Headache Society Committee for the Dissemination of the International Headache Classification. Igaku Shoin, 2007. [Japanese translation]
(2) Headache Classification Committee of the International Headache Society (HIS): The International Classification of Headache Disorders, 3rd edition (beta version).2013. Cephalalgia© International Headache Society.2013. SAGE.
http://www.ihs-classification.org/_downloads/mixed/International-Headache-Classification-IIIICHD-III-2013-Beta.pdf
(3) Japanese translation of the International Classification of Headache Disorders, 3rd edition (beta version) (ICHD-3β) (provisional proposal) [Japanese translation]
http://www.jhsnet.org/information/zu2byoumei_list20140317.pdf
(4) Yunus MB. Central sensitivity syndromes: a new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. Semin Arthritis Rheum. 2008. Jun;37(6):339-52.
(5) Japanese Society of Neurology (Editorial supervisor): Clinical Practice Guideline for Epilepsy Management 2010. Igaku Shoin, 2010. [In Japanese]
http://www.neurology-jp.org/guidelinem/tenkan.html
(6) Guideline for treatment of major depressive disorder by the Japanese Society of Mood Disorders, 2013 [In Japanese]
http://www.secretariat.ne.jp/jsmd/mood_disorder/img/120726.pdf
http://www.secretariat.ne.jp/jsmd/mood_disorder/img/120331.pdf
(7) Japan College of Fibromyalgia Investigation & National project team by Ministry of Health, Labour and Welfare (Editor): Fibromyalgia Guideline 2013. Japan Medical Journal 2013. [In Japanese]
http://minds4.jcqhc.or.jp/minds/FMS/CPGs2013_FM.pdf
(8) Japanese Society of Neurology/Japanese Headache Society (Editor Supervisor): Clinical Practice Guideline for Chronic Headache 2013. Igaku Shoin, 2013. [In Japanese]
http://www.jhsnet.org/guideline_GL2013.html
(9) Standards of NeuroTherapeutics: Chronic pain (ed Japanese Society of Neurological Therapeutics)
https://jsnt.gr.jp/guideline/mansei.html
(10) Standards of NeuroTherapeutics: Restless legs syndrome (ed Japanese Society of Neurological Therapeutics)
https://jsnt.gr.jp/guideline/restless.html
(11) Standards of NeuroTherapeutics: Dizziness and vertigo (ed Japanese Society of Neurological Therapeutics)
https://jsnt.gr.jp/guideline/memai.html
(12) Ministry of Health, Labour and Welfare Study Group on Chronic Pain. Appendix. Future Measures to Deal with Chronic Pain (recommendations). September 2010. [In Japanese]
http://www.mhlw.go.jp/stf/houdou/2r9852000000ro8f-att/2r9852000000roas.pdf
(13) 2007 Comprehensive Survey of Living Conditions. III. State of health of household members [In Japanese]
http://www.mhlw.go.jp/toukei/saikin/hw/k-tyosa/k-tyosa07/3-1.html
(14) 2007 White Paper on Suicide Prevention in Japan. Cabinet Office. Part 1. Current status of

suicide in Japan and history of suicide prevention measures. 11. Circumstances of suicide by day, time, and month. [In Japanese]
http://www8.cao.go.jp/jisatsutaisaku/whitepaper/w-2007/html/part1/b1_1_11.html
(15) Kachi, Takashi. History of pineal research, discussion and development. 2. 1954–1969. Journal of Hirosaki University of Health and Welfare. 3(1).9-18.2012. [In Japanese]
(16) Yamashima, Tetsumori. The discovery of adrenaline and Jokichi Takamine. Journal of Health, Physical Education and Recreation 59(8).518-527, 2009. [In Japanese]
(17) Bear, Connors, and Paradiso, editors. Neuroscience: Exploring the Brain, p. 391. Translated by Kato, Hiroshi *et al*. Nishimura Shoten, 2007. [Japanese translation]
(18) Japan Society of Ningen Dock/National Federation of Health Insurance Societies Subcommittee on Studies and Research on Laboratory Test Reference Values and their Utility, editors. A megastudy of 1.5 million individuals by the Japan Society of Ningen Dock and the National Federation of Health Insurance Societies. [In Japanese]
http://www.ningen-dock.jp/wp/wp-content/uploads/2013/09/%E3%83%97%E3%83%AC%E3%82%B9%E3%83%AA%E3%83%AA%E3%83%BC%E3%82%B9%E7%94%A8PDF%EF%BC%88140409%E5%B7%AE%E3%81%97%E6%9B%BF%E3%81%88%EF%BC%89.pdf
(19) Hamazaki.T. *et al*. Cholesterol Issues in Japan-Why Are the Goals of Cholesterol Levels Set So Low?" Ann Nutr Metab. 62:32-36.2013.
http://jsln.umin.jp/20130128-1ANMJpnversion.pdf (Japanese published version)
(20) Gerson, Max. A cancer therapy: Results of fifty cases and the cure of advanced cancer by diet therapy. Translated by Imamura, Koichi. Tokuma Shoten, 1989. [Japanese translation]
(21) Keio University Cognitive Behavioral Therapy Study Group, editors. 2010 Manual of Cognitive Therapy/Cognitive Behavioral Therapy for Depression. [In Japanese]
http://jact.umin.jp/pdf/cognitive_medical.pdf
(22) Zarogoulidis. P. *et al*. Time recall; future concept of chronomodulating chemotherapy for cancer. Curr Pharm Biotechnol. 14(6). 632-42. 2013.
(23) Ortiz-Tudela. E. *et al*. Cancer chronotherapeutics: experimental, theoretical, and clinical aspects. Handb Exp Pharmacol. (217). 261-88. 2013.
(24) Fujimura, Akio, editorial supervisor/author. Chronotherapy. Timing of drug administration and efficacy. 2nd edition, pp. 59–73. Japan Medical Journal, 2014. [In Japanese]
(25) Koyama, Natsu. Fundamental knowledge of pain and pain relief. Volume 1: Fundamentals. Gijutsu-Hyohron Co. Ltd., 2010. [In Japanese]

References

Japanese Headache Society Report of the Japanese Translation of Medication-overuse headache (MOH) [Japanese translation]
http://www.jhsnet.org/information/MOH_japanese_20140317.pdf
Hashikawa, Tsutomu. Cranial Nerves. Dictionary of Neurology [In Japanese]
http://bsd.neuroinf.jp/wiki/脳神経 (2012) [In Japanese]
Dopaminergic nervous system [In Japanese]
http://kanri.nkdesk.com/hifuka/sinkei28.php
Serotonergic nervous system [In Japanese]
http://kanri.nkdesk.com/hifuka/sinkei29.php
Kobayashi, Katsunori. Serotonin. Dictionary of Neurology [In Japanese]
http://bsd.neuroinf.jp/wiki/セロトニン (2012) [In Japanese]
Manual for Handling Disorders Due to Adverse Drug Reactions. Serotonin Syndrome. March 2010.

Ministry of Health, Labour and Welfare [In Japanese]
http://www.info.pmda.go.jp/juutoku/file/jfm1003003.pdf
Noradrenergic nervous system [In Japanese]
http://kanri.nkdesk.com/hifuka/sinkei30.php
Cholinergic nervous system [In Japanese]
http://kanri.nkdesk.com/hifuka/sinkei32.php 2014.7.11
Misawa, Hidemi. Acetylcholine. Dictionary of Neurology [In Japanese]
http://bsd.neuroinf.jp/wiki/アセチルコリン(2013) [In Japanese]
Kuriyama, Masaru. EBM Series. Alzheimer's disease. The right treatment. Hoken Corp., 2008.
Shinya, Hiromi, editorial supervisor/author. Illustrated Guide to Health and Happiness Starting from the Intestines. Shinsei Shuppan Inc., 2006. [In Japanese]
Koyama, Natsu. Fundamental knowledge of pain and pain relief. Volume 2: Clinical practice. Gijutsu-Hyohron Co., 2010. [In Japanese]
Shimoji, Koki. The science of pain relief: Looking into the true nature of pain and its causes, and new treatment methods, pp. 34–45. Softbank Creative Corp., 2011. [In Japanese]
Gerson, Charlotte *et al*. The Gerson Therapy: The Amazing Nutritional Program For Cancer and Other Illnesses. Translated by Abe, Koji *et al*. Tokuma Shoten, 2002. [Japanese translation]
Gerson, Charlotte *et al*. Healing the Gerson way: Defeating cancer and other chronic diseases. Translated by Ujiie, Kyoko. Jiyusha Inc., 2009. [Japanese translation]
Reiter, Russell J *et al*. Melatonin: Your Body's Wonder Drug. Translated by Ogawa, Toshiko. Kodansha Ltd., 1995. [Japanese translation]
Stallard, Paul. Think good - feel good: A cognitive behavior therapy workbook for children and young people. Translation supervised by Shimoyama, Haruhiko. Kongo Shuppan, 2006. [Japanese translation]
PsychologieLexikon.com Adrenalin (Epinephrin, Stresshormon, Neurotransmitter)
http://www.psychologielexikon.com/249-adrenalin-epinephrinstresshormon-neurotransmitter
Ministry of Health, Labour and Welfare. Evaluation of the Working Group on the Applicability of Criteria Concerning Medical Necessity. Psychiatry/Neurology Working Group. Document 3-1. [In Japanese]
http://www.mhlw.go.jp/file/05-Shingikai-11121000-Iyakushokuhinkyoku-Soumuka/0000044382.pdf
Drug package insert: IF Tryptanol [In Japanese]
http://www.info.pmda.go.jp/go/pack/1179002F1068_3_04/
Drug package insert: IF Noritren [In Japanese]
http://www.info.pmda.go.jp/go/pack/1179004F1024_1_15/
Drug package insert: IF Tofranil [In Japanese]
http://www.info.pmda.go.jp/go/pack/1174006F1078_3_03/
Drug package insert: IF Tegretol [In Japanese]
http://www.info.pmda.go.jp/go/pack/1139002C1082_2_12/
Drug package insert: IF Topina [In Japanese]
http://www.info.pmda.go.jp/go/pack/1139008F1027_1_10/
Website of the Department of Pharmaceutical Information Science, School of Pharmacy, Tokyo University of Pharmacy and Life Sciences [In Japanese]
http://www.pharmis.org/jp/cancerpain/6.2.htm
Drug package insert: IF Depakene R [In Japanese]
http://www.info.pmda.go.jp/go/pack/1139004G1040_1_02/
Drug package insert: IF Rivotril [In Japanese]
http://www.info.pmda.go.jp/go/pack/1139003C1044_1_07/

Drug package insert: IF Landsen [In Japanese]
http://www.info.pmda.go.jp/go/pack/1139003C1052_2_05/
Drug package insert: IF Risperdal [In Japanese]
http://www.info.pmda.go.jp/go/pack/1179038C1027_1_29/
Drug package insert: IF Lamictal [In Japanese]
http://www.info.pmda.go.jp/go/pack/1139009F1021_1_08/
Drug package insert: IF E Keppra [In Japanese]
http://www.info.pmda.go.jp/go/pack/1139010F1024_1_10/
Drug package insert: IF Mystan [In Japanese]
http://www.info.pmda.go.jp/go/pack/1139006C1030_1_09/
Drug package insert: IF Gabapen [In Japanese]
http://www.info.pmda.go.jp/go/pack/1139007F1022_2_05/
Drug package insert: IF Lyrica [In Japanese]
http://www.info.pmda.go.jp/go/pack/1190017M1028_1_11/
Ministry of Health, Labour and Welfare, ed. Pharmaceutical Industry Vision 2013. Documentation. [In Japanese]
http://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_iryou/iryou/shinkou/dl/vision_2013b.pdf

Drug package insert: Inderal [In Japanese]
http://www.info.pmda.go.jp/go/pack/2123008F1048_3_06/
Drug package insert: Arotinolol [In Japanese]
http://www.info.pmda.go.jp/psearch/html/menu_tenpu_base.html
Drug package insert: Dihydergot [In Japanese]
http://www.info.pmda.go.jp/go/pack/2160350F1269_1_04/
Sackett DL. *et al*. Evidence based medicine: what it is and what it isn't. BMJ 1996; 312(7023).71-72.
Astroarts The search for exoplanets [In Japanese]
http://www.astroarts.co.jp/hoshinavi/magazine/extrasolarplanet/planet1/page1-j.html
von Padova, Thomas. Das Weltgeheimnis: Kepler, Galilei und die Vermessung des Himmels. Translated by Fujikawa, Yoshiro. Hakusuisha Inc., 2014. [Japanese translation]
Japan Atherosclerosis Society. List of supporting members.
http://www.j-athero.org/outline/sanjo.html
Japanese Society of Cardiovascular Disease Prevention. List of supporting members.
http://www.jacd.info/jacd/sanjyo.html
Japan Society of Ningen Dock. Conflicts of interest.
http://www.ningen-dock.jp/society/coi

Chapter 2
Disorders that can easily develop into cephalic hypersensitivity syndrome

As I mentioned at the outset, this book has two objectives. The first is to make patients themselves aware of cephalic hypersensitivity syndrome, and how to look after themselves to prevent and treat it. The other is to let young doctors know that cephalic hypersensitivity syndrome cannot be treated by simply following the guidelines. If young doctors can stay focused on individual characteristics while deciphering the origin of the disorder, they will find it is actually far from intractable. I also hope to instruct young doctors on what initial treatment to use to prevent cephalic hypersensitivity syndrome from developing in the first place. The first step in treating cephalic hypersensitivity syndrome is to distinguish it from other conditions. The symptoms that patients complain of, including headache, dizziness / vertigo, stiffness and pain, numbness in the limbs, and insomnia, are also seen in other disorders. The key to distinguishing cephalic hypersensitivity syndrome is a broad-ranging, careful medical interview that asks about the patient's history of illness and medication over the past decade or more, going back several decades in some cases, as well as subjective symptoms overshadowed by the main complaint and even symptoms that may not be noticed by the patient himself or herself but are matters of concern to the patient’s family and other people around him/her. Of course, it is necessary to identify disorders that require urgent treatment and those that clearly need specialist therapy, but those are outside the main thrust of this book, and I will therefore not address them in detail. In this chapter, my focus is on describing the various disorders that often progress to cephalic hypersensitivity syndrome and their symptoms, as well as patients' characteristics and the identification, prevention, and treatment of cephalic hypersensitivity syndrome.

1 Headache

Many people who visit a doctor complaining of headache have already been treated at several other medical institutions. Headache can become chronic, transformed, and eventually intractable.

A condition originally caused by migraine, tension headache, straight neck, or eye fatigue becomes chronic and transformed, developing into cephalic hypersensitivity headache due to psychological stress and inappropriate treatments.

Medical interview for headache

Patients who present complaining of violent or splitting headache must be treated with caution. Observe their vital and neurological signs, and after ruling out inflammation, carry out an MRI immediately. The MRI should be used to rule out conditions such as brain hemorrhage, subarachnoid hemorrhage, cerebral infarction, and dissecting arterial stenosis or aneurysm. One blind spot in headache outpatient clinics is the intense pain caused by dissection of the vertebral artery. If an acute dissecting aneurysm is overlooked, this can be fatal. Even if it spontaneously improves to a chronic state, it may develop into a chronic illness syndrome (Case 42). The effectiveness or otherwise of Imigran (sumatriptan) nasal drops and oxygen inhalation are useful diagnostic resources for ordinary headache outpatient clinics. Both Imigran nasal drops and oxygen inhalation can be performed in outpatient treatment rooms. Changes in pain can be assessed by the use of a facial scale. If neither treatment is effective, a cautious attitude should be adopted, including referral to a specialist.

In many cases, headache is chronic. The technique used to take medical interviews of headache patients is extremely important. The true worth of medical interviews is not apparent if patients are just asked to fill in a form by themselves.

The medical interview should start by confirming three points: "Do you always suffer from this sort of headache?" "Have you often suffered from headache before?" and "Is this the first time you have experienced this sort of headache?" These questions are extremely important. Even if a patient answers "Yes" to the

question "Is this the first time you have experienced this sort of headache?" it is important to go on to ask "What about before?" and "What about ten years ago?" This may elicit a response such as "Oh yes, I used to suffer from headaches," or "Now that you mention it, this time it probably is worse than my usual headache."

In terms of headache frequency, do not fall into the easy trap of thinking that a headache several times a month means a migraine, sustained pain for a week to 10 days or more is a tension headache, and intermittent pain for several weeks two or three times a year is a cluster headache. Transformed migraine can be uncovered by a careful preliminary examination.

HIT-6 is an abbreviation for the Headache Impact Test, a questionnaire consisting of six questions that provide a simple score for the physical and mental effects of headache and their influence on daily life.

This test is widely used in headache outpatient clinics, and I value the score it provides. Leaving aside the issue of how to classify the severity of headache, people with a score of 60 or more can be viewed as experiencing at least some difficulties in daily life and as in need of proactive treatment.

Administering this questionnaire on a regular basis also provides an indication of the effectiveness of headache treatment.

Date _____ Name _____

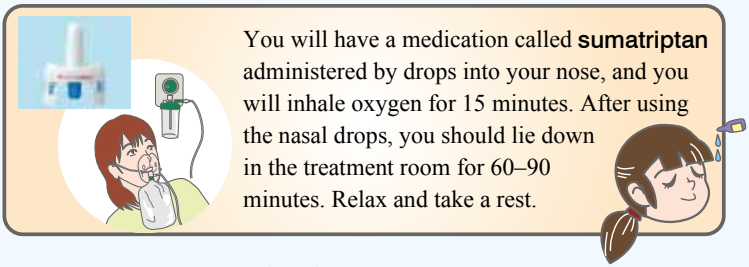
Nasal drop test Oxygen inhalation

- Administer Imigran nasal drop and observe whether or not it has any effect.
- Administer oxygen inhalation for 15 minutes and observe whether or not it has any effect.
- This reveals the type of headache.

Numerical Rating Scale for expressing the level of pain on an 11-point scale from 0 to 10

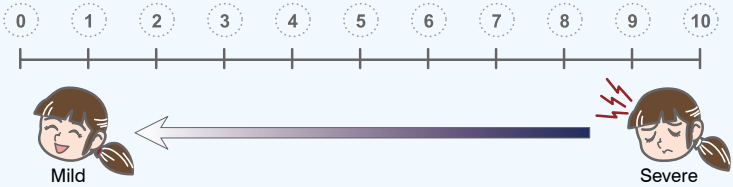
► How painful is your headache at this moment?

Draw a circle on the line below to show how badly it hurts now, with 10 being how painful it was at its worst.



► How painful is your headache 60 or 90 minutes after the nasal drop and oxygen inhalation?

Draw a circle on the line below to show how badly it hurts now, with 10 being how painful it was at its worst.



Thank you for your cooperation.

Kosuke Oota

Oota Medical Interview Form for Headache Patients

Please tick the boxes next to the answers that apply, and fill in numbers where necessary

	Migraine	Tension headache / Transformed headache	Cluster headache
This headache is ...	☐ The same sort of pain as always	☐ Similar to headaches I used to have before	☐ A sort of pain never previously experienced
Frequency of headache	☐ Between [ ] times and [ ] times a month (episodic)	☐ 1 week to more than 10 days (persistent)	☐ About once a year for several weeks Intermittently persistent Seasonal
Duration of each headache	☐ 4 hours to 3 days	☐ All day long	☐ Less than 3 hours
Time when it often occurs	☐ When relaxing, e.g., on weekends ☐ Headache present on waking up	☐ Worse in the evening	☐ No particular time ☐ Woken by pain during the night
Location of pain	☐ Mostly on one side ☐ Behind the eyes	☐ Usually at the back of the head, in the temples ☐ The whole head	☐ Behind the eyes ☐ Around the forehead
Characteristic type of pain	☐ Pounding, pulsating, or gushing Throbbing pain	☐ Like a painful band squeezing around the head ☐ Persistent pain that drags on	☐ Fierce piercing, gouging, or burning pain
Level of pain	☐ Want to stay still ☐ Bedridden when it is too bad	☐ Bearable ☐ Jobs such as work and chores are manageable	☐ Unable to keep still ☐ Roll around holding head ☐ Become manic/cry out
Impairment of everyday activities	☐ Not impaired	☐ Impaired	☐ Severely impaired
Exercise/ alcohol/ menstruation	☐ Gets even worse with exercise ☐ Gets worse in the bath ☐ Often more painful during, before, and after menstruation	☐ Gets better with exercise ☐ Happens after spending a long time in the same posture at work or in the house	☐ Drinking alcohol brings on headache ☐ Straining (like pushing out a bowel movement) or looking down makes headache worse
Characteristic symptoms other than headache	☐ Nausea ☐ Vomiting Sensitive to : ☐ light, ☐ sound, or ☐ smell ☐ See flashes or streaks of light, unable to read letters	☐ Stiff shoulders or neck muscles ☐ Light-headed dizziness ☐ Just touching the hair is painful ☐ Numbness of the head or face	☐ Bloodshot/tearful eyes ☐ Blocked or runny nose ☐ Sweaty forehead ☐ Swollen eyelids ☐ Contracted pupils or drooping eyelids
Other	☐ Often use painkillers (name of medication:) ☐ Painkillers ineffective ☐ Stress ☐ Insomnia ☐ Constipation ☐ Diarrhea		
	☐ Family history ( ) ☐ No family history		
Date	Name M/F Age		

Kosuke Oota

HIT-6™ Headache Impact Test

HIT is a tool used to measure the impact headaches have on your ability to function on the job, at school, at home, and in social situations. Your score shows you the effect that headaches have on normal daily life and your ability to function. HIT was developed by an international team of headache experts from neurology and primary care medicine in collaboration with the psychometricians who developed the SF-36® health assessment tool. This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please circle one answer for each question.

When you have headaches, how often is the pain severe?

never ▼ rarely ▼ sometimes ▼ very often ▼ always ▼

How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

never ▼ rarely ▼ sometimes ▼ very often ▼ always ▼

When you have a headache, how often do you wish you could lie down?

never ▼ rarely ▼ sometimes ▼ very often ▼ always ▼

In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

never ▼ rarely ▼ sometimes ▼ very often ▼ always ▼

In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

never ▼ rarely ▼ sometimes ▼ very often ▼ always ▼

In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

never ▼ rarely ▼ sometimes ▼ very often ▼ always ▼

☐	+	☐	+	☐	+	☐	+	☐
COLUMN 1 6 points each		COLUMN 2 8 points each		COLUMN 3 10 points each		COLUMN 4 11 points each		COLUMN 5 13 points each

To score, add points for answers in each column.

If your HIT-6 is 50 or higher:

You should share your results with your doctor. Headaches that stop you from enjoying the important things in life, like family, work, school, or social activities could be migraine.

☐
TOTAL SCORE

©2001 QualityMetric, Inc. and GlaxoSmithKline Group of Companies. All rights reserved.

Copyright, 2002 by QualityMetric Incorprated and GlaxoSmithKline
All rights reserved. No part of the Hit-6™ may be reproduced or transmitted in any form or by any means–electronic, mechanical, including photocopy, recording, or any information storage of retrieval system–without permission of the copyright holder. It shounld be used only as text.
Requests for permission to reproduce portions the Hit-6™ should be sent to Optum (fka QualityMetric Incorprated), 24 Albion Rd, Lincoln,RI 02865, or www.Optum.com
SF-36®, SF-36v2®, SF-12®, and SF-12v2® are trademarks of the Medical Outcomes Trust and are used under license. ACT™, DYNHA®, QualityMetric Health Outcomes™, SF-8™, and SF-10™ are trademarks of QualityMetric Incorporated. The SF-36v2® Health Survey is copyrighted by QualityMetric Incorporated.

Licensing & Registration
Requests for permission to reproduce the Hit-6™ should be sent to QualityMetric Incorporated, 24 Albion Rd, Lincoln, RI 02865, or www.qualitymetric.com.
Licensing & Registration
For permission to reproduce the survey and/or any associated intellectual property (e.g., trademarks, scoring algorithms, interpretation guidelines, and normative data) for any purpose must register or obtain a license at www.Optum.com or by calling 1-800-572-9394

Types of headache

A sort of pain never previously experienced

Many people are rattled when they experience a sudden splitting headache.

It raises the spectra of conditions such as brain hemorrhage and subarachnoid hemorrhage.

At the very least, a CT scan must be performed.

MRI is useful for identifying dissecting lesions, which are common in the vertebral artery.

Similar to headaches I used to have before

Patients who present for examination because of violent headache must be asked persistently about the sort of headaches they have experienced before.

A surprising number will answer "Now that you mention it, there was a time when I used to suffer from headaches and stiff shoulders."

This should lead you to suspect transformed migraine or cephalic hypersensitivity syndrome.

The same sort of pain as always

Patients who have been experiencing the same sort of headache and stiff shoulders for many years often have transformed migraine or cephalic hypersensitivity syndrome.

More concerned about dizziness / vertigo than headache

Bothered by bright lights and sound as well as an aching head

Frequency of headache

Between ( ) and ( ) times a month, episodic

In most cases, a headache that occurs about once a month, and at most once a week is a migraine.

Types include dizzy headache, ophthalmic headache, and headache with hypersensitivity to sound.

Persists for 1 week to 10 days or more

Most often the type known as tension headache.

Tension headache and transformed migraine are often difficult to distinguish, and a detailed medical interview questionnaire and examination are required.

About once a year for several weeks, intermittently persistent

This pattern is characteristic of cluster headache. It should be noted that as the headache symptoms in episodic migraine resemble those of cluster headache, it is easily misdiagnosed.

Indometacin or Voltaren (diclofenac sodium) suppositories are effective.

Severity of headache

A fierce headache generates two different types of response: wanting to lie down and stay still, and being in such pain that staying still is impossible, so that the patient has to keep moving or roll around holding their head. The former is more common in migraine, and the latter in cluster headache. These are treated in entirely different ways. Patients with cluster headache are often woken by intense pain during the night. Those with migraine may also wake up from sleep, but as the pain of migraine is comparatively less severe, sufferers often complain of pain when they wake up. As I have already mentioned, however, headaches that are so violent that they leave sufferers unable to move or serious conditions that would require an MRI, even if the patient is sufficiently mobile to visit a clinic, should be excluded here.

Wanting to stay still, bedridden when it is too bad

This is a common characteristic of migraine!

Patients tend to want to rest in a darkened and quiet room.

Bearable, jobs such as work and chores are manageable

Often the case in chronic migraine and chronic tension headache.

Common in mild to moderate cephalic hypersensitivity syndrome.

Unable to keep still, roll around holding head

The typical characteristic of cluster headache!

Association with exercise, bathing, menstruation, and alcohol

Gets worse with exercise

This is a characteristic of migraine and transformed migraine!

Tension headache, by contrast, usually improves.

Gets worse in the bath

This is frequently the case for migraine sufferers.

Often feel pain during, before, or after menstruation

This is frequently the case for migraine sufferers.

Drinking alcohol brings on the pain

Characteristic of cluster headache, although it is also often the case for migraine.

Many people are unable to drink alcohol during headache episodes.

Diverse migraine-associated symptoms

Many patients assume from the name "migraine" that this condition always involves a headache, but in fact in many cases, cephalic hypersensitivity syndrome is present and is associated with a wide variety of different symptoms. In the medical interview, it is vital to ask detailed questions not just about headache, but also about the symptoms described below. This is because different medications work better for different symptoms. Patients who visit a headache outpatient clinic must be asked persistently whether or not they also have any other symptoms that concern them. This is because they may not raise the subject of symptoms other than headache themselves.

Sensitivity to light, sound, and smell, and scintillating scotoma

One of the most important aspects of the medical interview prioritized in my headache outpatient clinic is to determine whether or not a patient is hypersensitive to light, sound, or smell by asking questions such as "Do you find light unpleasant or dazzling?", "Are you bothered by sounds?" and "Are you bothered by smells?" These are closely connected with the choice of medication. In specialist terms, migraine attacks associated with an aura and reflex epilepsy

may be treated with the same drugs. Various drugs are more effective for light, sound, and smells, specifically Depakene (sodium valproate)/Selenica (sodium valproate), Gabapen (gabapentin), and Topina (topiramate).

Light-sensitive migraine can be effectively treated with Depakene (sodium valproate)/Selenica (sodium valproate) or Topina (topiramate). Sound-sensitive migraine can be effectively treated with Tegretol (carbamazepine), Mystan (clobazam), Gabapen (gabapentin), and Topina (topiramate), which mainly soothe the temporal lobe. Smell-sensitive migraine can be effectively treated with Depakene (sodium valproate)/Selenica (sodium valproate) and Topina (topiramate), which soothe a broad area of the brain from the temporal lobe to the frontal lobe. Patients with chronic tension headache may also be hypersensitive to light and sound.

The phenomenon of flashing lights or a jagged pattern of light in front of the eyes, or vision of letters becoming partly blurred is known as scintillating scotoma and is a visual aura that precedes migraine.

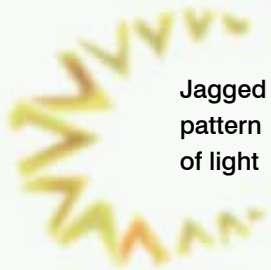
Column

●Ryunosuke Akutagawa and scintillating scotoma

Have you ever heard of "scintillating scotoma"?

Although most migraine patients have never heard this term, if you show them color photographs of the most common types of scintillating scotoma in a medical interview, they are surprisingly likely to say "This is what I see" or "That's my experience" in the medical interview.

Scintillating scotoma is a common visual impairment in which a jagged pattern of light appears in a person's vision, or the visual field narrows, making letters difficult to see and blurry. It frequently appears as a visual aura preceding migraine.



Jagged pattern of light

The well-known Japanese writer Ryunosuke Akutagawa also suffered from migraine, experiencing the classic symptoms of scintillating scotoma.

In his story *Cogwheels* (*Haguruma*), Akutagawa included the following description of scintillating scotoma.

"I discovered something strange in my visual field. Something strange? To wit, constantly spinning semitransparent cogwheels. I had had this experience several times before. The cogwheels gradually increased in number, half-obstructing my visual field, but not long afterward, after a little while they disappeared, to be replaced by the onset of a headache. This was what always happened."

Flashes and jagged pattern of light

The medical interview form for headache patients is an important gateway to the diagnosis of cephalic hypersensitivity syndrome, and going through it with care is the first step toward its correct diagnosis and treatment.

• Migraine-associated vertigo

Migraine-associated vertigo (vestibular migraine), in which dizziness / vertigo may be present in combination with other symptoms or by itself, is explained in the section on dizziness / vertigo.

• Migraine-associated allodynia

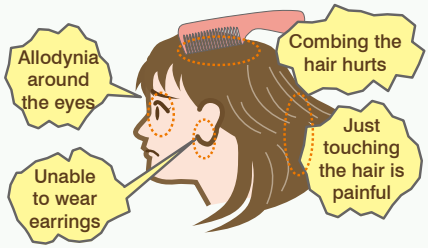
In many cases, allodynia is associated with migraine. The addition of stress to migraine, whether frequent or in the past, causes the brain to become hypersensitive and to feel numbness or pain from stimuli that would not be felt as painful by individuals in good health. Numbness may involve both sensory sensitization and hypoesthesia. Distinguishing between them is the first step in diagnostics, but this process is surprisingly hit-and-miss. For many patients attending clinics, numbness is hypersensitive allodynia. In the great majority of cases, this is effectively improved by the tricyclic antidepressants Tryptanol (amitriptyline) and Noritren (nortriptyline) and the antiepileptic Depakene (sodium valproate). It is far from an intractable symptom.

Column

●Cranial allodynia

Patients arrive complaining of a wide variety of symptoms: just touching their hair is painful, it hurts to comb or tie back their hair, wearing earrings is unpleasant, or the area around their eyes is painful and wearing glasses is difficult. These constitute cranial allodynia, which is associated with migraine. In most cases, it can be effectively treated with tricyclic antidepressants such as Noritren (nortriptyline) and Tryptanol (amitriptyline) or with antiepileptics such as Depakene (sodium valproate) and Tegretol (carbamazepine).

Patients with extracranial allodynia complain of uncomfortable numbness and pain in the limbs. It is most common in the arms. Patients may say that it is uncomfortable when something touches their arms or when they wear a wristwatch or belt. The treatment is the same as for cranial allodynia.



Cranial allodynia

Differentiating migraine and tension headache is difficult in clinical practice

If one asks whether these two conditions are easily differentiated in practice by means of the medical interview form for headache patients, the answer is no. At one point, the term "mixed-type headache" was used. This convenient name was recognized worldwide, but was excluded from the 1988 international classification on the grounds that the two types could be distinguished. Even for doctors who have been treating headache for many years, however, this is no easy task. Given the extent to which migraine and tension headache overlap, it may be more correct to speak of migraine-predominant mixed-type headache and tension-predominant mixed-type headache. Empirically, there are strong genetic and familial factors that contribute to migraine, whereas tension

headache develops when stiff shoulders or neck caused by maintaining a forced posture at work or in daily life becomes chronic and progresses to headache. If tension headache is treated inappropriately, it becomes chronic. Fortunately, the treatment for tension headache is not so different from that for migraine; the only difference between them lies in whether or not to prescribe triptan to be used as needed. The first-choice medications for tension headache also include Tryptanol (amitriptyline), Noritren (nortriptyline), and Depakene (sodium valproate). Highly experienced doctors who have been holding headache outpatient clinics for many years diagnose tension headache-predominant headache rather than tension headache alone. This is because some aspects of migraine may also be present. In addition to the first-choice medication, an experienced doctor will also prescribe ergotamine or triptan to be used as needed and observe its effectiveness. Such an empirical knowledge of diagnosis and treatment is not described in the Japanese Headache Society guidelines. This is a pitfall into which young doctors who are dependent on guidelines may easily fall.

In headache outpatient clinics, it is often difficult to make a clear distinction between migraine and tension headache. Tension headache was formerly referred to as "muscle tension headache," and as this name suggests, tension headache is often associated with symptoms connected to muscle tension. Mixed-type headache, in which elements of both migraine and tension headache are present, often develops into cephalic hypersensitivity syndrome. I often explain this to patients using the analogy of the "monster headache." Although it may have started out as migraine or muscular stiffness, these are exacerbated by a range of different factors and transformed into a "monster headache." One factor in such aggravation is stress. Another is the excessive use of different painkillers. The key to preventing this alteration is not to overlook mixed-type headache during the initial stage. Under the ICHD-3β classification criteria for headache based on the frequency of attacks and the duration for which the symptoms persist, headaches that combine the characteristics of migraine and tension headache are difficult to distinguish.

Chronic daily headache is actually cephalic hypersensitivity syndrome

Based on long experience, I regard the use of the name "chronic migraine" with disfavor. "Chronic migraine" was not defined in the first edition of the

International Headache Classification (1988), but was introduced into the second edition (2004), in tandem with the adoption of diagnostic criteria for drug abuse headache. As the diagnosis of chronic migraine presumes that drug abuse is not taking place, it is intimately connected with the diagnostic criteria for drug-abuse headache. The supplementary criteria for chronic migraine and the diagnostic criteria for drug-abuse headache were partly revised in 2006, but as patients with chronic migraine not infrequently abuse medication for acute headache, clinically the dividing line between them is unclear [1]. The purpose of the International Headache Classification is the diagnosis of individual episodes of headache, and the fact that it does not mesh with criteria that take account of previous history makes it inconvenient as a classification for clinical use. For this reason, the Clinical Practice Guideline for Chronic Headache edited by the Japanese Society of Neurology and the Japanese Headache Society in 2013 also mention Stephen Silberstein *et al*.'s diagnostic criteria for chronic daily headache which, although it is not mentioned in the International Headache Classification, is an expedient category for clinical use.

According to Silberstein *et al*.'s diagnostic criteria, headaches lasting at least four hours a day that continue for 15 or more days a month are regarded as chronic daily headache, which is subdivided into four types, including transformed migraine [2]. In other words, after headache has become chronic, it is characteristically difficult to classify whichever set of diagnostic criteria is used, and what is most troublesome is that although chronic ongoing headache can be classified at a glance as a single type of symptom, its different causes and underlying mechanisms mean that this classification is meaningless in clinical practice, as they affect the efficacy of treatment. On this point, I believe it is crucial to focus on the process of transformation. In this sense, the "transformed headache" I describe is different from Silberstein *et al*.'s definition. Rather than setting out detailed definitions such as "A headache with X characteristics continued to for Y days or more to meet Z criteria for ZZ items" as diagnostic criteria, I would like to propose the concept of "transformed headache" whereby the current headache is caused by some sort of original trigger, with a range of factors such as the abuse of painkillers, heavy psychogenic stress, and lifestyle habits that change brain chemicals bringing about changes in the original symptoms that result in persistent daily headache. This is because in clinical

practice, it is difficult to restrict the original trigger to migraine and classify it in past terms.

In this way of thinking, rather than classification into neat categories, the emphasis is on an in-depth, careful search for the disorder and its symptoms that triggered the condition. This is more effective for the purpose of clinical treatment. As I have already described in Chapter 1, diagnostic criteria and classifications should not lose sight of the underlying truth that their purpose is not efficient coding but the discovery of effective treatment.

In many cases, transformed headache is fomented by psychogenic stress and the use of multiple different painkillers. It is therefore difficult to cure with the antidepressants Tryptanol (amitriptyline) and Noritren (nortriptyline) and the antiepileptic Depakene (sodium valproate) alone. The help of other medications such as Topina (topiramate), Tegretol (carbamazepine), Risperdal (risperidone), and Abilify (aripiprazole) is also required. What is most important is fine adjustment in line with the origin of the patient's headache, based on a detailed medical interview. I treat such patients by prohibiting the regular use of over-the-counter painkillers, prescribing night therapy focused on antiepileptics and antidepressants, and helping them to improve their lifestyles and thinking. If muscle stiffness and tender or trigger points are also present, I add medication with a muscle-relaxing action such as Cercine (diazepam) or Rivotril (clonazepam), along with other therapies such as nerve block and thermal therapy.

Migraine-associated vertigo and vestibular migraine are discussed in detail in the section on dizziness / vertigo.

The increasing number of children with migraine

The number of children aged around 6–9 who suffer from headache is increasing. Many of them have a family history of headache, but this is not the whole story. I believe that it is also related to the frightening decrease in the amount of time children spend sleeping (see Page 176). Data from the Ministry of Education, Culture, Sports, Science, and Technology show that in 1970, elementary school students spent an average of 9 hours 23 minutes sleeping, but in 2000 this was only 8 hours 43 minutes, an average decrease of 40 minutes in a 30-year period. Data from the Ministry of Health, Labour and Welfare show

that an increasing number of children go to bed after 10 p.m., with a rapidly decreasing number asleep before 9 p.m. According to the WHO Europe 2004, children aged around 6–9 should sleep for 10 hours a night [3]. From a global perspective, Japan is a world leader in lack of sleep. There are concerns that as the proportion of women with jobs outside the home increases, children's hours of sleep will further diminish. The important first step in treatment is to ensure that they are getting sufficient sleep. Drug therapy comes after that. Although the Japanese Headache Society clinical guidelines on childhood migraine state that Tryptanol (amitriptyline) is the most common choice of medication, my own drug of choice is Depakene (sodium valproate)/Selenica (sodium valproate), as in the clinical guidelines on valproate-induced migraine (preliminary version). In intractable cases, I also use Tryptanol (amitriptyline) or Noritren (nortriptyline). Although ibuprofen and acetaminophen are the recommended medications to be taken as needed, I first see whether or not Cleamine (ergotamine tartrate) S 0.5 mg or Imigran tablets (sumatriptan) 50 mg are effective.

2 Dizziness / vertigo

It is surprising that there are so few clinics to treat dizziness / vertigo. Dizziness / vertigo ranks alongside headache, stiff shoulders, and lower back pain as one of the most common complaints. Although it is not perceived as such, it is actually a genuine form of pain. A surprisingly large number of people are troubled by dizziness / vertigo, most of whom will attend an ENT clinic. Even people with dizziness / vertigo originating in the inner ear are seldom given any instructions on how to perform special maneuvers to improve vertigo based on a practical explanation of the cause, and many of them are just treated with medication such as Merislon (betahistine mesylate). Even if it resolves spontaneously, dizziness / vertigo that are sufficiently severe to cause problems in daily life may be incorrectly dealt with or treated. For patients, this confusion in how dizziness / vertigo are handled clinically is a tale of woe. It has its roots in a shallow understanding of dizziness / vertigo on the part of working doctors. Intractable dizziness / vertigo may also involve psychological pain such as anxiety neurosis and depression. Too many doctors fail to understand that dizziness / vertigo is also a form of pain.

Cephalic hypersensitivity syndrome-associated dizziness / vertigo is a major component of my proposed disease concept of cephalic hypersensitivity syndrome. This type of dizziness / vertigo exhibits good improvement when treated according to the treatment algorithm for cephalic hypersensitivity syndrome. Over a decade ago, I was mocked by an ENT doctor who said that he had never heard a conference presentation supporting my contention of what is now known as migraine-associated vertigo: that if headache predominates, the patient is suffering from "headache vertigo," whereas if vertigo and dizziness predominate, the condition is "vertigo headache." Some ENTs still state publically today that they do not accept the existence of cephalic hypersensitivity syndrome.

Globally, although progress in research and treatment has been slow, a number of discoveries have been made that support my theory. With respect to the association between migraine and dizziness / vertigo in particular, Cutrer *et al*.'s study from 1992 and Dieterich *et al*.'s 1999 investigation described a variety of forms of migraine with dizziness / vertigo that did not meet the ICHD-2 criteria for basilar migraine, exhibiting aura symptoms such as phobia toward light, sound, and smell (I prefer the term "sensitivity" to "phobia") in addition to headache and dizziness / vertigo [4 5]. A paper co-authored by Brandt-Daroff and Lempert in 2009, who developed a method of treatment for dizziness / vertigo that will be described later, gave dizziness / vertigo as a symptom of migraine the name "vestibular migraine," and also showed that a certain percentage of migraine patients with dizziness / vertigo who are clearly suffering from migraine complicated by dizziness / vertigo despite not meeting the ICHD criteria for vestibular migraine, have never suffered from headache [6]. While making it clear that any explanation of the mechanism for migraine and dizziness / vertigo was only theoretical, both papers attempted to explain it as a phenomenon whereby hypersensitivity is induced in migraine patients by, for example, the asymmetrical release of neurotransmitters, hypersensitivity of the peripheral nerves due to an abnormal gene associated with Ca^{2+} channels (calcitonin gene-related peptide), or the occurrence of crosstalk in the peripheral or central nervous system. They further asserted that the effectiveness of medication for migraine such as β-blockers and Ca^{2+} antagonists as treatments for dizziness / vertigo associated with migraine constitutes evidence to back up this theory.

Migraine-associated vertigo is an internationally recognized condition

The term "migraine-associated vertigo" is not yet generally recognized among Japanese medical associations. In clinical terms, however, an association between migraine and dizziness / vertigo was identified in the 19th century.

Nevertheless, similar to scintillating scotoma, its mechanism has proven difficult to verify, and migraine and dizziness / vertigo have continued to be treated as separate conditions, and in extreme cases, patients seek treatment and are prescribed medication by specialists in different departments. People who suffer from severe nausea and vomiting, which frequently occur in conjunction with dizziness / vertigo, may also be treated by a gastroenterologist. I see patients whose symptoms have not only failed to improve, but who then also suffer from the side effects of medication, making their condition even more intractable.

In fact, when I investigated the patients in my clinic who were suffering from both headache and dizziness / vertigo, about 20–30% of those with dizziness also suffered from migraine. About 30–40% of patients with chronic migraine also suffer from dizziness [7]. Migraine and dizziness are closely related to each other, and dizziness improves if they are regarded as migraine-associated vertigo and treated in the same way as migraine.

As I described earlier, despite numerous reports of the connection between migraine and dizziness / vertigo, for a long time, this was not recognized internationally in terms of terminology, and there were no criteria for its classification. The phraseology "migraine-associated vertigo (vestibular migraine)" was first included as an addendum (appendix) in the revised International Classification of Headache Disorders (ICHD-3 β) published in July 2013.

The criteria for the classification of vestibular migraine in the ICHD are supposed to have been formulated by the International Headache Society with the support of the Bárány Society. This is the first time for the use of the term "headache vertigo" or "vertigo headache." These terms have been used by practicing doctors on the front line for many years and have gained international recognition, and for the time being, a provisional standard has been set out.

Benign paroxysmal positional vertigo (BPPV)

The Bárány Society is a society formed to commemorate Robert Bárány, who received the Nobel Prize in 1914 and was a distinguished researcher in the field of the neurology of equilibrium. In 1912, Bárány noticed that the BPPV experienced by the majority of patients who attended his dizziness / vertigo clinics constituted peripheral dizziness / vertigo triggered by disordered otoliths [8].

BPPV is present in more than half the cases seen in dizziness / vertigo clinics. It commonly occurs when getting up out of the bed, going to bed, rolling over, taking things down from a shelf, or pointing the head downward (such as during hair-washing). It most often consists of rotational vertigo lasting for only a few seconds, ten seconds at most. In a very few cases, rotational vertigo may continue for several minutes. There is no effective medication, and most people do not need to rest. Special maneuvers to improve vertigo are effective, but surprisingly few medical institutions explain these to patients or instruct them on how to perform them.

In-depth medical interviews of patients with BPPV, however, uncover the presence of headache or low-frequency hearing loss in an unexpectedly large number of cases. I believe that the cause is not just disordered otoliths, but that some sort of sensitivity in the epithelial cells within the cochlea or of the nerves is involved. The evidence is that medications to treat cephalic hypersensitivity syndrome are effective for patients of this type.

Psychogenic vertigo

There are two types of psychogenic vertigo. Some patients suffer from underlying organic or functional dizziness / vertigo of which concomitant psychogenic reaction is a complication, whereas in other cases, no particular signs of a nonpsychogenic cause are evident. Diverse chronic illness syndromes may be present, but hearing loss is minor in most cases. Psychogenic vertigo may be psychosomatic or be caused by anxiety neurosis/hypochondria, masked depression, hysteria, or other conditions [9]. These require proper treatment by a psychiatrist or a specialist in psychosomatic medicine. If treated inappropriately, they will aggravate and become intractable.

Orthostatic disturbance

In regular English, this means dizziness on standing up. It may rarely result in loss of consciousness. Children are often referred to a specialist. Orthostatic disturbance is caused by dysfunction of the autonomic nerves, particularly the sympathetic nerves. Most cases of orthostatic dizziness / vertigo are actually orthostatic disturbance. Dizziness and loss of consciousness on standing are mostly due to autonomic nerve dysregulation. Older people who are taking multiple drugs for heart disease and hypertension must adjust or reduce their medication. A tilt table can be used to test blood pressure and autonomic nerve dysfunction. Most households can also carry out the following simple orthostatic tests on the basis of blood pressure, pulse rate, and the patient's symptoms.

① Measure blood pressure and pulse rate in the supine position at rest.
② Measure blood pressure and pulse rate 1, 2, and 3 minutes after standing up.
③ Assessment: Orthostatic disturbance is suspected if systolic blood pressure (the higher number) drops by at least 21 mmHg, the pulse rate increases by at least 21 beats per minute, or at least three major symptoms occur.

Oota's simple test for orthostatic disturbance

ID		Name	
Test date		Name of examiner	

Blood pressure drops immediately after standing up	(dizziness / vertigo / low blood pressure occurs immediately after standing up)
Postural tachycardia syndrome	(no drop in blood pressure, but heart rate increased by standing up)
Neurally mediated syncope	(drop in blood pressure causes diminished consciousness or loss of consciousness)
Delayed orthostatic hypotension	(blood pressure drops 3–30 minutes after standing up)

Blood pressure at rest in the supine position	Blood pressure				Pulse rate	Subjective symptoms / comments
	1st	2nd	3rd	Average		

		Blood pressure	Pulse rate	Subjective symptoms	Dizziness / vertigo	Recovery time	
Standing blood pressure	Within 30 seconds immediately after standing up				Yes/No		Orthostatic hypotension
	1 minute after				Yes/No		
	3 minutes after				Yes/No		
	3 minutes after				Yes/No		Delayed orthostatic hypotension
	30 minutes after				Yes/No		

Note 1) Dizziness / vertigo within 30 seconds immediately after standing up are more common in children, and require further investigation.

Note 2) Dizziness / vertigo / hypotension within 3 minutes of standing up indicate classic orthostatic hypotension and classic autonomic nerve dysfunction.

Note 3) Dizziness / vertigo / loss of consciousness after standing up are common in older people. Delayed onset in particular can be the result of using multiple cardiovascular medications.

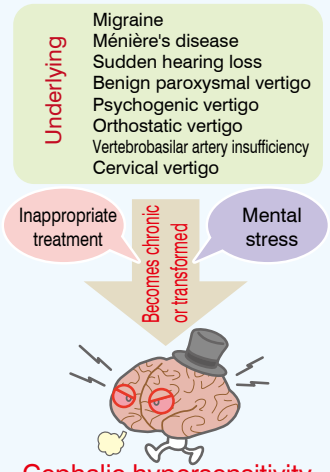
Note 4) Lie down flat immediately if nausea, dizziness / vertigo, feeling faint, and other symptoms that precede loss of consciousness or orthostatic hypotension occur.

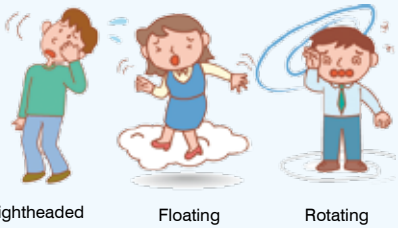
Diagnostic criteria for orthostatic disturbance,

divided into major and minor symptoms

Major symptoms	☐ Dizziness on standing, or prone to dizziness / vertigo	Minor symptoms	☐ Pulse pressure stenosis of at least 16 mmHg during orthostatic test
	☐ Feeling sick when standing, in the worst case falling over		☐ Drop in systolic blood pressure of at least 21 mmHg during orthostatic test
	☐ Feeling sick in the bath, or when seeing or hearing about something unpleasant		☐ Increase in pulse rate of at least 21 beats per minute during orthostatic test
	☐ A little movement causes palpitations or shortness of breath		☐ TII attenuation of at least 0.2 mV on standing ECG during orthostatic test or other changes
	☐ Difficulty in getting up in the morning, feeling unwell during the morning		
Minor symptoms	☐ Facial pallor	Assessment	1: At least 3 major symptoms
	☐ Loss of appetite		2: 2 major symptoms and at least 1 minor symptom
	☐ Intermittent complaints of abdominal colicky pain		3: 1 major symptom and at least 3 minor symptoms
	☐ Malaise or prone to tiredness		Exclusion of underlying conditions
	☐ Headache		
	☐ Prone to motion sickness in vehicles		

Kosuke Oota





Reproduced from Kosuke Oota, Increasing incidence of cephalic sensitivity dizziness / vertigo at my dizziness / vertigo outpatient clinic. 2nd edition.

Medical interviews for dizziness / vertigo

An experienced doctor can reach an approximate diagnosis by using a medical interview form for dizziness / vertigo. Simply accepting what the patient says and regarding the patient's description of their vertigo as rotational vertigo often leads to the wrong diagnosis. It is important to check whether or not it is associated with specific positions of the head and neck, if the patient is currently or has previously been prone to headaches, or if they are sensitive to light, sound, or smell.

Another point to note is that symptoms of dizziness / vertigo cannot be neatly filed away as diseases of either the ear or brain. They may also occur as a consequence of bradyarrhythmia in the heart. It is thus vital to monitor blood pressure, pulse rate, and arrhythmias in cephalic hypersensitivity syndrome clinics. If the pulse rate is slow or arrhythmia is suspected, the patient must be referred to a cardiologist. Focusing solely on the ear and brain in the search for the cause of dizziness / vertigo is dangerous. Caution is required, as in some cases dizziness / vertigo can be dramatically improved by pacemaker implantation.

Oota Medical Interview for Dizziness / vertigo

Please tick all those that apply.

☐ Feels more like floating	☐ Feels more like rotating
☐ Difficult to tell when it started	☐ Came on suddenly
☐ Persistent dizziness / vertigo	☐ Repeated dizziness / vertigo
☐ Not associated with hearing loss, tinnitus, or feeling that the ears are blocked	☐ Associated with hearing loss, tinnitus, or feeling that the ears are blocked
☐ Not related to changes in posture	☐ Related to changes in posture
☐ Not related to particular positions of the head and neck	☐ Related to particular positions of the head and neck
☐ Episodes are of comparatively long duration Around a few minutes	☐ Episodes are of comparatively short duration From a few seconds to less than a few minutes
☐ Previous history of transient ischemic attacks or cerebral infarction	☐ No previous history of transient ischemic attacks or cerebral infarction
☐ No previous history of a blow to the head, traumatic head injury, bleeding from the ears, or skull fracture	☐ Previous history of a blow to the head, traumatic head injury, bleeding from the ears, or skull fracture
☐ Currently suffering from hypertension ☐ Currently suffering from low blood pressure ☐ Dizziness on standing	☐ Not currently suffering from hypertension ☐ Not currently suffering from low blood pressure ☐ No dizziness on standing
☐ Currently suffering from heart disease ☐ Currently suffering from arrhythmia	☐ Not currently suffering from heart disease ☐ Not currently suffering from arrhythmia
☐ Currently prone to headaches ☐ Formerly prone to headaches ☐ Currently suffering from stiff shoulders	☐ Not prone to headaches ☐ Not currently suffering from stiff shoulders
☐ Bothered by light, noise, or smell	☐ Not bothered by light, noise, or smell
☐ Currently suffering from insomnia	☐ Sleeping well
☐ Previous history of psychiatric treatment	☐ No previous history of treatment

Kosuke Oota

Special maneuvers to improve vertigo for use at home

The Epley maneuver to treat dizziness / vertigo caused by otoliths

1

Starting posture

2

Look to the right.

3

Lie back, still looking to the right.
Hold that position for 30 seconds.

4

Look to the left.
Hold that position for 30 seconds.

5

Lie on your left side.
Hold that position for 30 seconds.

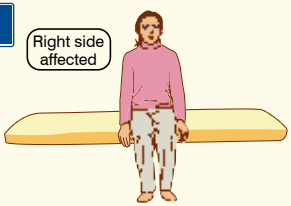
6

Get up on your left side.
Tip your head slightly forward.

Special maneuvers to improve vertigo for use at home

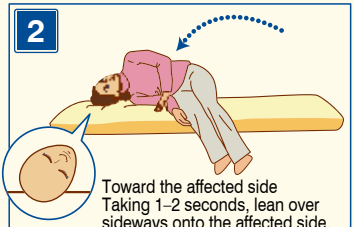
The Brandt-Daroff maneuver to treat dizziness / vertigo caused by otoliths

1



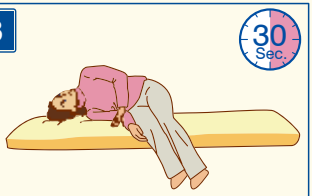
Do this somewhere where you will not be hurt if you fall over.
Sit straight upright, facing forward.

2



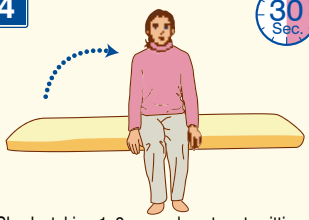
Toward the affected side
Taking 1–2 seconds, lean over sideways onto the affected side.
Look up at an angle of 45 degrees.

3



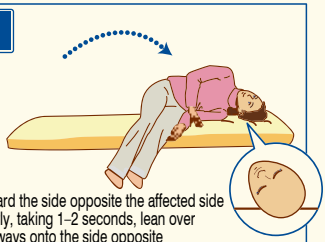
Hold that position for 30 seconds or until any dizziness or vertigo passes.

4



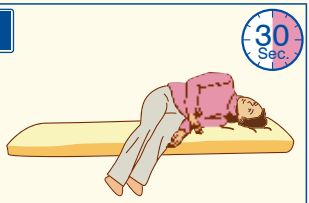
Slowly, taking 1–2 seconds, return to sitting upright and hold that position for 30 seconds.

5



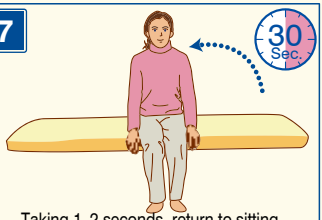
Toward the side opposite the affected side
Slowly, taking 1–2 seconds, lean over sideways onto the side opposite the affected side. Look up at an angle of 45 degrees.

6



Hold that position for 30 seconds or until any dizziness or vertigo passes.

7



Taking 1–2 seconds, return to sitting upright and hold that position for 30 seconds.

- **Repeat steps 1 ～ 7 five times each in a single session.**
  (Approximately 10 minutes)
- **Perform the maneuvers once each in the morning, in the daytime, and in the evening.**

In almost all cases, carrying out these maneuvers for 3–14 days continuously results in calculi being expelled from the semicircular canals, improving dizziness / vertigo.

Approximately 30% of patients, however, experience recurrence within a year.

If recurrence is repeated, continue performing these maneuvers once a day.

Try using special maneuvers to improve vertigo

Conditions related to dizziness / vertigo originating in the inner ear such as sudden hearing loss, BPPV, and Ménière's disease may become aggravated and intractable, and eventually cephalic hypersensitivity syndrome-associated dizziness / vertigo may develop. There are a large number of people suffering from dizziness / vertigo severe enough to cause them difficulties in everyday life and for which no treatment is effective. These special maneuvers to improve vertigo are simple movements that can be used at home. Some people complain that they actually make them feel worse to start with, but it does not cause harm and is worth trying, and if continued they can be surprisingly effective. Various different maneuvers for improving vertigo can be used: they include the Epley, Semont, Brandt-Daroff, and Lempert maneuvers, and which one is recommended depends on which semicircular canal or condition is causing the dizziness / vertigo. The Semont maneuver is a variation on the Brandt-Daroff maneuver, and I therefore recommend the latter as it is simple and easily continued, although it is not a universal remedy. Today, special maneuvers to improve vertigo are becoming popular, and more simple movements than those recommended by hospitals are coming into general use. An episode of the NHK television program Tameshite Gatten (which means "Try it and you'll understand") was broadcast on September 4, 2013 with the title "Solve dizziness / vertigo at home! A newly discovered maneuver for dramatic improvement" described special maneuvers to improve vertigo that resulted in improvements in nearly half of cases.

3 Tinnitus: Characteristics of tinnitus associated with cephalic hypersensitivity syndrome

In the medical interviews I carry out in cephalic hypersensitivity syndrome clinics, I always ask about tinnitus. Of course, no one sets out to have tinnitus treated by a neurosurgeon, but a surprising number of patients with cephalic hypersensitivity syndrome who visit a doctor complaining of dizziness / vertigo also have tinnitus. Although it is not subjectively severe enough to interfere with daily life, on questioning, they will confess that they do experience tinnitus along with their symptoms of headache and dizziness / vertigo. In this type of patient, tinnitus generally improves when the patient is treated for cephalic hypersensitivity syndrome. This treatment is particularly effective in patients with tinnitus associated with mild hearing loss of which they are unaware. However, many middle-aged and older patients with age-related hearing loss feel that some degree of tinnitus still persists even after their other symptoms have resolved in response to treatment. As I describe in the case studies, I have to tell such patients that tinnitus is generated within the brain and is something that they will need to live with for the rest of their lives. I tell them that as long as it does not interfere with daily life, they don't need to worry about it. Most of them are fine with this, and go on living their lives as normal. However, if severe hearing loss is present, the hearing aid treatment described below is required.

Recent research has identified the mechanism whereby tinnitus is generated as "phantom sounds generated by the brain." This encompasses a wide variety of factors, ranging from levels that are imperceptible on an everyday level to those that interfere with daily life, and its treatment is therefore far from straightforward. According to Seiichi Shinden et al., 90% of tinnitus is associated with hearing loss and is the result of the brain compensating for the absence of sound-related electrical signals that no longer reach it due to hearing loss by activating those areas and amplifying the resulting signals [10]. At this point, this hypothesis is persuasive, but actually verifying the specific changes that occur in brain cells in tinnitus is no easy matter [11]. That is, another factor emphasized by Shinden *et al*. is that anxiety, discomfort, and concentration, which are aggravating factors for tinnitus, vary greatly between individuals, making the cause difficult to identify even by investigating brain changes. However, they do state that tinnitus can be

improved in most cases by training by using a hearing aid to transmit signals to the brain from sounds that can no longer be heard unaided [10]. Eggermont *et al*. also proposed a slightly different method of treatment. They found that noninvasively stimulating and modulating the neural circuits for the auditory signals mistakenly generated by the brain from outside the brain resulted in long-term improvement. On the basis of these results, they developed an "acoustic coordinated reset neuromodulation device," an auditory modulation device that is now in the final stages of practical application testing in Europe [12]. Eggermont *et al*.'s modulation technique is a therapy for tuning the brain cells, and it is possible that this method may also be useful as a treatment for cephalic hypersensitivity syndrome in the future. Repetitive transcranial magnetic stimulation (rTMS), which is similarly being tried as a treatment for tinnitus mainly overseas [13], may also have a role to play in the future in the treatment of cephalic hypersensitivity syndrome.

Medical Interview for Tinnitus

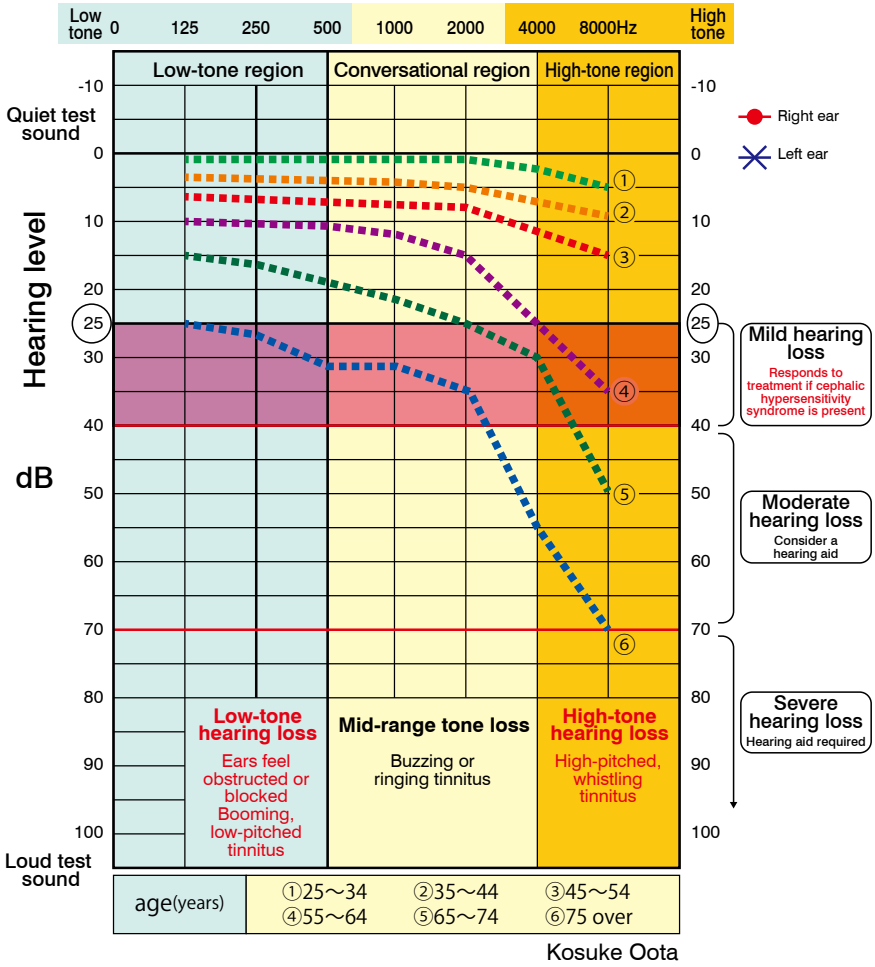
As described above, tinnitus is a sound *perceived* by the patient, and it is vital to ask carefully about their subjective symptoms while also carrying out objective hearing tests. These hearing tests are basically the same as those performed in regular health checkups. I always carry out hearing tests for patients who complain of dizziness / vertigo. They are helpful in identifying those tinnitus patients who will respond to cephalic hypersensitivity syndrome treatment. Tinnitus that improves in response to cephalic hypersensitivity syndrome treatment is almost always mild hearing loss in the range of around 25–40-decibels, represented by the pink band in the figure.

Audiogram: Tinnitus

No. Date

Name (age) M / F Investigator

Hidden hearing loss is present in most cases of tinnitus.
Tinnitus associated with low-tone hearing loss is treated with medication.
Tinnitus associated with high-tone hearing loss also requires hearing-aid treatment



Tinnitus treatment

I treat tinnitus associated with dizziness / vertigo in the same way as I do cephalic hypersensitivity syndrome, first assessing the patient's lifestyle habits, medications, and concerns by means of medical interviews before embarking on comprehensive treatment. Patients with a personality that makes them susceptible to cephalic hypersensitivity syndrome also often tend to suffer from chronic, aggravated tinnitus. They are also frequently hypersensitive to sound. Of the three arrows of cephalic hypersensitivity syndrome treatment – improving lifestyle, improving thinking, and night therapy – particularly important for tinnitus is improving thinking. The key to not allowing it to aggravate further is to be forward-looking, taking each slight improvement in symptoms as a plus and understanding that it will never disappear completely. The goal of treatment is thus not to eliminate tinnitus entirely, but to improve it to a level at which it does not interfere with daily life. A tinnitus questionnaire is useful in helping patients to visualize this and experience it for themselves [10].

In my clinical experience, patients who feel that their ears are blocked, hear a low-pitched booming sound, and have difficulty in perceiving low tones (low-tone hearing loss), as well as those who hear a high-pitched whistling sound and have difficulty in perceiving high tones (high-tone hearing loss) are more likely to notice a subjective improvement in symptoms as a result of treatment. Those who hear buzzing or ringing sounds and have difficulty in discerning mid-range tones find it somewhat more difficult to recognize improvements.

Some patients experience tinnitus even when hearing tests do not reveal any hearing loss. Such patients characteristically cannot identify their tinnitus as occurring particularly in one ear or the other, but perceive it as ringing inside their heads. Treatment for cephalic hypersensitivity syndrome is highly effective in such cases. The tinnitus resolves imperceptibly as the other symptoms of cephalic hypersensitivity syndrome also improve.

Headache, Dizziness / Vertigo, and Tinnitus: The Spectrum of Symptoms

When patients visit a doctor because they sense that something is physically wrong with them, they choose a clinic that specializes in the symptom about which they are most concerned. As described above, the two most important

symptoms of cephalic hypersensitivity syndrome are headache and dizziness / vertigo. Tinnitus is a symptom that is often associated with dizziness / vertigo.

These symptoms have been treated and studied in different departments for many years, but clinical studies have now been published in the fields concerned that show they should be understood as a single spectrum. A clinical study of dizziness / vertigo found that Meniere's disease and vestibular vertigo frequently overlap, and that some patients experience migraine headache, photophobia, phonophobia, and tinnitus during attacks of vestibular migraine [14]. An analytical study of the principal complaints of patients visiting an ENT outpatient clinic also found that in addition to the typical migraine symptoms of headache and dizziness / vertigo, other common subtypes of migraine symptoms included blocked ears, tinnitus, pain, and blocked nose, and that some patients were not receiving appropriate treatment under the current migraine classification system [15]. I am convinced that epilepsy represents the summit of cephalic hypersensitivity syndrome, and studies are now elucidating the shared mechanisms of the onset of migraine and epilepsy [16]. If headache, dizziness / vertigo, and associated tinnitus are understood as a spectrum of symptoms that share the same mechanism of onset, it is understandable that the treatment for cephalic hypersensitivity syndrome will be effective.

4 Headache, dizziness / vertigo, and stiff shoulders caused by straight neck

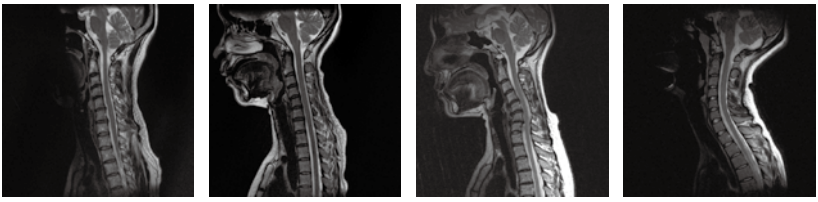
Bad posture

Recent years have seen an increasing number of patients suffering from symptoms including headache, stiff shoulders, dizziness / vertigo, and numbness of the arms. This may be because more and more people are now sitting at a desk for long hours using computers and smartphones. One of the conditions patients suffering from headache and stiff shoulders have is straight neck. This can be diagnosed from three X-rays scanned from the side with the neck bent forward, in an intermediate position, and bent backward. Straight neck is caused by abnormal contraction of the muscles that support the head.

From my own clinical experience, familial factors are present for over 30% of patients troubled by the symptoms of straight neck. In some families, you find that a grandfather, parent, and child are all suffering from straight neck. It is thus important to involve the whole family in its prevention.

Once straight neck has developed, if left untreated, it may cause intractable headache, stiff shoulders, nausea, dizziness / vertigo, and numbness of the hands that is sufficiently severe to hinder work. As there is no reliably effective treatment, doctors struggle with how to deal with these symptoms. In addition

Straight neck

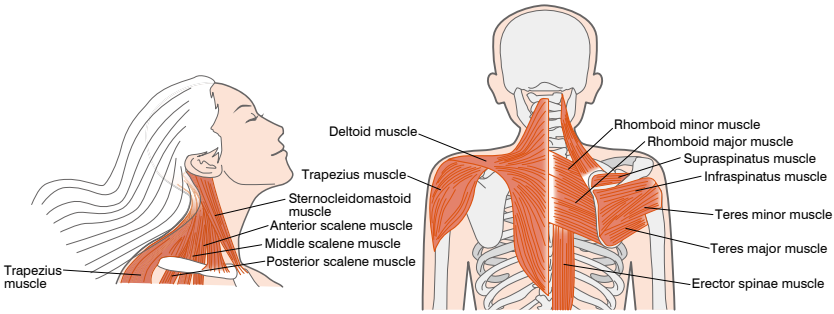


Straight neck　　Healthy

to congenital factors, the cause is believed to lie in abnormal contraction of the musculature supporting the head. As well as the medication I prescribe to treat cephalic hypersensitivity syndrome, I also proactively use treatments to ease the symptoms, including nerve block, thermal therapy, and acupuncture massage. At the same time, I also advise patients to sit well back in the chair, adjust the height of their computer to a height that comfortably matches their line of sight, tilt the monitor like an easel, and use a thin pillow. I tell them that while working, they should roll their head around, rotate their shoulders, and stretch their back. However, these instructions presuppose that atlantoaxial instability has been ruled out.

The atlantoaxial vertebrae are the first (atlas) and second (axis) cervical vertebrae, and are the site of a high concentration of the nerve ganglia that govern the autonomic nerves. If there is too much movement between the occipital and the cervical spine, the joint becomes unstable, resulting in disturbance of the autonomic nerves, particularly the sympathetic nerves. The latter become excited, causing a variety of symptoms including palpitations, nausea, and gastrointestinal symptoms. Distortion of the first cervical vertebra may also compress the vertebral artery, causing cerebrovascular disturbance with resulting symptoms such as headache, tinnitus, and dizziness / vertigo.

Returning the first cervical vertebra to its correct position alleviates any compression of the basal ganglia, relieves the state of tension of the sympathetic nerves, restores the balance of the parasympathetic and autonomic nerves, and relieves the patient from their various symptoms. In this condition, a problem at one location causes problems throughout the body.



Column

Stiff shoulders are a type of chronic pain

Although stiff shoulders are not usually described as "painful," this is actually just as much a type of chronic pain as lower back pain, although many people do not regard it as such simply because the word "pain" is not normally used to describe it in either Japanese or English.

Both lower back pain and stiff shoulders are the result of maintaining the same posture for a long time, which reduces the flow of blood and stiffens the muscles. If left unresolved, this can develop into chronic pain. When this happens, pain also occurs at sites other than the original location, initiating a vicious cycle. At this stage, it is difficult to treat with exercises alone. It rarely deteriorates to this stage in people who enjoy exercise but fail to perform enough. People who dislike exercise, however, are vulnerable to developing chronic pain. People who dislike exercise should not assume that they have to do something that involves "exercising." Rather, they should think in terms of taking breaks, and when switching between tasks, they should carry out the Oota Computer Exercises: rolling the head around, rotating the shoulders, and stretching out both arms, which takes less than a minute and can be done while sitting down.

Roll your eyes

Roll your head around your neck

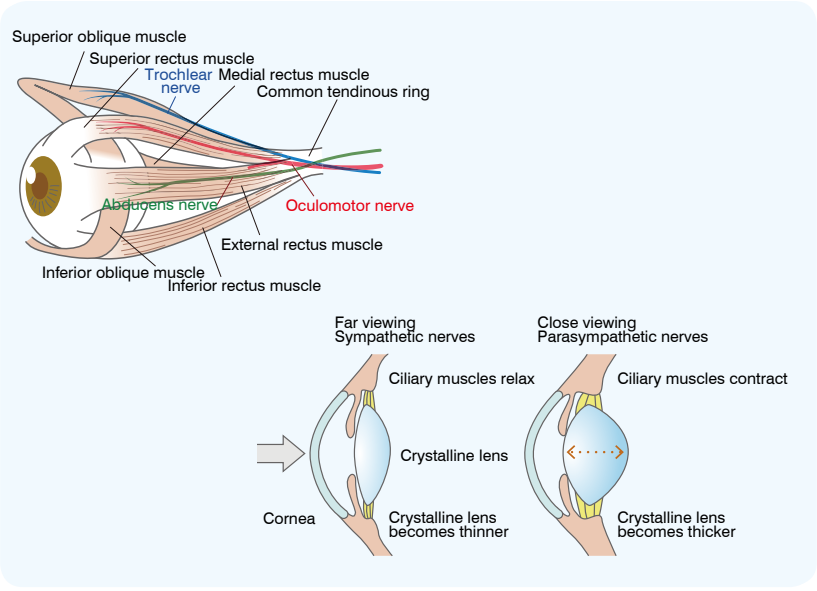
Rotate your shoulders and arms

See the Myojin-kan Neurosurgery Clinic website (headache and stiff shoulders): http://www.myojin-kan.jp/ill_zutu/

5 Headache and stiff shoulders caused by eyestrain

Eyestrain is the progression of eye fatigue. The movements of the eyeball are controlled by the oculomotor, trochlear, and abducens nerves. The movements of the pupil are controlled by autonomic nerves that branch off from the oculomotor nerve. Pupil dilation is controlled by sympathetic nerves, and contraction by parasympathetic nerves.

Working at a computer is also tiring for the parasympathetic nerves. As these regulate muscle relaxation and the tear glands, the result is eye muscle stiffness and decreased tears. In eyestrain, focusing at a nearby computer screen or other device for long periods activates the parasympathetic nerves. Meanwhile, the fact that the body is working activates the sympathetic nerves. Normally, the eyes and body must work in coordination to activate the parasympathetic and sympathetic nerves, but computer work forces them into a situation in which they are in opposition. Working at a computer is thus a task that tends to cause autonomic nerve disturbance.



Computer vision syndrome

Use glasses designed for computer work

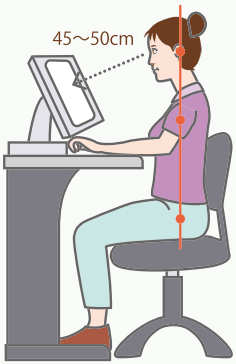
In Japan, this is also known as VDT (visual display terminal) syndrome [17]. Display screens are now an inescapable aspect of daily life, whether at work or at home. Using a device such as a computer, TV, mobile phone, or smartphone for long periods, however, leads to a range of problems for the eyes, body, and mind. Ocular symptoms include eyestrain, dry eye, cloudy vision, double vision, and diminished visual acuity. Bodily symptoms include stiffness and pain in the neck, shoulders, and arms, as well as headache, while mental issues include fatigue, depressed state, and irritability. They are of particular issue for people who spend long periods in front of the computer.

The cause is operating a computer for long periods of time. Words on a computer screen are not read as easily as those printed on paper. The printed word does not move, but the computer screen is constantly fluctuating. Attempting to focus on the screen means that the eye muscles must be in a state of permanent contraction. Contraction of the eye muscles, and especially of the medial rectus muscle, pulls both eyes inward. The ciliary muscles contract, overstimulating the autonomic nerves. Maintaining the same posture over long periods also imposes a static load on muscles. The bright blue light emitted by the display also affects the eyes. Bright blue light is very close to the ultraviolet region, and is the most energetic form of visible light. This means that it is not absorbed in the eye by the cornea or crystalline lens but reaches the retina, causing a decline in retinal function.

Low-intensity blue light, on the other hand, has a calming effect on the brain. Eye drops to ease eye fatigue and moisturize the eyes are available, as are special glasses to protect the eyes against the blue light emitted by liquid crystal monitors.

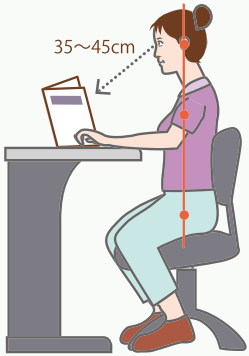
There are five preventive measures you can take.

1. As a corrective to long periods of work, look into the distance for 20 seconds after every 20 minutes of work.
2. Use computer glasses to protect your eyes from bright blue light and reflected light.
3. Use a different pair of glasses than your normal reading glasses, with the focal point set further away at the distance of the computer screen. Prescriptions for glasses must account for the need to maintain the eye's accommodatory function in a stable state for the distance between the eye and the computer screen. Have your prescription issued by an optometrist that uses a device called a visual function analyzer.
4. Sit on your chair in the correct posture, at right angles to the pelvic triangle.
5. Exercise by rolling your eyes, rolling your head around your neck, rotating your shoulders, and stretching your back.



Recommended sitting posture 1

Sit well back in the chair
Adjust the angle of the computer screen and the height of your chair to ensure a comfortable line of sight.



Recommended sitting posture 2

Sit with your legs apart, straddling the chair.

6 Sleep disorders: Can't sleep at night, but sleepy during the day

One-third of our lives is spent asleep. Healthy sleep provides the energy for the next day's activities, and sleep disorders have a major impact on everyday life. A variety of causes may be concealed behind sleep disorders, and my medical interview form for sleep disorders is helpful in discovering the correct way to treat them.

Sleep-related medical interview

From my 25-question medical interview concerning sleep, I have selected several questions concerning symptoms and their methods of treatment.

1&22. "Every night, I get so worried about whether or not I will be able to sleep, and sometimes the more I try to go to sleep, the less I am actually able to," and "I can't sleep in my own bedroom, but do sleep well elsewhere." The people who answer "Yes" to these questions are insomniac types who are frequently neurotic or psychologically unstable. They can be treated effectively with regular sleeping medication and anti-anxiety medication.

3. People who say that they "sometimes wake up more than 2 hours earlier than usual" can be treated far more effectively with antidepressants than with sleeping medication.

5&6. Snoring or apnea during sleep. These can easily be investigated in your own bedroom at home. You can also undergo testing (covered by health insurance) at the Myojin-kan Neurosurgery Clinic.

7&18. "I thrash around, shout, and grind my teeth (bruxism) while I'm asleep" and "Soon after falling asleep I experience sleep paralysis, and have nightmares and vivid, altered dreams. People who answer "Yes" to these two questions almost never respond to sleeping medication, but low doses of antiepileptic drugs are extremely effective.

8&9. "I stroke the wall with my hands and walk about, or I eat, open the refrigerator, or cook while I'm asleep. I don't remember this the next day." In extreme cases, some people may even cook a meal and eat it themselves. These symptoms are known as sleepwalking and sleep-related eating disorder (SRED), and can be treated with medication. In some cases, sleeping medication may not only be ineffective, but may actually aggravate the symptoms.

10&11. "My legs sometimes twitch convulsively while I'm asleep.," and "Soon after falling asleep my legs feel so hot and twitch or move restlessly, making it too uncomfortable to sleep." For these patients, too, sleeping medication is completely ineffective. Low doses of antiepileptic drugs and Parkinson's disease medication, however, are highly effective.

14&19. Symptoms such as "I feel unbearably sleepy during the day," and "I sometimes suddenly find myself going limp when I'm laughing or surprised" are specific to narcolepsy, also known as hypnolepsy and cataplexy. These patients require specialist investigation and treatment.

16. A patient who checks any of "If I wake up in the night, I have the following symptoms: palpitations, dizziness / vertigo, sweating, dry mouth, or headache" has tense sympathetic nerves in the autonomic nerve system, and is more effectively treated with α β-blockers or β-blockers than with sleeping medication.

20. People who check "Yes" to the question "I find it so difficult to get up in the mornings that I'm late for work or school" and feel heavy-headed when they wake up will find that their head is clearer on waking in the mornings if they take medication for migraine rather than sleeping medication.

Sleep-Related Medical interview 25

Please tick all the statements below that apply to your sleep and mental state in the past month.

1. ☐ Every night, I get so worried about whether or not I will be able to sleep, and sometimes the more I try to go to sleep, the less I am actually able to.
2. ☐ I wake up several times during the night.
3. ☐ I sometimes wake up more than 2 hours earlier than usual.
4. ☐ I sleep less than 4 hours a night.
5. ☐ I have been told that I snore while I'm asleep.
6. ☐ I have been told that I stop breathing while I'm asleep.
7. ☐ I thrash around, shout, and grind my teeth while I'm asleep.
8. ☐ I stroke the wall with my hands and walk about while I'm asleep. I don't remember this the next day.
9. ☐ I eat, open the refrigerator, or cook while I'm asleep. I don't remember it when I wake up.
10. ☐ My legs sometimes twitch convulsively while I'm asleep. Bedding at my feet moves around.
11. ☐ Soon after falling asleep, my legs feel so hot and twitch or move restlessly, making it too uncomfortable to sleep.
12. ☐ In the morning, I wake up with a headache.
13. ☐ In the morning, I don't feel that I have slept well.
14. ☐ I feel terribly sleepy during the day. I'm unbearably sleepy during meetings or classes.
15. ☐ I'm bothered by a loss of concentration or energy during the day.
16. ☐ If I wake up during the night, I have the following symptoms.
    ☐ Palpitations ☐ Dizziness / vertigo ☐ Sweating ☐ Dry mouth ☐ Headache
17. ☐ I feel down, have no motivation, and nothing feels worthwhile.
18. ☐ Soon after falling asleep, I experience sleep paralysis, and have nightmares and vivid, altered dreams.
19. ☐ I sometimes suddenly find myself going limp when I'm laughing or surprised.
20. ☐ I find it so difficult to get up in the mornings that I'm late for work or school.
21. ☐ I sometimes wake up so early in the morning that I can't stay up late at night.
22. ☐ I can't sleep in my own bedroom, but do sleep well elsewhere.
23. ☐ I'm stressed because of anxieties or worries about work, school, or family.
24. ☐ I can't give up drinking alcohol, smoking, drinking coffee, or using a computer or mobile phone before going to sleep.
25. ☐ I go to bed after midnight. I often use sleeping medication.

Please describe any other symptoms that concern you here.

Kosuke Oota

Oota Sleepiness Scale

Please answer the following questions to find out how severe your sleep disorder is.
A score of over 10 points indicates suspected sleep disorder.

Daytime sleepiness

How much do you feel like nodding off in the following situations?
Answer in terms of your recent daily life.

	Possibility of nodding off			
	None	A little	Possibly	Yes
1. While reading a newspaper, magazine, book, or other written material	0	1	2	3
2. While attending a meeting, seminar, or lecture	0	1	2	3
3. While watching a film in a cinema or a theatrical performance	0	1	2	3
4. While riding in the passenger seat of a car	0	1	2	3
5. During an afternoon break	0	1	2	3
6. While waiting for the traffic lights to change while driving	0	1	2	3
7. While talking to people	0	1	2	3
8. While watching TV at home	0	1	2	3
9. While relaxing after lunch or dinner	0	1	2	3
10. While filling in a household account book or writing a letter	0	1	2	3

Mild: 10 points or less
Moderate: 11–20 points
Severe: 21 points or more

Total points

Kosuke Oota

Your answers to these ten questions indicate the severity of your sleepiness. If it is moderate or severe, please see the 12 Pointers for Dealing with Sleep Disorders and the Sleep Guideline for Health Promotion 2014: 12 Messages for Sleep published on the Ministry of Health, Labour and Welfare website and described on the following page, and try and improve your sleeping habits.

Dealing with sleep disorders in everyday life

The following 12 Pointers for Dealing with Sleep Disorders are a revised version of the guidelines formulated by the Empirical Research Group for the Formulation of Guidelines for the Diagnosis and Treatment of Sleep Disorders Funded by a 2001 Ministry of Health, Labour and Welfare Intramural Research Grant for Neurological and Psychiatric Disorders. They perfectly summarize the key points for dealing with insomnia. Among these, "Get up at the same time every day" and "Rather than going to bed early to get up early, getting up early makes it easier to go to sleep early" are easy to understand and are more persuasive and effective than any sort of instruction. Getting up at the same time every morning, however, is a very difficult goal for single people to achieve. It becomes much easier with family cooperation. In 2014, "Sleep Guidelines for Health Promotion 2014: 12 Messages for Sleep" were issued by a Ministry of Health, Labour and Welfare Research Group [18]. They comprise concrete advice tailored to the lifestyle patterns of young people, the working generation, and the elderly, and other than the fact that the evidence for each of them is clearly set out, their content is broadly the same. They are published on the website, and this should be referred to in combination with this book.

12 Pointers for Dealing with Sleep Disorders (Revised Version)

(1) Go to bed once you start feeling sleepy, rather than sticking to a particular bedtime.
   - Determinedly attempting to go to sleep will sharpen your mind, making sleep more difficult.

(2) Get up at the same time every day.
   - Rather than going to bed early to get up early, getting up early makes it easier to go to sleep early.

(3) Instead, actively try and go to bed late and get up early.
   - If you stay in bed until late on a Sunday, Monday morning will be tough.
   - If you spend too long in bed, you will have less of a feeling that you slept well.

(4) If you nap during the day, do so for 20–30 minutes before 3 p.m.
   - Too long a nap will make you feel spaced out.
   - A nap in the late afternoon or after will adversely affect your sleep that night.

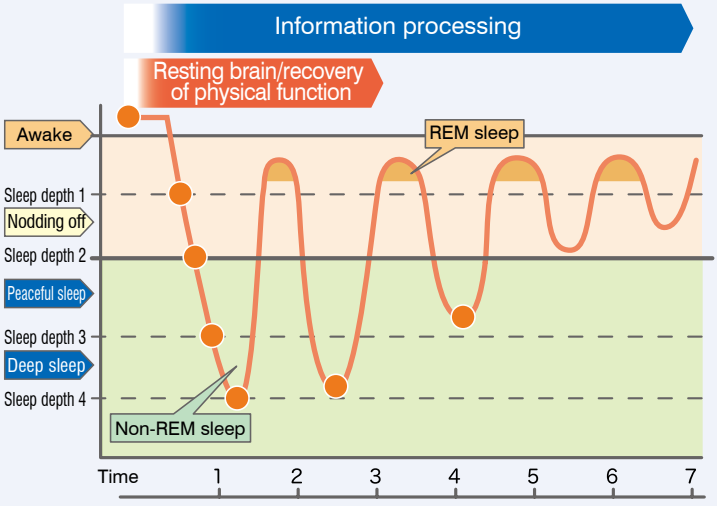
(5) Drinking alcohol before bed leads to insomnia.
  • Having a drink instead of taking sleeping medication diminishes deep sleep, and may cause you to wake during the night.
(6) People spend different amounts of time asleep, and it's enough if you are not troubled by sleepiness during the day.
(7) Avoid stimulants, and relax in whatever way best suits you before going to bed.
(8) Use the morning light to adjust your body's circadian rhythm for good sleep.
(9) Eat three meals a day at regular mealtimes, and acquire the habit of performing regular exercise.
(10) Caution is needed if you snore loudly or stop breathing, or if your legs twitch or feel restless during sleep.
(11) See a specialist if you still feel very sleepy during the day despite having slept well.
(12) Sleeping medication is safe if you take it correctly according to the doctor's instructions.

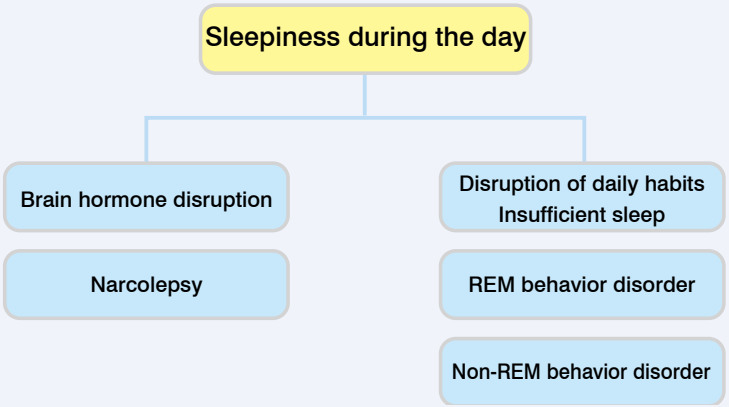
Parasomnia

Our sleeping pattern consists of a 90-minute cycle of non-REM sleep and REM sleep. This cycle is repeated 4–5 times a night. Parasomnia is a disorder that occurs when for some unknown reason, this switch does not go smoothly, and patients perform actions while still asleep or half-asleep. Parasomnia includes symptoms that appear during non-REM sleep, such as the somnambulism and night terrors common among children, and those that appear during REM sleep, such as severe sleep talking. Parasomnia should be suspected in patients who do not feel they have slept well when they wake up, those who are sleepy and cannot concentrate sufficiently during the day, and those who are easily tired. Although extreme cases are easily identified, bruxism, vivid, altered dreams, and nightmares are surprisingly easy to overlook. Bruxism that is sufficiently severe to prevent sleep can be diagnosed with a single glance in the mouth (see photograph). A low dose of Rivotril (clonazepam) is highly effective. From the first night it is used, nightmares, sleep paralysis, bruxism, and sleep talking simply disappear without a trace. Patients once again wake up refreshed in the morning. They immediately recover their spirits. Although parasomnia is frequently overlooked, it can be cured immediately. Narcolepsy is one distinctive form of parasomnia.

Patients with bruxism may develop visible bony prominences in the mouth.

Normal sleep





Causes of sleepiness: Parasomnia

Non-REM behavior disorder

- Feeling half-awake
- Somnambulism (sleepwalking)
- Sleep talking
- Nightmares
- Bruxism
- Restless legs syndrome (RLS)
- Periodic limb movement disorder (PLMD)
- Sleep-related eating disorder (SRED)

Occur due to disturbances of the autonomic nerves, motor system, and cognitive process during sleep or between sleeping and waking. Patients have no memory of their actions while they were asleep. SRED, in which patients eat and drink and may even cook a meal while asleep, is more common in women.
Effectively treated with Rivotril (clonazepam), Topina (topiramate), and Bl Sifrol (pramipexole hydrochloride).

REM behavior disorder

- Sleep apnea
- Vivid, altered dreams, nightmares
- Rapid movements of the arms and legs
- Violent behavior

Common in men aged over 50, this may be a precursor of Parkinson's disease or Lewy body disease. The elimination of causative substances such as drugs or alcohol is effective, as are Rivotril (clonazepam) and Bl Sifrol (pramipexole hydrochloride). These aggravate sleep apnea, however, and care must therefore be taken with the dosage.

Orexin and narcolepsy

From theory to the development of sleeping medication

Narcolepsy is a type of sleep disorder. Patients wake up repeatedly when they should be asleep, and go to sleep at times when they should not be feeling sleepy. In 1998, a group led by Takeshi Sakurai identified orexin, a substance that regulates sleep and waking that is associated with the onset of narcolepsy [19]. Orexin plays an important role in maintaining and controlling the normal pattern of sleep and waking, and narcolepsy has been shown to be a neurodegenerative condition that occurs specifically in orexinergic nerves. The projection regions of the orexinergic nervous system are the same as those of the serotonergic, dopaminergic, and other main nervous systems, and are also associated with emotion and the regulation of eating.

Insomnia medications include both non-benzodiazepines such as Myslee (zolpidem) and Lunesta (eszopiclone) and the melatonin receptor agonist Rozerem (ramelteon), and in November 2014, Belsomra (suvorexant) was also launched on the market as an orexin receptor agonist. All of these are examples of drugs developed on the basis of theories derived from hormone studies of sleeping and waking.

Oota Differential Diagnosis of Hypersomnia

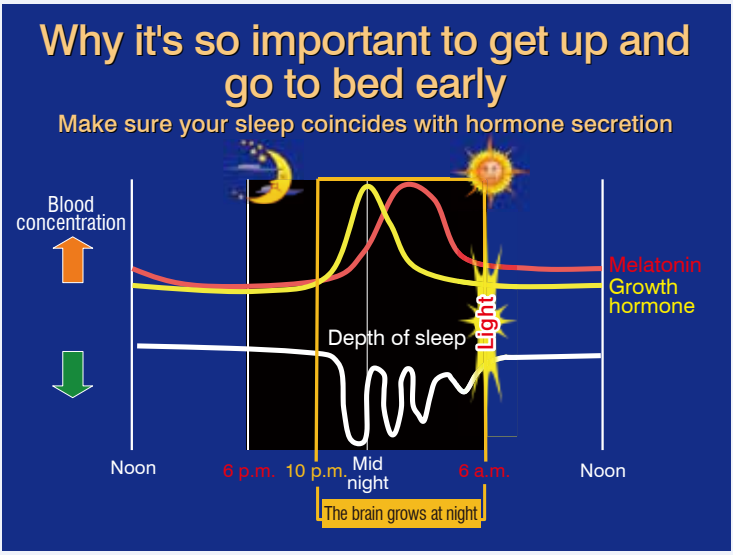
	Narcolepsy	Symptomatic hypersomnia	Hypersomnia of unknown origin
Main symptom	Sleepiness and episodes of falling asleep without warning during the day	Sleepiness and falling asleep during the day	Sleepiness and falling asleep during the day
Minor symptoms	Episodes of suddenly going limp induced by surprise or laughter	Headache, dizziness / vertigo	Headache, dizziness / vertigo, dizziness on standing
Length of naps	Short (less than 30 minutes)	Long (around 1 hour)	Long (around 1 hour)
Refreshed after sleep	Yes	No	No
Waking in the morning or after a nap	Easy	Often hard	Often hard
Time between going to bed and falling asleep	Short	Short to long	Short to long
Waking during the night	Yes	Yes	Infrequent
Total time spent sleeping	7–8 hours (normal range)	6–10 hours	6–10 hours
Cause	Diminished orexin (brain hormone)	Disruption of daily habits Short time spent asleep Vivid, altered dreams, nightmares, bruxism, sleep talking, restless legs syndrome, periodic leg movements, snoring, apnea	Unknown
Tests	Abnormalities revealed by oral inspection, Polysomnography (PSG), Multiple sleep latency test (MSLT), and Genetic screening	Abnormalities frequently revealed by oral inspection and PSG	No abnormalities revealed by oral inspection or PSG
Treatment	Improve daily habits, Central nervous system stimulants, Modiodal (modafinil) and Ritalin (methylphenidate) are effective	Improve daily habits, Rivotril (clonazepam) and other antiepileptics CPAP therapy	Improve daily habits, Central nervous system stimulants are usually ineffective

Kosuke Oota

Why it's so important to get up and go to bed early

Making sure that their children get enough sleep is an important task for parents. The Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare have both issued warnings on bedtimes for both children and adults. Rather than telling people to go to bed early, they advise them to get up earlier. Growth hormones, as their name suggests, act to increase height and weight during infancy, childhood, and youth, and are essential to the development of both primary and secondary sexual characteristics. Once adulthood has been reached, these hormones have a role to play in repairing and restoring the body. Melatonin is a hormone that is involved in the rhythm of sleeping and waking.

An examination of changes in the secretion of growth hormone and melatonin during the day reveals that these both increase at night. What used to be called the "witching hour" is the time when sleep is at its deepest. Mysteriously, this is almost exactly the time at which the secretion of growth hormone and melanin peaks. It is also a period of deep sleep. This cannot possibly be a coincidence.



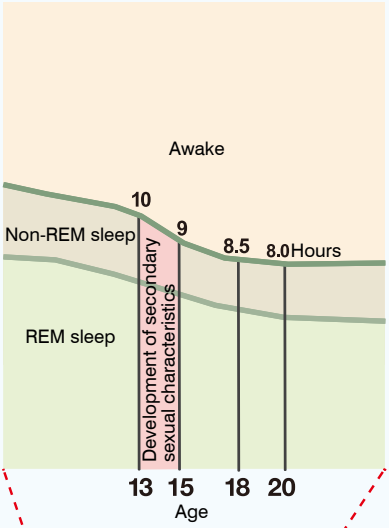
Just how harmful going to bed after midnight, when the date has already changed to the next morning, is to your health can be seen by the fact that it has been suggested that it diminishes sleep quality, decreases learning ability, does not enable recovery from fatigue, and leads to early aging.

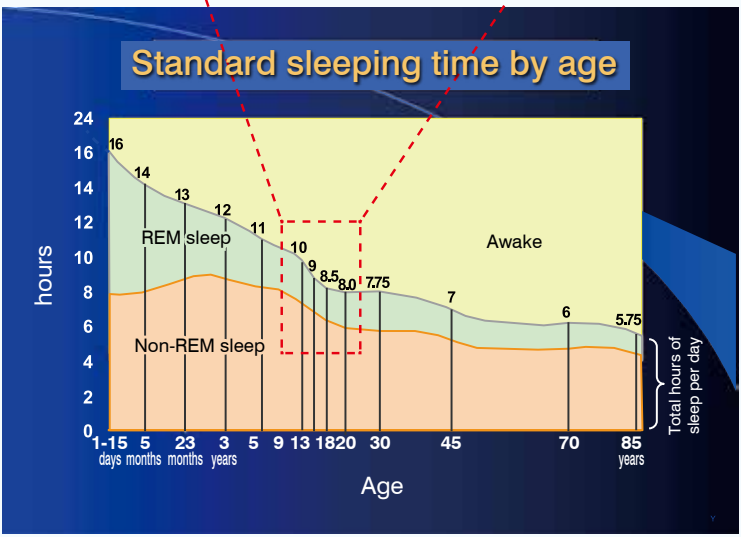
A rising number of children have cephalic hypersensitivity syndrome: The amount of time children spend sleeping is decreasing at a frightening rate

Children aged between around 3 and 9 years old need 11 hours of sleep a day, and older children and teenagers need around 10 hours. But how much do they actually get? An increasing number of children now sleep for fewer than 9 hours a night. They are growing up and maturing too early.

The brain organizes memories and learning during sleep. A well-known study found that subjects who were given a nine-digit finger-tapping test the same day and after a night of sleep scored significantly better on the test the following day. A study carried out outside Japan found that candidates accepted by leading universities slept an average of 8 hours a night during the examination period.

The conclusion is that parents must be educated to ensure that their children get the right amount of sleep for their age. If parents take the lead in staying up late, their children will follow them along this path. It is believed to be one reason for the rising number of emotionally disturbed children. Put simply, elementary schoolchildren should aim to sleep for 10 hours a night, junior and senior high school students for 9 hours, and university students for 8 hours [20].


Awake
10
9
8.5
8.0Hours
Non-REM sleep
REM sleep
Development of secondary sexual characteristics
13 15 18 20
Age


Standard sleeping time by age
hours
24
16
14
12
10
8
6
4
2
0
16
14
13
12
11
10
9
8.5
8.0
7.75
7
6
5.75
REM sleep
Non-REM sleep
Awake
1-15 days
5 months
23 months
3 years
5
9
13
18
20
30
45
70
85 years
Age
Total hours of sleep per day

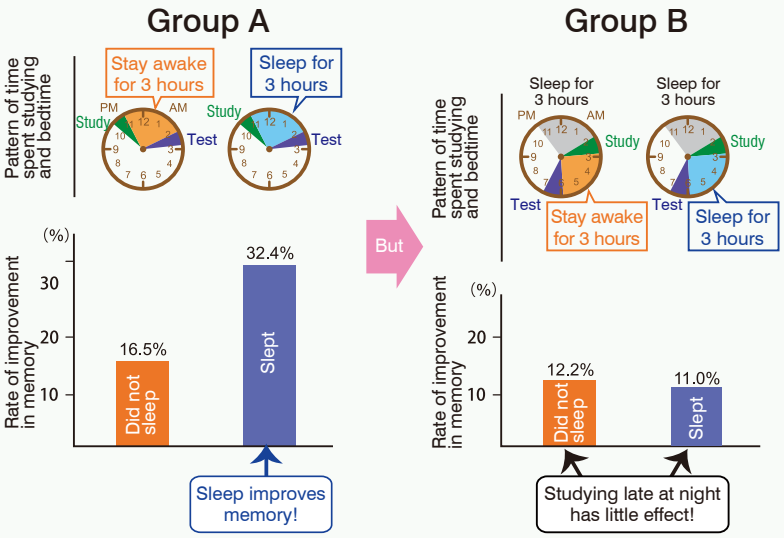
Column

●The trick to teaching children the importance of sleep

To deal with lack of sleep in children, providing a simple explanation of the relationship between school grades and sleep elicits a reaction not only from the parents, but from children too. The result is far more effective than any treatment.

Group A scored well on the test after only a short sleep (3 hours).

Group B also slept for the same amount of time, but staying up to study late at night meant that their test results did not improve.



Adapted from *Daikin no kangaeru omise* (The Daikin Thinking Shop)
https://www.daikin-labo.com/recent.php?r_id=626

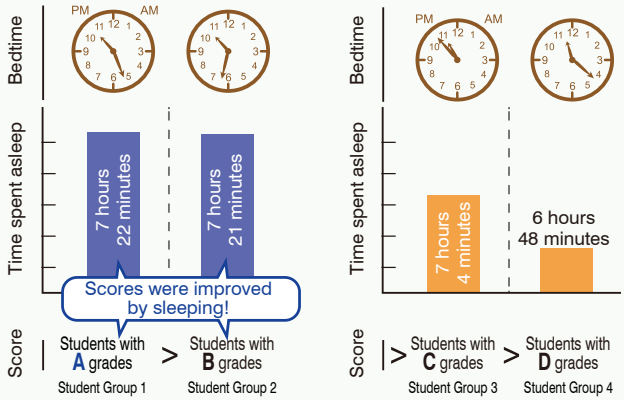
Human beings organize their memories during sleep. While we are sleeping, necessary experiences are stored in the memory and unnecessary ones are deleted, meaning that sleep is extremely important.

Going to bed after 11 p.m. resulted in lower test scores.

The best time to go to bed was by 10:30 p.m.

Ideally, turn the light out at 10 p.m.

Group A, which slept for 7 hours 22 minutes, had the best test scores.

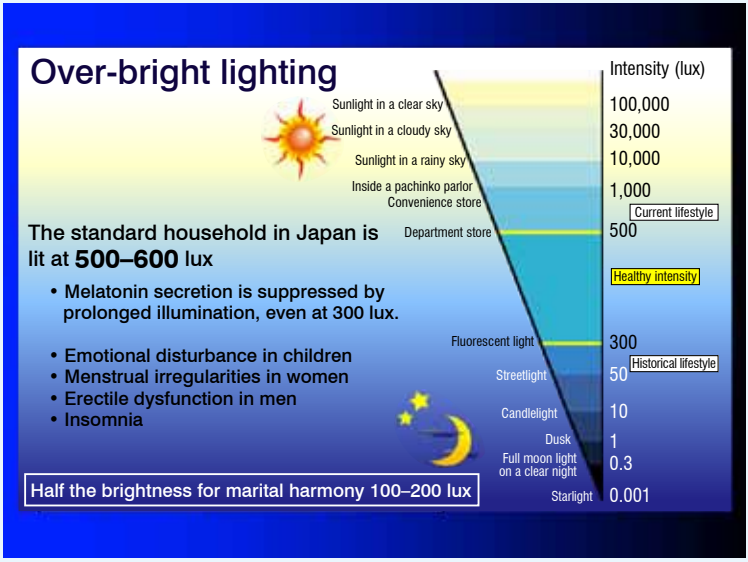


Adapted from *Daikin no kangaeru omise* (The Daikin Thinking Shop)
https://www.daikin-labo.com/recent.php?r_id=626

Source: Wolfson AR. & Carskadon MA. "Sleep schedules and Daytime Functioning in Adolescents" Child Development Vol. 69, No. 4, 875–887 (1998)

Children's rooms are frighteningly light

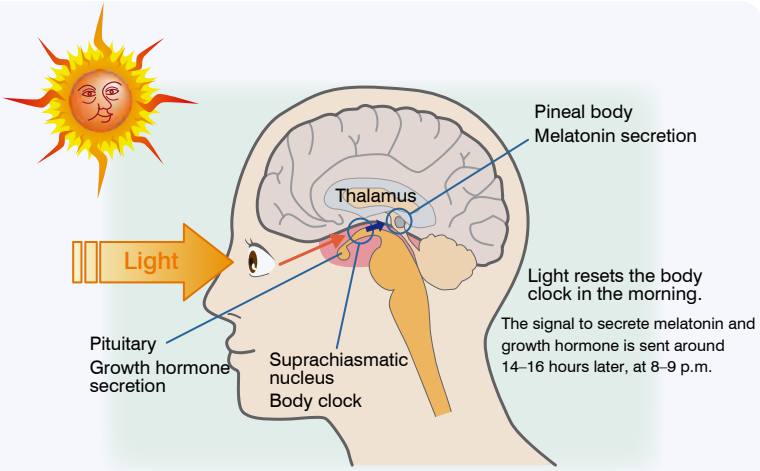
Something I have noticed is that many people with cephalic hypersensitivity syndrome are sensitive to light. Light intensity is measured in a unit called "lux." Before the era of fluorescent light, most households were lit at around 300 lux or below. Some time has now passed since fluorescent light fittings became popular, and in the intervening period, they have evolved. Today, thanks to these lights, our society is too brightly lit. The intensity of the light itself has increased. Moreover, many light fittings now use double bulbs. The standard household in Japan is now lit at 500–600 lux, meaning that children's rooms and dining rooms are now brighter than is actually necessary. Lights that are too bright are a chronic irritation to the brains of growing children. Their brains become tired, and they are at risk of developing emotional disturbance or cephalic hypersensitivity syndrome.



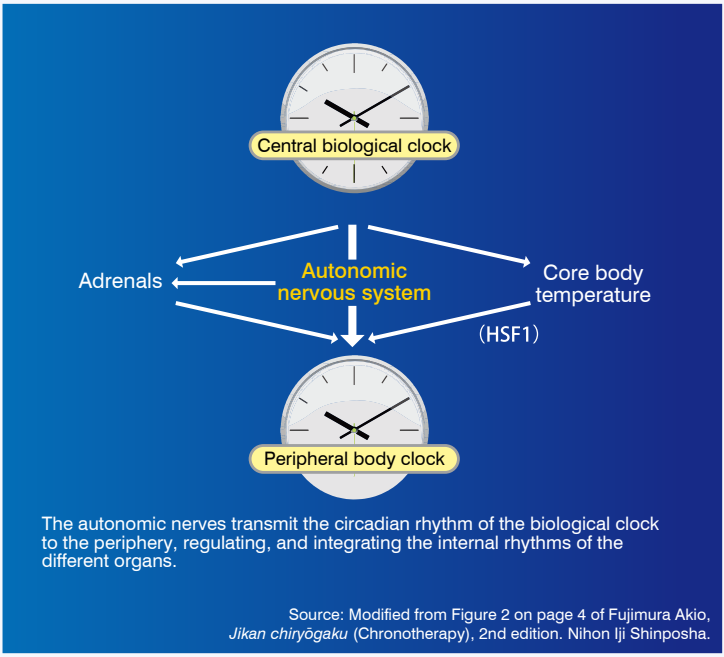
Bright lighting does not only affect children; it is also believed to cause menstrual irregularities in women, erectile dysfunction in men, and insomnia. Melatonin secretion is suppressed by prolonged exposure even at 300 lux. Around 300–500 lux is considered the appropriate level of household lighting. I have heard the happy news from one couple that lowering the lighting in the dining room to around 400 lux as a counterpoint to the kitchen and TV, and reducing it in the bedroom to indirect lighting at 100–200 lux, enabled them to resume their marital relations. I think there can be nothing worse than being exposed to bright, high-intensity light, paying expensive electricity bills, and putting up with children's irritability and a husband's impotence. The solution is incredibly simple. If you think I'm pulling your leg, try dimming the lights in your room and see what happens. You can use an illuminance meter to measure how bright your room is.

As a guideline, it should be under 500 lux. I have heard of children's bedrooms measuring 600–700 lux, and in extreme cases up to 800 or 900.

The Shibuya Longevity Health Foundation will carry test light levels and provide guidance on appropriate light levels on request.



The body clock commands the circadian variation in hormones



The autonomic nerves transmit the circadian rhythm of the biological clock to the periphery, regulating, and integrating the internal rhythms of the different organs.

Source: Modified from Figure 2 on page 4 of Fujimura Akio, *Jikan chiryōgaku* (Chronotherapy), 2nd edition. Nihon Iji Shinposha.

7 Restless Legs Syndrome (RLS)

Restless legs syndrome may sound like a somewhat unusual name, but it is actually a proper medical condition. When sufferers are resting or remaining still, their legs feel restless or irritated, and they have an irresistible urge to move them. They may also feel a variety of hot, painful, crawling, or bubbling sensations in addition to restlessness and irritation, and many sufferers say that the discomfort is completely indescribable.

In my medical interview form for restless legs, I am most interested in the answers to Questions 4 and 5: "Do you ever have a need to move around because of uncomfortable sensations?" and "Do these sensations improve when you move around?" Given that this is a "completely indescribable" condition, people deal with it in a very wide variety of ways, not just by shaking their legs around but by walking up and down the corridor or around the house even in the dead of night, sticking their legs outside the bedding even in midwinter to counter hot sensations, applying compresses or coolants to the soles of their feet or the backs of their calves, or having family members knead their feet for over an hour in some cases.

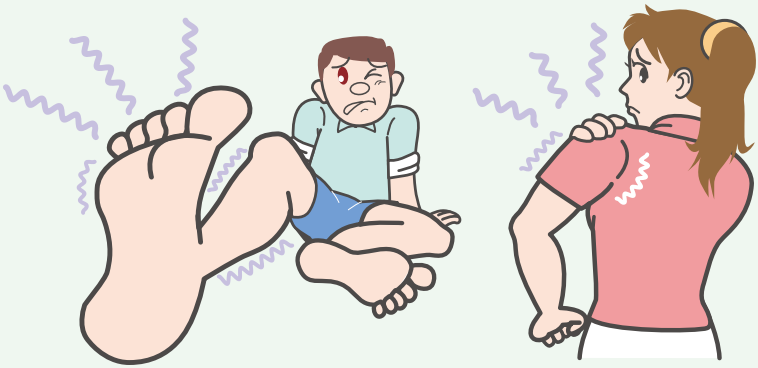
One characteristic of restless legs syndrome is that its symptoms appear while the sufferer is at rest, but older people or desk workers with low levels of activity also say that they appear during the day. An in-depth medical interview is necessary. Factors such as stress are associated with the exacerbation of symptoms, and it is also important to confirm the patient's background, including matters such as family structure and living environment.

The cause of restless legs syndrome is believed to be abnormal sensitivity of receptors for the brain hormone dopamine. Iron-deficiency anemia has also been cited as a cause, suggesting that there may be a relationship between iron metabolism and dopamine metabolism[21]. Restless legs syndrome is dramatically improved by a single medication, at just a low dose. This releases many people from their suffering, both in daily life and as a result of insomnia. What is required is the detection of restless legs syndrome via a careful medical interview, and its appropriate treatment.

When going to bed or while lying in bed, you have unbearably uncomfortable feelings of irritation or restlessness mainly in the feet, calves, or other parts of the leg that make it impossible to keep still. Shaking the leg around makes it feel better.

The 12 Pointers for Dealing with Sleep Disorders published by the Ministry of Health, Labour and Welfare also points out that "Caution is needed if you snore loudly or stop breathing, or if your legs twitch or feel restless during sleep," and this disorder can interfere with sleep and also affect daily life. Its exact cause is unknown, and some people worry about it without realizing that it is a disease, but in almost all cases it improves with the right treatment.

Although it is generally known as "restless legs syndrome," it can also affect areas other than the legs, with some patients complaining of uncomfortable symptoms in the arms and shoulders. At my hospital, we are provisionally terming this **"whole-body restless syndrome."** Sufferers complain of a wide variety of symptoms in addition to restlessness.

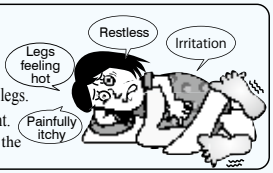


Oota Restless Legs Syndrome Severity Scale

What are "restless legs"?

- ☐ Your legs feel restless or irritated when you are resting or staying still.
- ☐ It feels so uncomfortable you have an unbearable urge to move your legs.
- ☐ The restlessness or irritation improves or disappears when you move your legs.
- ☐ The restlessness or irritation appears or worsens between evening and night.

*Restlessness and irritation are not restricted to the legs, but may occur in the arms or neck, or extend throughout the whole body.



▼Please circle the answer to each of the questions below that best applies to the state of the above symptoms during the past week.

1. **How severe were the uncomfortable sensations?**

4	Very uncomfortable	3	Uncomfortable	2	Somewhat uncomfortable	1	Slightly uncomfortable	0	Not at all

2. **How often did these sensations occur?**

4	Very frequently (6–7 days a week)	3	Frequently (4–5 days a week)	2	Sometimes (2–3 days a week)	1	Occasionally (once a week)	0	Never

3. **For how long did these sensations persist?**

4	A very long time (over 8 hours a day)	3	A long time (3-8 hours a day)	2	For some time (1–3 hours a day)	1	A short time (less than 1 hour a day)	0	Not at all

4. **Did you have the desire to move around because of these uncomfortable sensations?**

4	Very strongly	3	Strongly	2	Somewhat	1	Mildly	0	Not at all

5. **Did these sensations go away when you moved around?**

4	No improvement at all	3	A little improvement	2	About the same	1	Complete or almost complete improvement	0	No uncomfortable sensations

6. **How badly was your sleep impaired by these uncomfortable sensations?**

4	Very badly	3	Badly	2	Moderately	1	A little	0	No effect

7. **How bad was your tiredness or sleepiness during the day?**

4	Very bad	3	Bad	2	Moderate	1	Mild	0	None at all

8. **How badly was your daily life affected by these uncomfortable sensations?**
e.g., family life, housework, social activities, school, or work

4	Very badly	3	Badly	2	Moderately	1	A little	0	No effect

9. **How badly was your mood affected by these uncomfortable sensations?**
i.e., Did you become angry, depressed, sad, anxious, or irritated?

4	Very badly	3	Badly	2	Moderately	1	A little	0	No effect

10. **How severe do you think your restless legs syndrome is yourself?**

4	Very severe	3	Severe	2	Moderate	1	Mild	0	I don't have restless legs syndrome

Total	points

*For office use

Severity	Mild	Moderate	Severe	Very severe
	≤10 points	11–20 points	21–30 points	≥31 points

Name _____ Date _____

Produced with reference to the International Restless Legs Syndrome Study Group. Validation of the International Restless Legs Syndrome Study Group Rating Scale for restless legs syndrome. Sleep Med 2003;4(2):121–132.

8 Periodic Limb Movement Disorder (PLMD)

You should have slept well, but don't feel that you slept deeply, and feel sleepy during the day

This is a companion condition to restless legs syndrome. Periodic abnormal movements of the limbs occur repeatedly during sleep, causing waking and insomnia. These abnormal movements almost always occur in the legs and consist mainly of dorsiflexion of the big toe and ankle, and flexion of the knee for around 0.5–5 seconds at 20–60 second intervals. They are believed to occur in 1-4% of the population and become more common with age, reaching a prevalence of over 30% among those over 65 years [22]. In many cases, sufferers themselves are only aware of insomnia, and have no idea that their limbs are moving while they are asleep. They may see a doctor because their partner has been unexpectedly kicked during the night, or has noticed abnormal movements of their toes. Movements of the leg muscles can be assessed by means of all-night polysomnography, but this test is not covered by health insurance, and if family members are willing to cooperate, then interviews with them can provide a valuable source of information. Depending on the patient, it may be necessary to explain things carefully to them and carry out the test. These leg movements mainly occur during non-REM sleep, and if a patient is aware of spasms in their legs while they are awake then this by itself may be sufficient for diagnosis. Like restless legs syndrome, its etiology is also unknown, and the list of aggravating factors is also almost identical, including stress, alcohol, smoking, and iron-deficiency anemia. Depending on the patient's symptoms, the treatment for periodic limb movement disorder may comprise the antiepileptic drugs Rivotril (clonazepam) or Landsen (clonazepam) or the Parkinson's disease medications BI Sifrol (pramipexole hydrochloride) or Neodopaston (carbidopa/levodopa). Although these are fast-acting, long-term continued administration is required, and the minimum dose should therefore be prescribed.

Oota Periodic Leg Movements during Sleep (PLMS)/ Periodic Limb Movement Disorder (PLMD)

Medical Interview Form

	Question	Circle Yes or No
1)	Do you get sufficient sleep? From : to : _____ hours	Yes No
2)	Do you wake up feeling that you have slept well?	Yes No
3)	Do you wake up during the night? (about times)	Yes No
4)	When you wake up, is your comforter out of place or thrown off?	Yes No
5)	Are you ever aware of your arms or legs moving suddenly during sleep?	Yes No
6)	Do you ever hit out with your elbow during sleep?	Yes No
7)	Do you ever make kicking movements with your legs during sleep?	Yes No
8)	Have your family ever said anything about movements of your arms or legs during sleep?	Yes No

If your family has said anything about this, please specify it here.

Kosuke Oota

The mysterious relationship between restless legs syndrome and periodic limb movement disorder

I said above that restless legs syndrome and periodic limb movement disorder (also known as "periodic leg movements during sleep") are companion disorders. The legs are so restless that it is impossible to sleep, or their periodic movement prevents deep sleep. In both cases, the major worry for patients is insomnia. These are truly mysterious conditions. A decrease in the brain hormone dopamine is believed to be one cause.

Restless legs syndrome is believed to occur when neurotransmission is impeded by a decrease in dopamine levels and the wrong signals are sent to the brain, causing an uncomfortable restless sensation. BI Sifrol (pramipexole hydrochloride) is an effective treatment for moderate to severe cases. This is a medication used to treat Parkinson's disease that acts to increase dopamine levels. Mild cases can be effectively treated with Rivotril (clonazepam) or Gabapen (gabapentin). Around 70% of patients with restless legs syndrome also experience periodic leg movements during sleep [21]. In mild to moderate cases, this can be treated with Rivotril (clonazepam), and in severe cases, BI Sifrol (pramipexole hydrochloride) is effective. Despite the fact that these two conditions have the same cause and are treated with the same medications, their symptoms are completely different. They also differ in their time of onset. Restless legs occur before sleep when the sufferer is still awake, whereas periodic leg movements start once the sufferer has gone to sleep. They are an intriguing combination.

Restless legs syndrome is surprisingly little known, and almost no one has ever heard of periodic limb movement disorder. Even many doctors have no idea of its existence. Periodic limb movement disorder is also known as PLMS, which may stand for either "periodic limb movement in sleep" or "periodic limb movement syndrome." The terminology has yet to be made consistent. The Japanese translation of "periodic limb movement disorder" is somewhat pretentious, so when explaining it to patients, I use "periodic leg movements during sleep" as it is simpler to understand. Like restless legs, it may also occur in the arms, but is overwhelmingly more frequent in the legs. I have yet to see any diagnostic guidelines or dedicated medical interview form for the diagnosis of periodic limb movement disorder. Although the sleep disorder medical interview

form that I use to diagnose insomnia does come in handy, it is difficult to use for the diagnosis of periodic leg movements during sleep. At present, it can only be diagnosed by exclusion. When no other cause of insomnia can be identified, rather than simply filing it away as psychophysiological insomnia (see note), which is one type of physiological insomnia due to focusing too hard on going to sleep, it is important to suspect the possibility of periodic leg movements. If the patient has an understanding partner, their husband or wife can be asked to monitor their legs during sleep. A wide range of useful information can be gained in this way, ranging from snoring and rolling over to bruxism, sleep talking, arm and leg movements, and periodic limb movements. When there is no means of obtaining this information, it is important that patients be asked to stop taking any sleeping medication that has long ceased to work and be given a prescription for a low dose of Rivotril (clonazepam) or Landsen (clonazepam), so the effect can be observed. This may be highly effective in reducing the feeling of not having slept enough on waking up, the daytime sleepiness that is characteristic of periodic leg movements, and in restoring motivation.

Mr. Restless and Mr. Periodic

Mr. Restless
Restless Legs Syndrome

Mr. Periodic
Periodic Limb Movement Disorder

Symptoms	Mainly restlessness in the legs	Periodic sudden movements of the big toe, ankle, and other joints
Time of onset	While awake, before going to sleep	After going to sleep
Cause	Lack of the neurotransmitter dopamine, etc.	
Treatment	Antiepileptic drugs, Parkinson's disease medication	

A polysomnography test provides a score of the severity of periodic leg movements by showing how often they occur in a set time period. However, as it is not covered by health insurance for periodic leg movements during sleep, it is very rarely used in practice. I would like to emphasize that periodic leg movements during sleep should always be suspected in the case of insomnia of unknown origin.

As an aside, decreased dopamine production can be caused by a lack of iron in the central nervous system, meaning that iron-deficiency anemia may also be involved. I occasionally encounter anemic patients in my own clinics. It may be necessary to consider prescribing iron to some patients.

(Note) Psychophysiological insomnia: Chronic insomnia caused by becoming more tensed up the more you try and sleep, originally triggered by the experience of not having been able to go to sleep easily. This is a psychological form of insomnia that does not involve any other medical issue.

9 Allodynia unrelated to migraine

Doctors involved in outpatient care often have the impression that allodynia is a somewhat incomprehensible condition, but in fact, it is not uncommonly encountered in clinics. The pain of allodynia comprises uncomfortable numbness and painful sensations that are difficult to put into words. Patients may develop a headache merely by touching their hair, feel strange numbness or pain around their eyes, or have numbness only in their arms, and in many cases, they themselves are confused by their symptoms and unable to describe them adequately. It is easy for busy outpatient doctors to regard them as problem patients.

As I mentioned earlier, allodynia is frequently associated with migraine. In this case, it can be cured if properly diagnosed. For allodynia that is not associated with migraine, however, the situation is more complicated. For this reason, outpatient doctors tend to give it a wide berth.

Long-term pain following nerve damage due to a fracture or injury is termed "complex regional pain syndrome" (CRPS) by the International Association for

the Study of Pain, and its major symptoms include allodynia, skin discoloration, dyshidrosis, edema, restricted joint range of motion, and muscle atrophy. The Ministry of Health, Labour and Welfare has issued a Japanese version of the CRPS assessment index [23].

Complex regional pain syndrome includes causalgia, which is prolonged burning pain resulting from nerve damage due to a specific type of injury, namely a bullet wound. In shoulder-hand syndrome, intense pain and swelling occur in the fingers on the paralyzed side around 1 month after a stroke. If the edema extends throughout the entire arm and the paralyzed arm is left to hang down, it may cause subluxation or dislocation of the shoulder joint and damage to the ligaments, with patients complaining of a variety of types of pain from the shoulder to the fingers. Shoulder-hand syndrome is a progressive, intractable condition. Repeated, violent pain is treated with tricyclic antidepressants or antiepileptic drugs. Patients who do not respond to these may undergo spinal cord stimulation therapy with implantation of an epidural stimulus electrode.

Central nervous pain (thalamic pain) appears as abnormal numbness and pain in the arms and legs of the paralyzed side after a stroke. These are a unique form of discomfort and pain that are nothing like the numbness and pain experienced by healthy people. They are the result of the nerves that transmit sensation from the limbs and trunk to the brain being cut as the result of a stroke (normally a brain hemorrhage). The lack of transmission of normal sensations rattles the brain, causing it to become overexcited and hypersensitive. The sensitized brain then creates its own sensations of discomfort and pain. It is treated with tricyclic antidepressants or antiepileptics. The deep brain stimulation therapy used to treat Parkinson's disease may be used in intractable cases.

Allodynia may also appear as postoperative pain syndrome following thoracic or abdominal surgery. Many such cases of non-migraine-associated allodynia are intractable, and as the underlying conditions are also complicated, the reality is that outpatient doctors tend to steer clear of them.

Column

Pain transmission speeds

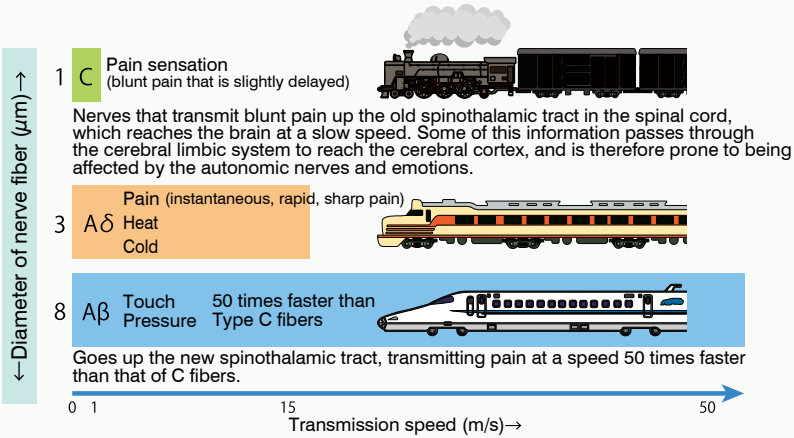
There are three types of nerve fibers that are responsible for the neurotransmission of skin sensations: Type A, Type B, and Type C fibers. Pain is mainly transmitted by Type Aδ and Type C fibers. Type Aβ fibers, which transmit sensations of touch and pressure, are also believed to be involved in allodynia of the sort in which just touching the hair brings on a headache, or when the legs prickle, feel hot, or tingle after going to bed.

In terms of the speed at which a pain stimulus is transmitted from the periphery, it is clear from the figure that Type C fibers, which simply transmit pain, have the slowest transmission speed. A comparison with trains makes this easy to understand. In the figure showing the thickness of nerves and transmission speed, the thickest of these three types of fibers with the fastest speed is Type Aβ, which is like a bullet train. Type Aδ, the next fastest, is like an express train, whereas Type C fibers are like the local train that stops at every station. Compared with the fibers that transmit touch and pressure sensations, those that transmit pain have

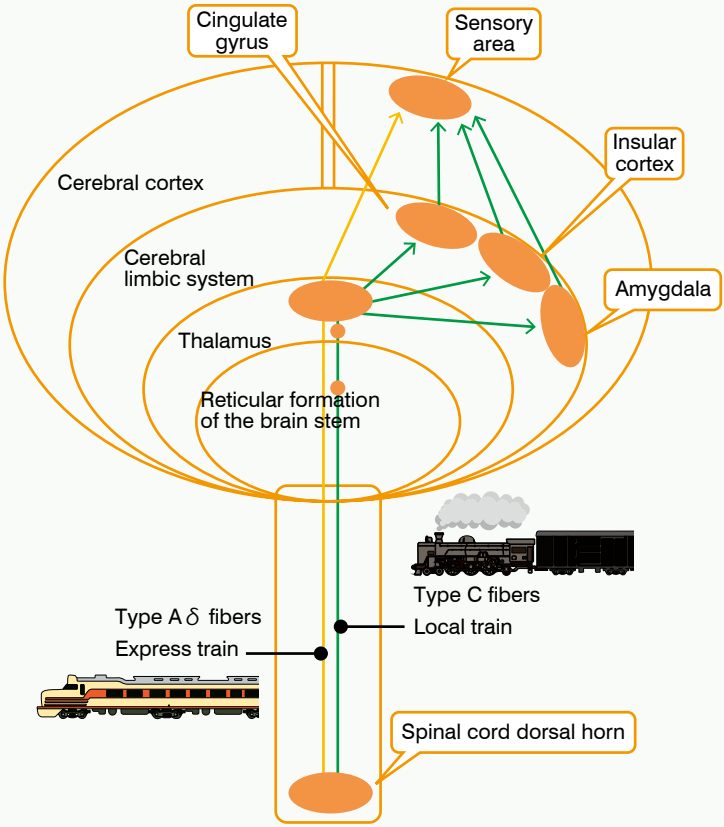
Types of nerve fibers and their roles

Type	Diameter (μm)	Myelinated	Transmission speed (m/s)	Function	Role
Aα	15	Yes	100	Motor afferent	Transmission of information about muscle contraction and relaxation, movement control of skeletal muscles
Aβ	8	Yes	50	Afferent	Transmission of information about skin touch and pressure sensation
Aγ	5	Yes	20	Motor	Transmission of information to muscle spindles
Aδ	3	Yes	15	Afferent	Rapid transmission of pain, hot, and cold sensations
B	3	Yes	7	Autonomic	Slow transmission of pain and itchiness. Autonomic nerve preganglionic fibers
C	1	No	1	Afferent autonomic	Autonomic nerve postganglionic fibers

an extremely slow transmission speed. Why is pain transmitted so slowly even though it is an important protective response? There must be some reason. These three different types of nerve fibers have different pathways leading to the central nervous system (illustrated in the route map). Type Aδ fibers take an almost direct route, passing through the thalamus to the sensory area. Type C fibers undergo various modifications before they reach the hypothalamus and reach different locations such as the cingulate gyrus, insular cortex, and amygdala. Type Aδ fibers are like the express train from Fukuyama that goes directly to Tokyo, stopping only at the major stations of Osaka, Kyoto, and Nagoya, whereas Type C fibers are like a local train that offloads freight at Okayama and takes it on at Kobe, as well as splitting into different sections going to Toyama, Nagano, and Tokyo while heading slowly to its destination. They are easily affected by what happens at each station, and the content of what they transmit is prone to being modified. This comparison of Type C fibers to a local train actually reflects the body's clever defense mechanisms.

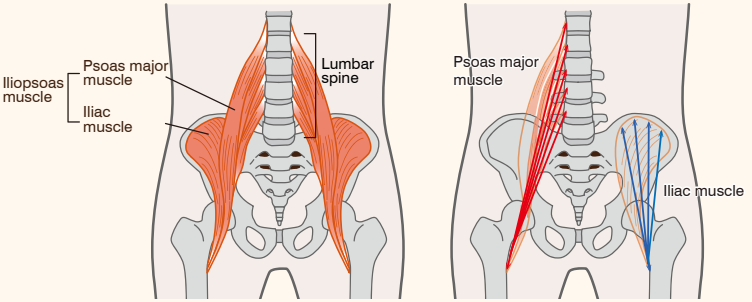


Column


Cingulate gyrus
Sensory area
Insular cortex
Cerebral cortex
Cerebral limbic system
Amygdala
Thalamus
Reticular formation of the brain stem
Type C fibers
Local train
Type A δ fibers
Express train
Spinal cord dorsal horn

10 Chronic lower back pain: Muscle stiffness due to static muscle load

Why does lower back pain become chronic? This is one of the most common forms of chronic pain. Often seen in people whose job means they spend long periods sitting or standing, it is the result of static muscle load generated by maintaining the same posture for long periods. When an unnatural posture becomes habitual, muscle stiffness develops into chronic pain. Sarcopenia (disuse atrophy) of the muscles that support the lower back due to lack of exercise is another cause of chronic lower back pain.



The main muscle that causes lower back pain is the iliopsoas muscle, which supports the lumbar spine and the pelvis. It is essential not to rest this muscle just because it is painful, or it will become stiff and hard. There is no need, however, to force yourself to engage in painful exercises or movements. The iliopsoas muscle is actually a large muscle group that is attached to the lumbar spine, pelvis, and femur, and walking is therefore the first step in treatment. The greatest risk factor for lower back pain is maintaining the same posture for long periods at work. It therefore affects more people who do not perform sufficient exercise or who don't walk because they dislike exercise. If you can find a moment to take some time for yourself, go for a walk. The anatomical diagram will give you a good idea of how the iliopsoas muscle supports the lumbar spine. Just 30 minutes of walking a day is highly effective for preventing lower back pain.

People who suffer from lower back pain often also complain of other symptoms such as headache, insomnia, and constipation, and require guidance on how to balance the rhythm of their daily lives.

11 Myofascial pain syndrome

Myofascial pain syndrome is a transformed form of the familiar pain generated by muscle stiffness. Many patients complain of pain in several different places. Palpation reveals localized taut bands in the muscles. Pressing on these hard with a finger causes pain to appear in a different area. This is known as "referred pain." Muscle stiffness and pain may range from discomfort to intense pain that restricts movement and interferes with daily life, but is a completely standard condition. In most cases, it spontaneously improves and disappears within a few days to 1–2 weeks. If it becomes aggravated, however, it can develop into myofascial pain syndrome. This becomes chronic in many cases, and in recent years the opinion has been expressed that it should more appropriately be known as chronic myofascial pain (CMP).

What causes the aggravation of muscle pain is either repeated dynamic or static muscle load or chronic action on the muscles. Repeated or continuous muscle contraction load disturbs the blood flow to the muscle involved. If this interference in blood flow continues, pain-producing substances such as prostaglandins and bradykinins are produced. This causes further muscle

contraction and spasms, damaging the muscle fibers and causing fibromyalgia. If fibromyalgia is not treated or dealt with properly, the resulting chronic pain, numbness, and aching can develop into cephalic hypersensitivity syndrome and indescribably uncomfortable and intense pain, allodynia. It is my conjecture that this mechanism may underlie the alteration and progression of myofascial pain syndrome into fibromyalgia. This pain does not show up as abnormalities in blood tests or on X-rays, CT, MRI, or other forms of diagnostic imaging.

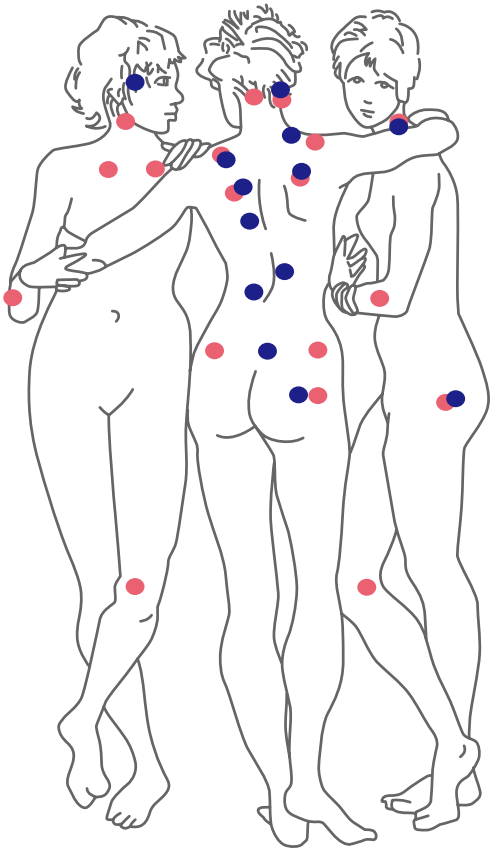
As reference, I am reproducing below the diagnostic criteria for myofascial pain syndrome published in *Myofascial Pain and Dysfunction: The Trigger Point Manual* (2nd Edition) by David Simons in 1999 [24].

- Palpable muscles contain palpable taut bands.
- The taut bands contain tender points (sites) where a sharp pain is felt.
- When a tender point is pressed, the patient feels that the current pain, including surrounding areas, comes from the tender point.
- Physical range of motion is restricted because of this pain.

Conditions such as migraine, stiff shoulders, dizziness / vertigo, and restless legs are often improved by improvements in daily habits and thinking and night therapy. If stubborn muscle stiffness and tender points are present, however, patients will not be cured by the treatment algorithm for cephalic hypersensitivity syndrome alone. If the patient meets the criteria set out in the diagnostic guidelines for the various rheumatic diseases, they may be referred to a specialist, but almost all those who come to me seeking treatment exhibit few objective medical signs despite complaining of intense pain.

Tender points

- Fibromyalgia
- Myofascial pain syndrome



The Three Graces, daughters of Zeus

In addition to myofascial pain syndrome and fibromyalgia, other disorders in which patients complain of pain throughout the body in the absence of any obvious abnormal test results or lesions and in which an inflammatory reaction eventually becomes evident as they progress include polymyalgia rheumatica syndrome and spondylarthritis (ankylosing spondylarthritis and serum-negative spondylarthritis). These disorders have many subtypes, and at the stage when a patient initially presents with a chronic illness syndrome, they are extremely difficult to distinguish. In all cases, symptomatic treatment takes center stage: the first-choice initial treatment is non-steroidal analgesics, and during long-term treatment with these, cephalic hypersensitivity syndrome may develop separately from the underlying condition. If these conditions progress and become severe, the resulting emotional disturbance and mental stress excite the sympathetic nerves, and the pain fibers in the muscles containing the taut bands also become excited, resulting in a vicious cycle of muscle contraction, reduced blood flow, spasms, and muscle fiber damage. It is worth trying all the different symptomatic treatments available, from nerve block to acupuncture massage.

I personally use *Tsumujikaze-kun* magnetic acupuncture needles to provide stimulation around the nails and cranial area. These magnetic needles are in the form of a ball pen and can be carried in a suit pocket for immediate use as and when required. When timed to coincide with breathing, this can also be used as breathing therapy.

I originally trained as an anesthesiologist, and used to administer nerve block as an outpatient treatment. In recent years, tender points and trigger points (points that induce pain when touched) have become the focus of attention in the clinical treatment of the diffuse pain seen in conditions such as fibromyalgia, polyenthesitis, and myofascial pain syndrome. In many cases, much remains unknown concerning the mechanism of onset of the underlying condition, and standard treatments have yet to be established. I had already focused on trigger points well before these disease concepts had become widely known in clinical institutions in Japan, and used nerve block at these trigger points in addition to medication in cases of stubborn pain, particularly persistent pain associated with stiffness, when it was clear that they could not be resolved solely with drug treatment.

Trigger points are a strange lot. Many myofascial pain syndrome and fibromyalgia trigger points seem to be located at the same sites as the acupuncture points used in oriental medicine. Actual painful points cannot be identified on CT or ultrasound, or described in such precise term as "X cm above the knee." You have to work out approximate locations from the patient's description of "somewhere around there" and episodes of pain, and search for the actual trigger points from the patient's reaction to the pain generated by pressing them with a finger. At that time, I would carry out nerve block of the trigger points I had identified with 2 cc of a 0.5% solution, the weakest available, of the local anesthetic xylocaine administered with a 27G needle, the finest available at that time. The combination of drug treatment and nerve block at tender points, with the addition of nerve block of the cervical sympathetic nerve ganglion (stellate ganglion) (see note) for stubborn pain, was sufficient to release patients from persistent pain. It is important in treatment to deal with the symptoms properly from the beginning. It is a good piece of clinical wisdom to provide the right initial treatment, thus preventing the pain from subsequently being transformed in complex ways.

The syringe I was using to carry out nerve block injections

(Note) Stellate ganglion block: The stellate ganglion in the neck gains its name from the fact that it is a star-shaped concentration of autonomic nerves, mainly sympathetic nerves. Nerve block of the sympathetic nerve ganglia in the neck and lower back is used to treat chronic pain.
Nerve block utilizes a weak local anesthetic or laser irradiation. The stellate ganglion controls the sympathetic nerves in the head, face, neck, shoulders, arms, lungs, and heart.

Column

●Acupuncture points and nerve block

Acupuncture points are said to be transit points for the meridians that form the pathways through which spirit flows. Many of them are located on tendons, attachments between tendons and bones, in the hollows between two muscles, and above nerves and blood vessels. The Iceman, a 5,300-year-old mummy discovered in an Alpine glacier, was reported to have tattoo-like marks at the sites of acupuncture points, indicating that he may have suffered from backache. The art of diagnosis and treatment on the basis of meridians and acupuncture points is said to have emerged a little more than 2000 years ago in China. If it was already known when the Iceman was still alive, the theory that ancient China was the birthplace of acupuncture treatment becomes a little shaky, and it may be inferred to have existed since the dawn of humanity in the Stone Age. The WHO produced a list of 361 standard acupuncture points in 2006. Today, acupuncture points are designated in both Chinese/Japanese characters and the international alphabetic notation. From the perspective of the venerable history of acupuncture treatment dating back to prehistoric times, the nerve block treatment practiced in pain clinics is in its mere youth, but one that may become the treatment of the future.

12 Chronic constipation: The retention of toxins in the body

As already described in Chapter 1, patients with a chronic illness syndrome often also suffer from chronic constipation. Various forms of stress can disrupt the autonomic nerves, creating susceptibility to constipation, and this has a negative effect on the homeostasis of the entire body, creating a vicious cycle. Chronic constipation cannot be cured unless this is resolved at the source. As I described earlier, most of the production of serotonin, the mother of all hormones that is important in the treatment and prevention of cephalic hypersensitivity syndrome, takes place in the intestines. Balancing the intestinal environment also helps strengthen immunity. To put it the other way around, cephalic hypersensitivity syndrome and chronic constipation tend to occur in combination with each other, and must thus also be treated at the same time. Among the three arrows of my treatment algorithm for cephalic hypersensitivity syndrome, the "four-wheel drive" of sleep, exercise, bowel function, and diet is particularly important for the treatment of chronic constipation.

Dealing with chronic constipation: The miraculous power of enemas

I recommend the following three-step process for dealing with stubborn chronic constipation.

(1) Fluid intake, magnesium oxide, and laxatives

The first step is to soften the stool inside the bowel to the point at which it can be expelled. If the bowel is packed with hard stool, it is no use administering an enema or using laxatives, as these will just make things more uncomfortable. The first point is to drink plenty of fluids. Avoid soft drinks, sports drinks, coffee, and tea, and instead drink water or non-caffeinated teas. Magnesium oxide increases the water content of stool, thereby softening it. Then, for the second step, using a laxative at this point makes bowel movements easier to pass. Unless the patient also makes an effort to start to review his or her diet, get enough sleep, and engage in the right sort of rhythmic movement, however, this will not resolve the root of the problem.

(2) The miraculous power of enemas

In most cases, the two steps described above are enough to improve

constipation, but for cases of intractable constipation that do not respond to this treatment I recommend warm-water enemas. This is the third step of the process. As described above, enemas are not effective on their own. As I mentioned in Chapter 1, coffee enemas are an important method of treatment in Gerson therapy alongside dietary therapy. Here, rather than the "medical" glycerin enema, I will describe how to administer an enema with warm water, which is non-irritating and can easily be carried out on an everyday basis. As an aside, the facilitators of the Miss Japan competition are among those promoting health through enemas. The condition for remaining beautiful over the years is not external appearance but rather to have beautiful intestines, autonomic nerves, and serotonin.

• Water (warm-water) enema

Water enemas have a long history. The Essene Gospel of Peace from the Dead Sea Scrolls, written 2000 years ago, is said to contain a detailed description of an enema. The excerpt below is quoted in The Gerson Therapy (definitive edition).

"I tell you truly, the angel of water shall cast out of your body all uncleannesses which defiled it without and within. And all unclean and evil-smelling things shall flow out of you, even as the uncleannesses of garments washed in water flow away and are lost in the stream of the river. I tell you truly, holy is the angel of water who cleanses all that is unclean and makes all evil-smelling things of a sweet odor....

Think not that it is sufficient that the angel of water embrace you outwards only. I tell you truly, the uncleanness within is greater by much than the uncleanness without. And he who cleanses himself without, but within remains unclean, is like to tombs that outwards are painted fair, but are within full of all manner of horrible uncleannesses and abominations.

So I tell you truly, suffer the angel of water to baptize you also within, that you may become free from all your past sins, and that within likewise you may become as pure as the river's foam sporting in the sunlight ....

Seek, therefore, a large trailing gourd, having a stalk the length of a man; take out its inwards and fill it with water from the river which the sun has warmed. Hang it upon the branch of a tree, and kneel upon the ground before the angel of water, and suffer the end of the stalk of the trailing gourd to enter your hinder parts, that the water may flow through all your bowels.

Afterwards, rest kneeling on the ground before the angel of water and pray to the living God that he will forgive you all of your past sins, and pray to the angel of water that he will free your body from every uncleanness and disease.

Then let the water run out from your body, that it may carry away from within it all the unclean and evil-smelling things of Satan. And you shall see with your eyes and smell with your nose all the abominations and uncleannesses which defiled the temple of your body; even all the sins which abode in your body, tormenting you with all manner of pains. I tell you truly, baptism with water frees you from all of these. Renew your baptizing with water on every day of your fast, till the day when you see that the water which flows out of you is as pure as the river's foam. Then betake your body to the coursing river, and there in the arms of the angel of water render thanks to the living God that he has freed you from your sins. And this holy baptizing by the angel of water is: Rebirth unto the new life." [25]

It is astonishing that even in ancient times people were aware of enemas as a way of becoming healthy. Of course, I do not recommend that you try and follow this technique word-for-word today. Fasting and bowel irrigation are ways of staying healthy that have been popular for thousands of years, and even more surprisingly, they have been known not only as ways of physically expelling unclean substances but also as means of achieving a calm mental state.

A wide variety of types of enema set are available on the market, but rather than high pressure enemas, one that shoots the water into you from high up in a single go, choose one that lets it flow in gently.

- **Coffee enema (chamomile enema, vegetable juice enema)**

In simple terms, coffee enemas detoxify the liver through the action of caffeine and palmitic acid salts. Physiological experiments have shown that this effect cannot be obtained by drinking it. Coffee enemas were accidentally discovered during the First World War, when anesthetics were unobtainable; a nurse poured the remains of a doctor's coffee into the warm water for an enema being administered to ease the pain of a wounded soldier, and found that it had a stronger analgesic effect. Gerson took this technique and incorporated

it into Gerson therapy, and since then, further studies have led to the present technique.

The action of palmitic acid salts in the rectum stimulates the visceral nervous system, encouraging intestinal peristalsis. It also promotes the secretion of bile, which has a detoxifying effect, enhancing the various detoxification functions that are performed within the liver. As a result of these actions, this method is effective in resolving constipation, providing analgesia and sedation, and improving the internal environment of the bowel. The procedure is described in detail in books on Gerson therapy.

In Gerson therapy, other recommended variations for fluids to be used instead of coffee, depending on the patient's state of health, include chamomile tea, coffee diluted with chamomile tea, and vegetable juice (with the fiber sieved out)[25].

(3) Repeated juice fasts lasting 3–5 days

Some patients with cephalic hypersensitivity syndrome have suffered from constipation for years and have become constitutionally prone to it. Long-drawn-out constipation is very difficult to resolve by three-step process alone. Even if they understand the importance of the four-wheel-drive lifestyle, they may not be able to put it into practice in their own lives. In this case, what I recommend is juice fasting. By "juice," I don't mean the cans or bottles sold in the shops, but fresh, unsalted fruit or vegetable juice. Using only fruit because of the taste is not a good idea. Combine carrots and green vegetables with fruit such as apples and oranges, and drink 1–2 liters a day. Drink a total of at least 2 liters of fluid per day. For people who find it impossible to make fresh juice, replacing it with commercially available (unsalted) vegetable juice is better than nothing. Carry on with this regimen for 3–5 days. After this, spend another few days eating easily digestible foods such as rice porridge and oatmeal before returning to a normal diet. Keep repeating this cycle.

13 Chronic fatigue: The accumulation of toxins in the mind

Fatigue is a red light to protect the body

Fatigue is a commonplace experience in daily life: "I'm tired because I haven't played tennis in such a long time," or "I'm tired after dealing with a difficult customer." Normally, tiredness is dissipated after a rest, a break, or sleep. This is what is known as "physiological fatigue." Normal tiredness is a temporary decrease in effectiveness when either body or mind is under strain, and it returns to normal after resting. Ordinarily, the sort of physical tiredness caused by playing tennis and the sort of mental tiredness caused by dealing with a difficult customer are regarded as different things, but the mechanism of fatigue is far from simple, and today it is believed that there is a complex interrelationship between muscle fatigue (peripheral fatigue) and brain fatigue (central fatigue).

Physical tiredness is mainly muscle fatigue. In this state, muscles no longer contract easily as a result of continued use, the energy source (glycogen) required for movement has been used up, and lactic acid levels have increased. In recent years, however, a theory has been gaining traction in which lactic acid is necessary for recovery from fatigue, and that the actual cause is a disturbance of the balance between potassium and sodium in muscle cells. If potassium leaks out of cells, the extracellular positive charge increases, causing muscle contraction, and if this continues to occur, potassium resorption will not happen in time, making it no longer possible for the muscle to contract[26]. This is the state of muscle fatigue. Recovery requires allowing the muscles to cool down and then relaxing the body by soaking in warm water or something similar, as well as taking in sufficient nutrition and rest.

Mental tiredness is an emotional state in which a person doesn't feel like doing anything and feels irritated, and is a form of tiredness induced by circumstances such as concentrating on a detailed task, going to a lot of trouble for someone, or feeling intense anxiety. The brain hormones serotonin, dopamine, and noradrenaline, which are part of monoamine neurotransmitter systems, are believed to be involved. However, the details are as yet not well understood. Good-quality sleep is essential for recovery, to calm down the excited brain and allow it to rest.

Physical and mental tiredness are not two different things, but are believed to happen together. For example, the level of tiredness differs depending on psychological state. If you play tennis because you enjoy it, both how tired you feel and your subsequent recovery will be different from if you had been reluctant to play. And when dealing with a difficult customer, the muscles throughout your body will unconsciously clench, unlike times when you are talking to a good friend. In this way, fatigue is one of the mechanisms whereby the motor nerves and autonomic nerves act in a balanced way to preserve the body in its "normal" state. Like fever and pain, "fatigue" is an important danger signal that helps to protect our bodies.

Cephalic hypersensitivity syndrome and chronic fatigue

Normal tiredness dissipates after rest, but if it is not possible to obtain the rest necessary for recovery and a situation of intense mental stress continues, fatigue accumulates and becomes chronic, meaning that a short break is no longer sufficient for recovery. This state is known as chronic fatigue, and in Japan, approximately 30% of workers are believed to suffer from it. Chronic fatigue that continues for several months or more without an identifiable cause can be thought of as a sign that cephalic hypersensitivity has developed as a result of the danger signal of fatigue arriving too strongly in the brain over a long period. As I mentioned earlier, there is a complex interrelationship between physical tiredness and mental tiredness. Both cause muscle clenching and stiffness as a result of impaired blood flow if the same stress continues for a long period. This appears in the form of symptoms such as stiff shoulders, headache, and lower back pain. I earlier described how normal tiredness, like pain, does not become a pathological condition if it is dealt with properly before it becomes too bad, but if it is treated improperly, for example by the overuse of painkillers or nutritional drinks, a vicious cycle can develop, with the result being cephalic hypersensitivity syndrome. The symptoms of cephalic hypersensitivity syndrome induced in this way by chronic fatigue can mostly be reversed by cautiously discontinuing drugs that have been overused, getting away from severely stressful situations, working on improving thinking, leading a balanced lifestyle with a good rhythm of eating, bowel evacuation, and sleep, and calming down the hypersensitized reactions of the brain. The Japanese Society of Fatigue Science has proposed

using the term "idiopathic chronic fatigue" to describe prolonged fatigue of unknown origin that does not meet the diagnostic criteria for chronic fatigue syndrome (described below), and some of those cases of idiopathic chronic fatigue may include cephalic hypersensitivity syndrome which have been triggered by chronic fatigue.

14 Disorders that are difficult to distinguish from cephalic hypersensitivity syndrome

There are some types of chronic illness syndrome that appear very similar to cephalic hypersensitivity syndrome, but that do not respond to treatment for the latter. In my view, although in these disorders some symptoms are fueled by cephalic hypersensitivity syndrome, the nature of the underlying disease must have a different pathology from that of cephalic hypersensitivity syndrome. There are no established methods of treatment for any of these conditions, but it is worth trying out Gerson therapy, not only the dietary therapy but also coffee enemas, as this is effective in treating degenerative conditions.

Fibromyalgia (FM)

It used to be that fibromyalgia was mainly treated in departments of rheumatology. Attitudes toward fibromyalgia have recently changed markedly, however, with an increasing tendency to involve specialists in other areas, such as neurology, psychosomatic medicine, and psychiatry in its care. In fibromyalgia, pain similar to muscle stiffness is evident at multiple locations (18 sites) throughout the body (see Page 198). It usually appears at the back of the head and in the neck, shoulders, and chest, with tender points also seen in the lower back and limb joints. Patients complain that the pain is severe enough to interfere with daily life, and in many cases, this pain cannot be left untreated. It is important to take account of concomitant conditions, age, and sex.

The appropriate treatment for fibromyalgia has yet to be discovered. It is necessary to determine whether or not spondylarthritis and other rheumatic disorders, as well as conditions that resemble them, such as polyenthesitis, are

also present. A detailed medical interview prior to examination is therefore essential.

Antidepressants and antiepileptics such as Tryptanol (amitriptyline), Depakene (sodium valproate), Gabapen (gabapentin), and Topina (topiramate) may be effective treatments for fibromyalgia in some cases. Lyrica (pregabalin) was approved for the treatment of fibromyalgia in June 2012. However, a survey of drug package inserts and conference presentations reveals that the dose of Lyrica (pregabalin) is 150–450 mg/day, taken twice a day, and at that dose, the incidence of side effects such as dizziness as well as drowsiness is high. There is a tendency to increase the dose in order to alleviate the pain. Lyrica (pregabalin) alone is ineffective, and as over 30% of patients also have a psychiatric disorder, many of them are already taking psychotropic drugs, meaning that they will be taking multiple medications.

Juvenile fibromyalgia (JFM) has been on the increase in recent years [27]. Treatment should start by reviewing patients' living environments and by trying non-drug therapies. Antidepressants and antiepileptics should not be carelessly prescribed. Fibromyalgia is more common in women. One factor that may underlie the increasing youth of patients and that should not be overlooked is stress arising from the mother-daughter relationship. In any case, fibromyalgia is difficult to diagnose and treat in a single department, and is a disorder that should be treated by a highly experienced doctor with wide-ranging knowledge in collaboration with rheumatologists, psychiatrists, and pain clinic doctors, among others.

Although many fibromyalgia patients also suffer from depression, to suggest that this is a psychogenic disorder is an extreme opinion. Fibromyalgia is regarded as a bizarre disease, in which abnormal, chronic pain occurs at 11–18 sites around the body, interfering with daily life. Guidelines for the clinical management of fibromyalgia were formulated in 2013, but these do not cover multidisciplinary treatment involving other professionals such as orthopedic surgeons, anesthesiologists, doctors of psychosomatic medicine, internists, clinical psychologists, and acupuncture massage practitioners. I believe that fibromyalgia was originally myofascial pain syndrome. Japan lags behind other

countries when it comes to the treatment of myofascial pain syndrome. Too many doctors have no idea of the significance of trigger points. The pain of this disorder cannot be cured by Loxonin (loxoprofen sodium hydrate) or compresses.

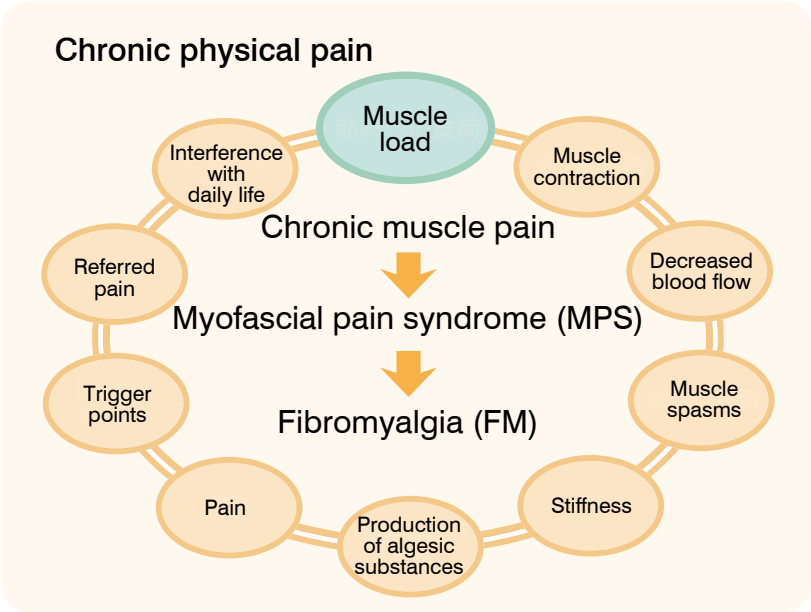
Trigger points have a long history, with S. Martyn being the first to use the term "referred pain" in 1864. In 1938, Jonas Kellgren described referred pain as a phenomenon observed when intramuscular injections of highly concentrated saline induced pain at distant sites unrelated to nerve courses. The problem is that if only this referred pain is treated, the trigger points themselves will become intractable. Even worse, referred pain can increase to more than 11 sites, just as cancer cells travel here and there around the body, with the trigger points getting lost as a result, and this can be said to be fibromyalgia. From my perspective, it is an iatrogenic condition caused by inappropriate treatment, and in this respect, it is a form of cephalic hypersensitivity syndrome. A study by Roland Staud *et al*. divided 62 women with fibromyalgia randomly into three groups that were treated with intramuscular injections of lidocaine, intramuscular injections of saline, and a placebo control, and found that for primary hyperalgesia of the shoulders and buttocks, lidocaine injections reduced pain significantly compared with saline injections. Fibromyalgia clinical pain decreased significantly after injections, but there was no difference between lidocaine and saline [28]. In my experience, lidocaine muscle block is also effective for fibromyalgia if trigger points can still be identified.

In any case, fibromyalgia fascinated Yunus so profoundly and led him to arrive at the concept of central sensitivity syndrome. I believe that half of its features can be described as cephalic hypersensitivity syndrome, while the other half cannot.

Chronic fatigue syndrome

No other disease is so impossible to resolve. To start with, its name is wrong. This is because it is actually a terrible condition that interferes with work and daily life to an extent that is hardly conveyed at all by the simple words "chronic fatigue." Problematically, conclusive diagnostic criteria do not yet exist. Neither the diagnostic criteria set out by the Ministry of Health, Labour and Welfare nor those of the Japanese Society of Fatigue Science are conclusive. In other words,

this condition can only be diagnosed by exclusion. Progress on elucidating its pathological mechanism is slow, and unlike menopausal syndrome, it cannot be identified through a blood test. One of my patients brought me a checklist used by Osaka City University, and the outcome measure used in that is the most comprehensible and convenient that I have yet seen. The main symptom is abnormal fatigue. Secondary symptoms vary widely, as shown in the figure. These symptoms resemble those of fibromyalgia, and are the reason that they are regarded as closely associated conditions.



The impossibility of objectively evaluating abnormal tiredness means that patients are regarded as slackers, both in the home and at work. The lack of objective signs also means that they are disliked by doctors, who prefer not to engage with them and in extreme cases may treat them as malingering. They are isolated from both society and the medical establishment. The most troubling problem is that as they are not recognized as suffering from an intractable disease or physical disability, and they are not eligible to receive welfare services even

if they require a wheelchair. At one point (1999), it did attract public attention with the production of diagnostic criteria by the Ministry of Health, Labour and Welfare (then the Ministry of Health and Welfare) and the documentary film Voices from the Shadows was taken up by the media, but it has yet to be officially designated as an intractable disease.

People need to realize that chronic fatigue is not the same thing as chronic fatigue syndrome. Its name is so misleading that I would like to propose that it be changed to "hyper-fatigue syndrome," with the focus on the abnormal nature of the fatigue rather than its duration. This would provide a better understanding of the nature of this condition, and make it easier for those around to be sympathetic.

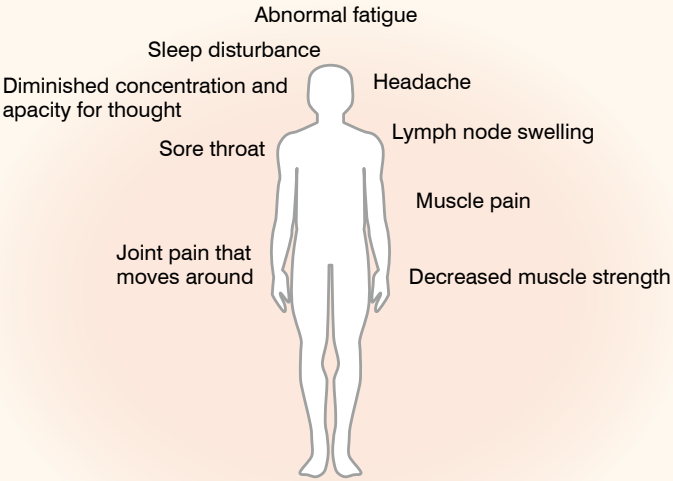
Like fibromyalgia, chronic fatigue syndrome is more common in women. I have the impression that many sufferers have experienced conditions such as atopic dermatitis, engaged in over-enthusiastic dieting, or suffered from menstrual irregularities, and that they tend to be either thin or overweight. Its medical nature is gradually becoming clearer, and I anticipate that its Japanese name will change in the near future. In fact, in the United Kingdom and Canada it is known as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)[29].

Two particularly interesting studies are currently underway. The first is based on the theory of abnormal ATP production[30] and is highly persuasive. ATP is an energy source that is synthesized in mitochondria within cells. Vitamin B complex and vitamin C and minerals such as magnesium are also involved. Anemia is more common in women, meaning that iron, which is involved in all sorts of metabolic processes, is also deficient. ATP is most efficiently produced from sugars, but is also often produced from fat. On this basis, it is my conjecture that the pathological condition underlying chronic fatigue syndrome may be sarcopenia (see note). One of the tests carried out in cases of chronic fatigue syndrome is a glucose challenge test. Chronic fatigue syndrome patients are believed to exhibit a low rise in blood sugar in the challenge test (non-reactive hypoglycemia). It appears that other substances such as insulin, free fatty acids, and potassium may also be involved. Another interesting study result is that brain positron emission tomography (PET) scans of patients with severe chronic fatigue syndrome have revealed the presence of inflammatory changes[31]. Issues

with the resolution of these images mean that they are not conclusive, but this research is hopeful.

In any event, this is an unknown condition that should not be treated in the same way as cephalic hypersensitivity syndrome. Yunus included it in his concept of central sensitivity syndrome, but I feel that their underlying pathological mechanisms may be different. In some cases, it is gradually progressive, but it often comes on suddenly or is triggered by some sort of infection, and compared with patients with cephalic hypersensitivity syndrome, in most cases, patients with chronic fatigue syndrome have a clearer memory of the initial episode. I think it is likely to represent some sort of infection or inflammatory disease. There is no known effective treatment whatsoever, although I recommend that chronic fatigue syndrome patients with infectious symptoms attempt Gerson therapy. Given its pathology, this can be anticipated to have some effect.

(Note) Sarcopenia: The practical definition is "A syndrome characterized by a progressive and generalized decrease in skeletal muscle mass and strength, associated with physical disability, reduced quality of life, and the risk of mortality or other adverse outcome." It is recommended that sarcopenia be diagnosed when a decline in muscle function (muscle strength or physical performance) is present in addition to decreased muscle mass.



Comparison of chronic fatigue and chronic fatigue syndrome

	Chronic fatigue	Chronic fatigue syndrome
Characteristics	A state in which fatigue accumulates under prolonged circumstances of being unable to obtain sufficient rest, and recovery is not immediate. Patients recover if stress is reduced and they get sufficient rest. Headache, severe stiff shoulders, and backache may also be present, but these improve with medication for cephalic hypersensitivity syndrome.	Unendurable generalized malaise and systemic pain result from even a small amount of movement. This may have been preceded by an infection, but the abnormal generalized malaise is of sudden onset. Frequently associated with a sore throat and lymph node swelling. Patients do not recover despite getting plenty of rest and changing their environment. Medication for cephalic hypersensitivity syndrome alleviates pain and stiffness, but does not improve the condition.
Medical diagnostic criteria	None. The Ministry of Health, Labour and Welfare has recommended checklists for avoiding death from overwork (karōshi): the Self-Diagnosis Checklist for Assessment of Workers' Accumulated Fatigue and the "Checklist for Assessment by Family Members of Workers' Accumulated Fatigue."	Exist. In Japan, they include the diagnostic criteria issued by the Japanese Society of Fatigue Science and the draft diagnostic criteria issued by the Ministry of Health, Labour and Welfare.
Genetic factors	May occur in anyone. Not genetically transmitted.	Genetic factors may be present.
Treatment	Reconsider rhythm of daily life, and identify and improve sources of stress. Reconsider diet, including eating more fresh vegetables and avoiding alcohol. Get plenty of rest and sleep.	There is currently no effective treatment, but as for chronic fatigue, reconsidering the rhythm of daily life and diet are important. Patients do not improve despite getting rest and sleep, and it is vital that their family and friends understand that they develop unendurable generalized malaise after doing even a small amount of movement, and provide them with emotional support.

Menopausal syndrome

Regular menopausal syndrome refers to symptoms due to diminished hormone levels that are overwhelmingly seen in women. These are both mental and physical symptoms caused by a rapid decrease in the hormone estrogen. It is diagnosed by a medical interview using an index such as the Kupperman Menopausal Index or the Simple Menopausal Index, and blood tests to measure estradiol (E2), follicle stimulating hormone (FSH) levels, and the balance of the two. Hormone imbalances can be treated with hormone replacement therapy, which is available in many obstetric and gynecology clinics. Its symptoms may be summed up in a single word: diverse. They may include headache, dizziness / vertigo, tinnitus, stiff shoulders, lower back pain, numbness, muscle pain, insomnia, hypersomnia, fatigue, polyhidrosis, dry mouth, nausea and vomiting, abdominal pain, diarrhea or constipation, slight fever, and depressed mood. Many doctors shrink from those patients who go on and on about their ailments with a gloomy face. Some of those women who do not seem to respond to any treatment and whose daily life is thrown into disarray, however, may respond well to the treatment for cephalic hypersensitivity syndrome. Although I do not dismiss their complaints completely out of hand, before sending them home I tell them that menopausal syndrome is a natural process for women and that they should not be impatient as they will definitely return to normal,.

In my experience, those women whose symptoms of menopausal syndrome have been aggravated by cephalic hypersensitivity syndrome may respond to treatment to some extent, but it does not work for those who have already gone over the edge.

The Kupperman Menopausal Index (Japanese version)

Calculation of the index: Total score for (sum of severity scores for each symptom × weighting)

Syndrome	Symptom					Weighting
	Type	Severity				
		Severe (3)	Moderate (2)	Mild (1)	Absent (0)	
Vasomotor neuropathy-like symptoms	Hot flashes	☐	☐	☐	☐	4
	Sweating	☐	☐	☐	☐	
	Chills in the lower back or hands and feet	☐	☐	☐	☐	
	Shortness of breath	☐	☐	☐	☐	
Paresthesia-like symptoms	Numbness of the hands and feet	☐	☐	☐	☐	2
	Decreased sensation in the hands and feet	☐	☐	☐	☐	
Insomnia	Difficulty in going to sleep at night	☐	☐	☐	☐	2
	Wake up easily during the night	☐	☐	☐	☐	
Neurosis	Easily agitated	☐	☐	☐	☐	2
	Neurotic	☐	☐	☐	☐	
Depression	Fret about insignificant matters (often become depressed)	☐	☐	☐	☐	1
Dizziness / vertigo	Feel dizziness / vertigo or nausea	☐	☐	☐	☐	1
Generalized malaise	Easily tired	☐	☐	☐	☐	1
Joint pain/ muscle pain	Stiff shoulders, lower back pain, pain in hand/arm/leg joints	☐	☐	☐	☐	1
Headache	Head hurts	☐	☐	☐	☐	1
Palpitations	Experience heart palpitations	☐	☐	☐	☐	1
Formication	Sensation like ants crawling over the skin	☐	☐	☐	☐	1

Formulated with reference to the Acta Obstetrica et Gynaecologica Japonica 61(7), 2009. N240 Table E-9-5)-1.

Conclusion: The chronic illness syndrome of cephalic hypersensitivity syndrome is a form of mental chronic pain

The autonomic nerves are a somewhat complicated subject, but in simple terms, just as the stomach and intestines are responsible for digesting and absorbing food, the autonomic nerves are responsible for digesting and absorbing what happens in the mind. Cephalic hypersensitivity syndrome is a pathological condition in which digestion and absorption by the autonomic nerves, the nerves of the mind, are impaired. As I have already mentioned, the sympathetic nerves are autonomic nerves that act in daylight, and the parasympathetic nerves are those that act at night. Although brain activity and the mind are related in terms of their cycles, the brain and the mind are not the same. Stress exerts a range of effects on both body and mind via the brain, and physical and mental states both affect the brain. Bodily stress and psychological stress both stimulate the autonomic nerves and are closely related to mood, appetite, and sleep.

There is a type of pain called "sympathetic nerve-dependent pain." This is a general term for pain to which the action of the sympathetic nerves contributes, such as nerve damage to the sympathetic nerves: not only physical stimuli but also psychological stress, as well as environmental factors such as low atmospheric pressure, can be felt as pain. Anger, fear, anxiety, interpersonal relationships and other sources of mental stress, prolonged work, and physical stress such as warm/cold stimuli all stimulate the sympathetic nerves, which physically transmit this stress to muscle. This means that a rise in stress is felt as muscle stiffness, hardening, or pain. Stress-induced pain also tends to relapse and intensify. The sympathetic nerves, which are controlled by the mind, generate muscle pain and exert a negative action in its exacerbation. Stress acts on the mind and is reflected in the autonomic nerves. Continued negative chronic stress causes mental fatigue, exhausts the autonomic nerves, and tires the muscles. This results in the development of a range of chronic illness syndromes that interfere with daily life, including depression, insomnia, chronic pain, and chronic fatigue. Of the various forms of mental fatigue, fatigue due to preoccupation is the most severe form of chronic pain. The mind can be released from preoccupation by the Magic Mirror method (see Page 76). Cephalic hypersensitivity syndrome is a disease created by the mysteries of the mind.

Chapter 2

Quoted Sources

(1) Takeshima, Takao. Chronification of migraine headache: clinical feature and mechanism of chronic migraine and medication overuse headache.
Japanese Journal of Clinical Neurology. 50.990-993. 2010. [In Japanese]
(2) Japanese Society of Neurology/Japanese Headache Society (Editor): Clinical Practice Guideline for Chronic Headache 2013. Igaku Shoin. [In Japanese]
http://www.jhsnet.org/guideline_GL2013.html
(3) World Health Organization Regional Office for Europe. European Centre for Environment and Health. Bonn Office. WHO technical meeting on sleep and health. 2004.
http://www.euro.who.int/__data/assets/pdf_file/0008/114101/E84683.pdf
(4) Cutrer.FM., et al. Migraine-associated Dizziness. Headache. 32:300-304.1992
(5) Dieterich.M., et al. Episodic vertigo related to migraine (90 cases): vestibular migraine? J Neurol (1999) 246 :883–892.
(6) Lempert. T., et al. Vertigo as a Symptom of Migraine. Basic and Clinical Aspects of Vertigo and Dizziness: Ann. N.Y. Acad. Sci. 1164: 242–251 (2009).
(7) Komiyama, Sakurako, et al. Clinical characteristics, vestibulocolic reflex and vestibulo-ocular reflex in patients with migraine-associated vertigo. Equilibrium Res Vol. 72(6). 493-500.2013. [In Japanese]
(8) Nanba, Koji. Bárány: The man and his work. Hiroshima University Forum Volume 26, Issue 3 (No. 314). 1994. p.33 [In Japanese]
http://home.hiroshima-u.ac.jp/forum/1994-09/30-35.pdf
(9) Japan Society for Equilibrium Research (Editor): Resources for the Standardization of Diagnostic Criteria for Dizziness and Vertigo: 1987 Report of the Committee for the Standardization of Diagnostic Criteria for Dizziness and Vertigo: Psychogenic Vertigo [In Japanese]
http://memai.jp/shindan/shindan-frame.html
(10) Shinden, Seiichi (Author), Ogawa, Kaoru (Editorial supervisor). Tinnitus can be cured in 90% of cases: Calming the over-excited brain makes the noise stop. Makino Shuppan. 2014. [In Japanese]
(11) Langers. RM. et al. Tinnitus does not require macroscopic tonotopic map reorganization. Frontiers in Systems Neuroscience. 6. 69-83. 2012.
(12) Eggermont. JJ. & Tass. PA. Maladaptive neural synchrony in tinnitus: origin and restoration. Frontiers in Nuerology. 6. 1-17.2015.
(13) Langguth. B. et al. Neuroimaging and neuromodulation: complementary approaches for identifying the neural correlates of tinnitus. Frontiers in Systems Neuroscience. 6. 30-49. 2012.
(14) Lopez-Escamez. JA. et al. Accompanying symptoms overlap during attacks in Menière's disease and vestibular migraine. Front. Neurol., 15 December 2014 | volume 5| Article 265|
http://dx.doi.org/10.3389/fneur.2014.00265
(15) Sabra. O., et al. Frequency of Migraine as a Chief Complaint in Otolaryngology Outpatient Practice. BioMed Research International. Volume 2015, Article ID 173165.
(16) Rogawski.MA. Migraine and Epilepsy- Shared Mechanisms within the Family of Episodic Disorders. In: Noebel JL., et al. Ed. Jasper's Basic Mechanisms of the Epilepsies [Internet]. 4th edition. Bethesda (MD): National Center for Biotechnology Information (US); 2012.
(17) Formulation of the new Guidelines for the Occupational Health and Safety Management of VDT Work
Announced by the Ministry of Health, Labour and Welfare, April 5 2002 [In Japanese]

http://www.mhlw.go.jp/houdou/2002/04/h0405-4.html
(18) Health Service Bureau, Ministry of Health, Labour and Welfare. Sleep Guideline for Health Promotion 2014: 12 Messages for Sleep [In Japanese]
http://www.mhlw.go.jp/file/04-Houdouhappyou-10904750-Kenkoukyoku-Gantaisakukenkouzoushinka/0000042751.pdf
(19) Sakurai, Takeshi. Investigation of the physiological function of orexin. [In Japanese]
http://www.md.tsukuba.ac.jp/basic-med/pharmacology/orexin.pdf
(20) Roffwarg. HP. et al. Ontogenetic Development of the Human Sleep-Dream Cycle. The prime role of “dreaming sleep” in early life may be in the development of the central nervous system. Science. 152.604-619.1966.
(21) Kamishima, Kunitoshi (Editorial supervisor). A New Approach to Clinical Neurology. 8. Sleep Disturbance and Substance-Related Disorders. Medical View Co. Ltd., 2006. pp 136-137. [In Japanese]
(22) National Center of Neurology and Psychiatry. Sleep Medicine Platform. Restless Legs Syndrome and Periodic Limb Movement Disorder. [In Japanese]
http://sleepmed.jp/platform/entry13.html
(23) Sumitani, Masahiko et al. Diagnosis and treatment of CRPS. Anesthesia 21 Century 10(3).32.13-18. 2008. [In Japanese]
(24) Japanese Society for the Study of Myofascial Pain Syndrome. Trigger Points [In Japanese]
http://www.jmps.jp/medical/diagnosis
(25) Gerson, Charlotte et al. The Gerson Therapy: The Amazing Nutritional Program For Cancer and Other Illnesses. Translated by Abe, Koji et al. Tokuma Shoten. 2002. [Japanese translation]
(26) Pedersen TH. et al. Intracellular acidosis enhances the excitability of working muscle. Science. Aug 20.305(5687):1144-7. 2004.
(27) Ting TV. et al. Juvenile Fibromyalgia: Diagnostic Challenges and Treatment Options. Practical Pain Management. Volume 11. Issue #7.2011.
http://www.google.co.jp/url?sa=t&rct=j&q=&esrc=s&source=web&cd=5&cad=rja&uact=8&ved=0CEcQFjAE&url=http%3A%2F%2Fwww.practicalpainmanagement.com%2Fprintpdf%2F9465&ei=UaT6U_jmHMuUuASA24GYBw&usg=AFQjCNE_cZTLmUYFNPvQvRblmfE_EhdEfA&bvm=bv.73612305,d.dGc
(28) Staud R. et al. Analgesic and anti-hyperalgesic effects of muscle injections with lidocaine or saline in patients with fibromyalgia syndrome. Eur J Pain. Jul; 18(6):803-12. 2014.
(29) Carruthers, Bruce M. et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Clinical Case Definition and Guidelines for Medical Practitioners. An Overview of the Canadian Consensus Document.
http://sacfs.asn.au/download/consensus_overview_me_cfs.pdf
(30) Booth. NE., et al. Mitochondrial dysfunction and the pathophysiology of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS). Int J Clin Exp Med. 5(3):208-220. 2012.
(31) Myhill.S. et al. Targeting mitochondrial dysfunction in the treatment of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS)- a clinical audit. Int J Clin Exp Med. 6(1):1-15. 2013.

References

Shimizu, Toshihiko. Stop Taking Medication and Cure Your Headache. Headache Treatment Q&A. One-Two Magazine-sha. 2007. [In Japanese]
Shimizu, Toshihiko. The Brain is Screaming. Are Headache, Vertigo, Tinnitus, and Insomnia Really

Caused by "Cephalic Hypersensitivity Syndrome"?! Kodansha plus Alpha Books. 2012. [In Japanese]
Tagusagawa, Yoshihiko. Theory and Practice of Migraine Treatment. Bungeisha. 2013. [In Japanese]
Goto Hideo. Advice for Curing Migraine Your Doctor Should Read. Kenko Journal-sha. 2013. [In Japanese]
Takabayashi, Katsue. Basic Knowledge of VDT Syndrome. All About. [In Japanese]
http://allabout.co.jp/gm/gc/301749/
Japan Society for Equilibrium Research Committee for the Standardization of Diagnostic Criteria for Dizziness and Vertigo (Editor). Guidelines for the Management of Benign Paroxysmal Positional Vertigo (For Doctors). Equilibrium Res Vol. 68(4). 218-242.2009. [In Japanese]
Kamishima, Kunitoshi (Editorial supervisor). A New Approach to Clinical Neurology. 8. Sleep Disturbance and Substance-Related Disorders. Medical View Co. Ltd. 2006. [In Japanese]
Uchiyama, Makoto (Chief Editor). Psychiatry Lumiere for Specialists 8. Care and Treatment of Sleep Disturbance in Psychiatric Disorders. Nakayama Shoten. 2009. [In Japanese]
Kohyama, Jun. Children's Sleep. Sleep is Nutrition for the Brain and Mind. Mebae-sha. 2003. [In Japanese]
Miike, Teruhisa (Editor). School Refusal Clinic. Understanding the Pathology of School Refusal from Sleep Education. Shindan to Chiryo-sha. 2009. [In Japanese]
Koyama, Natsu. Pain Relief (HP) Referred Pain. [In Japanese]
http://www.shiga-med.ac.jp/~koyama/analgesia/history.html
Wikipedia: Acupuncture point
http://en.wikipedia.org/wiki/Acupuncture_point
Special Interest Groups on Trigger Point [In Japanese]
http://k-tp.jp/professional/document
Japanese Society of Neurology (Editorial supervisor): Clinical Practice Guideline for Epilepsy Management 2010. Igaku Shoin. 2010
http://www.neurology-jp.org/guidelinem/tenkan.html
Guideline for treatment of major depressive disorder by the Japanese Society of Mood Disorders, 2013.
http://www.secretariat.ne.jp/jsmd/mood_disorder/img/120726.pdf
http://www.secretariat.ne.jp/jsmd/mood_disorder/img/120331.pdf
Japan College of Fibromyalgia Investigation & National project team by Ministry of Health, Labour and Welfare (Editor): Fibromyalgia Guideline 2013. Japan Medical Journal. 2013.
http://minds4.jcqhc.or.jp/minds/FMS/CPGs2013_FM.pdf
Standards of NeuroTherapeutics: Chronic pain (ed Japanese Society of Neurological Therapeutics)
https://jsnt.gr.jp/guideline/mansei.html
Standards of NeuroTherapeutics: Restless legs syndrome (ed Japanese Society of Neurological Therapeutics)
https://jsnt.gr.jp/guideline/restless.html
Standards of NeuroTherapeutics: Dizziness and vertigo (ed Japanese Society of Neurological Therapeutics)
https://jsnt.gr.jp/guideline/memai.html
New CFS Diagnostic Guidelines by the Japanese Society of Fatigue Science
http://www.fuksi-kagk-u.ac.jp/guide/efforts/research/kuratsune/fatigue/fatigue05.html

Chapter 3
The mechanism of cephalic hypersensitivity syndrome:
Theoretical predictions from observations

As you will know after reading Part 2, the symptoms commonly experienced by the patients who attend my clinics include headache, stiff shoulders, dizziness / vertigo, numbness in a limb, and insomnia. Often they have been suffering for a long time, having undergone tests at several different hospitals without any cause having been discovered, and some have been told "There's nothing wrong with you." Dictionaries define "indefinite complaint" as "a state in which patients complain of a range of subjective symptoms despite no apparent organic disease being present" (Kojien) and "complaints of vague physical illness that do not constitute a specific disorder. These may include heavy-headedness, being easily tired, and lack of appetite" (Digital Daijisen). Over many years of facing up squarely to the complaints of such patients and engaging in their treatment, I have come up with the following three hypotheses.

Hypothesis 1: Many of the chronic illness syndromes suffered by patients are caused by cephalic hypersensitivity syndrome.

Hypothesis 2: Cephalic hypersensitivity syndrome can be explained in terms of the molecular biology of synaptic plasticity.

Hypothesis 3: A biopsychosocial model is appropriate for the treatment of cephalic hypersensitivity syndrome.

These hypotheses have yet to be fully scientifically investigated, but some scientists have proposed similar concepts, and findings that back up my theories have been published. The greatest support for them is the fact that patients are actually cured, but here I will describe some of the arguments that have been suggested at this stage.

1 Hypothesis 1: Many of the chronic illness syndromes suffered by patients are caused by cephalic hypersensitivity syndrome

Yunus' concept of Central sensitivity syndrome (CSS)

Muhammad Yunus, a professor in the Division of Rheumatology of the University of Illinois College of Medicine in the United States, has proposed the concept and the term of central sensitivity syndrome (CSS) on the basis of his treatment and studies of fibromyalgia and rheumatism patients. Although we come from different standpoints, mine as a neurosurgeon and neurologist and his as a rheumatologist, and I identify the complaints of patients who experience "pain" in the broadest sense as the common denominator, whereas Yunus emphasizes the symptoms of fibromyalgia, we are both following similar trajectories. However, Yunus' concept of CSS is not described in the Japanese Fibromyalgia Guidelines 2013, and I will therefore summarize its important points here.

① Definition of central sensitivity syndromes

Yunus defines central sensitivity syndromes as a group of illnesses that meet the following two conditions[1]. The figure shows the current conceptual diagram of CSS.

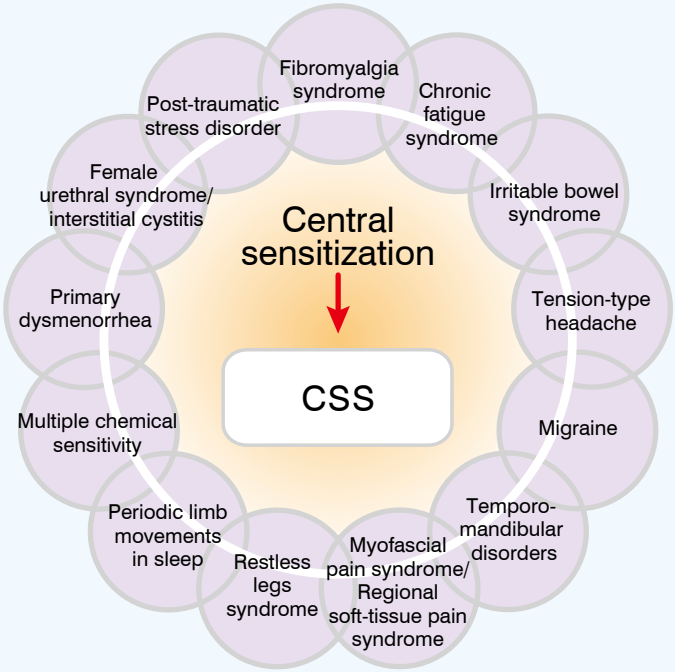
(a) Mutual associations between the CSS members

(b) Presence of central sensitization

Mutual Association

Yunus carried out an in-depth study of the commonalities between the various different central sensitivity syndromes, focusing mainly on fibromyalgia patients, and summarized the results. Based on this investigation, there are currently 13 syndromes accepted as central sensitivity syndromes, including some with symptoms that are obviously associated in clinical terms even though research studies have yet to establish sufficient evidence and that further research is expected to substantiate[2]. This is why the legend to the conceptual diagram emphasizes that it shows the disorders and syndromes that are “currently” classified as CSS, as it is possible that more may be identified as belonging to this category in the future[1–3].

Currently proposed members of the CSS family
with overlapping relationships and
a common pathophysiological link of central sensitization



Source: Figure 1 of Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin Arthritis Rheum. 2007;36(6):341.

Presence of central sensitization

Central sensitization refers to the development of hypersensitivity not only to uncomfortable stimuli such as pressure and heat, but also to touch and other stimuli that are not normally uncomfortable[2]. In terms of clinical signs, it appears as the amplification of pain from heat, mechanical stimuli, and other types of stimuli, hyperalgesia, and the spread of pain and uncomfortable sensations, all of which become chronic. Central sensitization is defined as the hyperexcitation of the central nervous system, and the aforementioned symptoms appear after peripheral stimuli as a result of the alteration of sensory processing. The table shows the neurochemical substances and neuroreceptors involved in central sensitization.

Neurochemicals and neuroreceptors involved in central sensitization

Neuromodulators/neurotransmitters released by activated C-nocireceptors presynaptically	
Substance P (SP)	Somatostatin
Calcitonin-gene-related peptide (CGRP)	Galanin
	Nerve growth factor
	Glutamate
Vasoactive intestinal peptide (VIP)	Aspartate

Post-synaptic neuroreceptors/neuroeffector targets	
Neurokinin 1 (NK1)	Metabotropic glutamate (mGlu)
N-methyl-D-aspartate (NMDA)	Tyrosine kinase B (Trk-B)
Alpha-amino-3-hydroxy-5-methyl-4-isoxaloeproprionate (AMPA)	Protein kinase gamma (PKC-gamma)
	Vanilloid subfamily (TRPV-1, TRPVL-1)

Source: Table 1 of Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin Arthritis Rheum. 2007;36(6):342.

Substance P causes secondary nerve excitation and the expansion of regions of pain that is characteristic of central sensitization. The release of neurochemical substances such as substance P, nerve growth factor, and glutamate overexcites the synapses, resulting in the release of the magnesium block on NMDA receptor channels. The activated NMDA receptors increase intracellular calcium inflow, which causes changes in the cell membrane and activates protein kinases, phospholipases, nitric oxide synthases, and other enzymes that have a major effect on central sensitization. This series of reactions results in neuroplasticity. Substances including dopamine, serotonin, noradrenaline, GABA, enkephalin, and adenosine are all involved in central sensitization[2].

- **Central sensitization is the common factor in central sensitivity syndromes (CSS)**

Yunus mentions the following evidence of central sensitization for 12 of the 13 disorders and syndromes shown in the figure, with the exception of periodic limb movements in sleep[2].

- **Fibromyalgia**

Patients exhibit a generalized exaggerated pain response by digital pressure. They are reportedly hypersensitive to a range of stimuli [including heat, cold, electric, quantitative sensory testing (QST), and sound]. Central sensitization has also been suggested in fMRI and EEG studies of response to stimuli.

- **Chronic fatigue syndrome**

Many aspects remain unknown. A study of chronic fatigue syndrome patients, of whom nearly half had myalgia, demonstrated hypersensitivity to electric stimuli, but not in the overlying skin or subcutaneous locations.

- **Irritable bowel syndrome**

Discomfort in the lower abdomen and lower back are the two main markers of central sensitization. Most studies have used balloons as a stimulus, but central sensitization has also been demonstrated by using heat and electric stimuli. Patients with irritable bowel syndrome exhibit both rectal and cutaneous allodynia. Central sensitization has also been suggested in fMRI and PET studies of rectal and cutaneous stimuli.

• **Tension headache**

A facilitated spinal nociceptive flexion reflex was evident in response to stimuli (pressure or heat) in both cranial and extracranial sites. Central sensitization was also shown by cerebral-evoked potential and a deficient pain inhibitory response by a diffuse noxious inhibitory control mechanism. However, a lack of central sensitization has also been reported by cutaneous heat and electric stimuli.

• **Migraine**

Enhanced sensitivity to stimuli (mechanical, heat, cold, CO_2 laser) has been demonstrated in both cranial and extracranial sites. Hypersensitivity to sound and light has also been shown. Cutaneous allodynia on the forearms and around the eye sockets is also evidence of central sensitization.

• **Temporomandibular disorders**

Temporomandibular disorders represent a heterogeneous group of disorders in patients with or without structural pathology. Only the myofascial variety by Research Diagnostic Criteria is included as a central sensitivity syndrome. Hyperresponsiveness to both facial and extracranial stimuli (pressure, heat, ischemia, and hypertonic saline) has been recorded.

• **Myofascial pain syndrome/regional soft-tissue pain syndrome**

Yunus *et al*. regard these two syndromes as constituting the same entity. In both, hypersensitivity to stimuli is evident at both symptomatic and distant sites. Amplified responses to pressure, heat, cold, electric stimulus, and vibration are present.

• **Restless legs syndrome**

Punctate stimulation by pin prick reveals generalized hyperalgesia in the arms and legs.

• **Multiple chemical sensitivity**

Multiple chemical sensitivity is a time-dependent sensitization that elicits central sensitization as the result of repeated exposure to environmental chemicals. Although there is almost no experimental evidence other than noise sensitivity, studies of other central sensitivity syndromes exist that show similarities with chemical sensitivity.

- **Primary dysmenorrhea**

Patients with dysmenorrhea exhibit lower thresholds for stimuli (pressure, heat, and electric stimulus) in the abdomen, back, and extremities during menstruation.

- **Interstitial cystitis**

Sensitivity to bladder distension with physiological saline and muscle pressure increases.

- **Post-traumatic stress disorder**

Like temporomandibular disorders, the mechanism of sensitization is still at the hypothesis stage. It is believed that sensitization is induced by emotional stress rather than chemicals. Further studies are required.

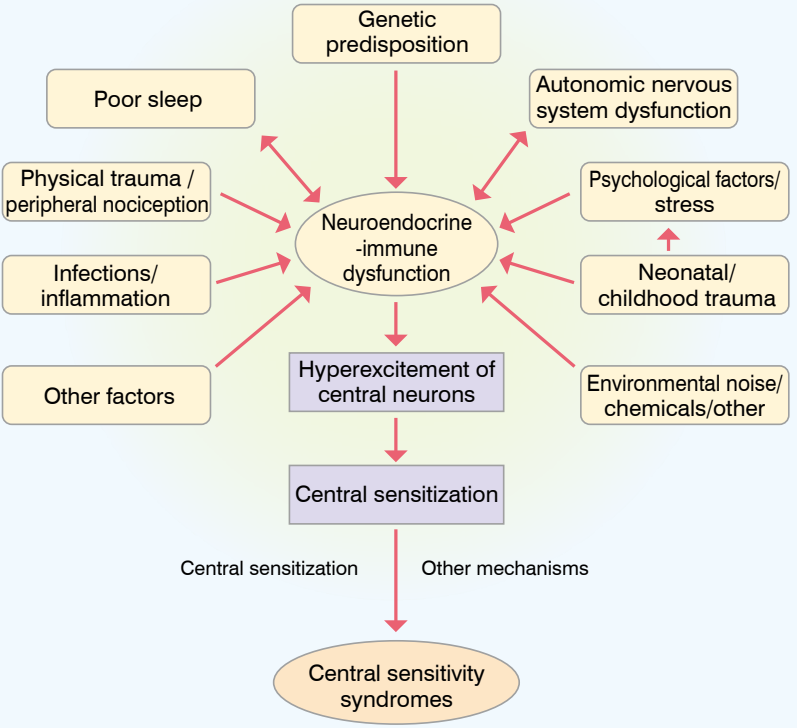
- **Depression and other mental disorders**

Many studies have shown that patients with central sensitivity syndromes also suffer from depression or other mental disorders. The relationship between pain and depression is a complex one, however, with many different factors involved, and there is insufficient direct evidence for central sensitization to sensory function in depression. Depression is associated with all the disorders classified as central sensitivity syndromes, but overlap does not necessarily mean total overlap. Studies on anxiety and panic disorder are extremely limited.

Factors that may contribute to, or trigger, central sensitization

The figure shows a simplified schema of factors that may contribute to central sensitization and central sensitivity syndrome.

Simplified suggested biopsychosocial mechanisms for central sensitization and central sensitivity syndromes with interacting factors



Source: Figure 2 of Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin Arthritis Rheum. 2007;36(6):342.

Yunus explains genetic predisposition, the autonomic nervous system, neuroendocrine dysfunction, psychological factors and infection, inflammation, trauma, sleep, and environmental factors[2].

• Genetic predisposition

Pain is generally known to be modulated by genetics. Polymorphisms such as T102C polymorphism (5-HT2A receptor) and serotonin-transporter gene polymorphism have been reported in fibromyalgia, irritable bowel syndrome, temporomandibular disorder, migraine, chronic fatigue syndrome, and depression.

• Autonomic nervous system

Spectral analysis of heart rate variability has revealed overactivity of the sympathetic nerves and underactivity of the parasympathetic nerves in disorders including fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, and restless legs syndrome.

• Neuroendocrine dysfunction

Hypothalamic-pituitary-adrenal (HPA) axis dysfunction with hypocortisolism is common to many forms of central sensitivity syndromes (fibromyalgia, chronic fatigue syndrome, chronic headache, and post-traumatic stress disorder). The relationship between low cortisol and central sensitization is still unclear, but a stress mechanism may be involved.

• Psychological factors

Anxiety, stress, depression, and other psychological problems are common in central sensitivity syndromes, and studies have shown that their relationship may be bidirectional. However, data are sparse regarding the association between psychological distress and central sensitization. Adverse experiences in childhood may promote long-term neuroplasticity, causing mental and physical symptoms similar to those of central sensitization in adults.

• Infection, inflammation, trauma, sleep, and environmental factors

General or local viral infections, as well as trauma, are reported to trigger central sensitivity syndrome symptoms through the action of inflammatory mediators that activate nociceptive fibers with resultant central sensitization.

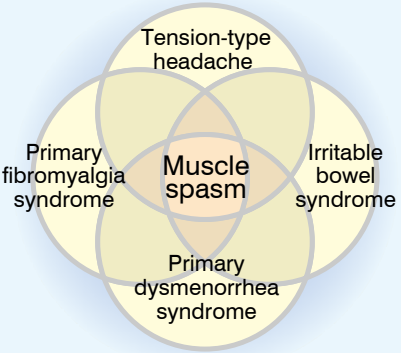
Non-restorative sleep may also cause central sensitization. Central sensitization as measured by algometry and nociceptive stimuli are also associated with poor sleep. Environmental stimuli such as noise may also induce central sensitization.

② Historical development of the concept of central sensitivity syndromes

Yunus has summarized the history of his concept of central sensitivity syndromes in the table below.

Yunus is a doctor and researcher who specializes in fibromyalgia. While treating fibromyalgia patients, he noticed commonalities among four diseases and syndromes (primary fibromyalgia syndrome, tension-type headache, primary dysmenorrhea syndrome, and irritable bowel syndrome), and first expressed these in the form of a Venn diagram in 1984. At that point, the common mechanism for these four conditions was unclear, and almost nothing was known about central sensitization. He therefore depicted the common factor as "muscle spasm," the idea of which had been popularized by the Mayo Clinic. The initial diagram was received with suspicion [1 4]. It may be presumed that Yunus' concept was not accepted without resistance by the medical community from the fact that two of the publications listed in the table were an abstract and a supplement rather than easily obtainable, well-known journal articles.

The first proposed concept of overlapping syndromes shown in a Venn diagram in 1984



Source: Figure 2 in Yunus MB. Central sensitivity syndrome: a new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. Semin Arthritis Rheum. 2008 Jun;37(6):345.

History of central sensitivity syndromes

1981	First data-based demonstration of associations among fibromyalgia syndrome and tension-type headache, migraine, and irritable bowel syndrome.	Yunus MB, *et al*. Primary fibromyalgia (fibrosotis): clinical study of 50 patients with matched normal controls. Semin Arthritis Rheum 1981;11:151–71.
1984	First conceptual depiction (by a Venn diagram) of an interrelationship among several central sensitivity syndrome members with similar and overlapping features. Muscle spasm theorized to be the common pathophysiologic link.	Yunus MB. Primary fibromyalgia syndrome: current concepts. Compr Ther. 1984 Aug;10(8):21–8.
1985	Use of the terminology "stress-related syndromes".	Yunus MB, Masi AT. Association of primary fibromyalgia syndrome with stress-related syndromes. Clin Res 1985;33(4)(Abst):923a.
1989	"Affective" mechanism is suggested for fibromyalgia syndrome and overlapping syndromes, including several medical ("functional") as well as the psychiatric condition described as "affective spectrum disorder".	Hudson JI, Pope HG Jf. Fibromyalgia and psychopathology: is fibromyalgia a form of "affective spectrum disorder"? J Rheumato Suppl 1989;19:15–22.
1994	The collective term "dysfunctional spectrum syndrome" is suggested implying the dysfunction of the neurohormonal system as the common binding mechanism among the central sensitivity syndrome members.	Yunus MB Psychological aspects of fibromyalgia syndrome: a component of the dysfunctional spectrum syndrome. aillieres Clin Rheumatol. 1994;8(4):811–37.
2000	The nosology "central sensitivity syndromes" is coined based on the evidence that fibromyalgia syndrome and overlapping members of the central sensitivity syndromes family demonstrate central sensitization to multiple stimuli. Central sensitization is proposed to be the common pathophysiological binder of the central sensitivity syndrome diseases.	Yunus MB. Central sensitivity syndromes: a unified concept for fibromyalgia and other similar maladies. Journal of Indian Rheumatism Association. 2000 Mar;8(1):27–33.

Adapted from Table 1 in Yunus MB. Central sensitivity syndrome: a new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. Semin Arthritis Rheum. 2008 Jun;37(6):346.

③ From fibromyalgia to central sensitivity syndromes: Clinical significance

Yunus' worldview and the clinical significance of central sensitivity syndromes

Finally, I will explain the background to how Yunus came to coin the term "central sensitivity syndrome" despite being a fibromalgia researcher, and his emphasis on its clinical significance. This was based on his own worldview, which rejects the dualisms (see note) prevalent in medical science of mind versus body and disease versus illness, and emphasizes the importance of the biopsychosocial approach and patients' subjective complaints of pain in clinical practice as a whole, not just the treatment of central sensitivity syndromes [5]. Yunus supports Engel's 1977 "biopsychosocial" concept and terminology, and in addition to explaining the mechanism of pathophysiologic central sensitization as the common factor in disorders classified as central sensitivity syndromes, he also emphasizes the importance of biopsychosocial factors in their treatment. He poses the question to the medical establishment of the fundamental nature of "treatment" devised in collaboration with real-life patients by combining effective drug therapies with other types of treatment, as opposed to the idea that standard, guideline-based treatment is the gold standard.

In view of these points, the concept of central sensitivity syndrome championed by Yunus is clinically significant for two major reasons. The first is that elucidating the mechanism common to central sensitivity syndromes would make it possible to avoid the enormous drug development costs and time required for clinical trials for different conditions as well as to alleviate patients' sufferings earlier by using drugs that will clearly be effective on theoretical grounds [2]. The other is that providing a pathophysiological explanation rather than just dismissing patients' pain and unhappiness as nothing but "mental problems" helps to maintain good doctor-patient relationships and enables doctors to provide more satisfactory medical care [1].

Studies of the pathophysiological mechanisms of central sensitivity syndrome disorders are expected to make further advances while incorporating gene analysis techniques. On the other hand, it should not be forgotten that choices

of treatment that have a theoretically solid explanation should not be excluded, even if they cannot all be "scientifically" explained. Yunus' concept of central sensitivity syndromes will undoubtedly undergo further development in the future, but this is where its historical significance lies at this point.

(Note) Dualism: Here, this refers to the mind-body dualism propagated by the 17th-century philosopher Descartes, in which the mind (spirit or soul, ego or psyche, consciousness) exists separately from the things of this world (corporeal or physical).

④ My own concept of "cephalic hypersensitivity syndrome" and Yunus' central sensitivity syndromes

Toshihiko Shimizu may have been the first person to use the Japanese phrase "*nō kabin syōkōgun*" to refer to headaches developed from migraine. This concept partially overlaps my concept of cephalic hypersensitivity syndrome; however, it mainly focuses on headache. Unfortunately, Shimizu did not write about the mechanism of the syndrome, omitted scientific discussions, and presented only a small number of clinical cases [6]. To the best of my knowledge, Yunus originally demonstrated a spectrum of diseases common to central sensitivity or hypersensitivity. Therefore, here I will describe my own theoretical concept of cephalic hypersensitivity syndrome in comparison with Yunus' central sensitivity syndromes.

Definitions of the terminology used in my theory

Cephalic hypersensitivity syndrome

The series of symptoms caused by hypersensitivity of the brain are the result of the synaptic plasticity and functions for the maintenance (or adaptation) of homeostasis that are built in to all animals. Symptoms such as headache, stiff shoulders, lower back pain, fatigue, and misery are induced by chronic physical or mental stress or the overuse of medication, which disturb the autonomic nerves or brain hormone homeostasis and are transformed into various manifestations of chronic pain.

Synaptic plasticity

This refers to the plasticity of the efficiency of neurotransmission across

synaptic connections as a result of the increase or decrease in synaptic connections due to sensory, emotional, and intellectual stimuli. This plasticity contributes to long-term potentiation (LTP) or long-term depression (LTD) in neurons. Neurotransmission efficiency varies according to nerve activity in accordance with what stimuli have been experienced.

Homeostasis maintenance (or adaptation) functions

The integrated biological regulatory system that comprises the nervous system, immune system, and endocrine systems is the foundation of the mechanisms for the maintenance of homeostasis. Synaptic plasticity does not stop at neuronal plasticity, but is intimately related to changes in the immune and endocrine systems, and this transformation is remembered as alterations in the expression of neuronal genes in the cerebral limbic system (the hippocampus and amygdala) and the hypothalamic-pituitary-adrenal (HPA) axis to develop a new "system." Alterations in this system are passed down from the mother to the next generation. The plasticity of the entire system thus involves a genetic component and varies by age and sex. Adaptation includes both individual and evolutionary adaptations.

Chronic illness syndromes and pain

Chronic illness syndromes are manifestations of "pain," and suggest the type of noxious/nociceptive stimulus. Nociceptive stimuli include input from the sensory organs or periphery (exogenous stimuli) and input generated by emotion or thinking (endogenous stimuli).

My theory is a concept that overlaps with that of Yunus in many ways, but differs on the following points. Yunus emphasizes the commonalities among a group of disorders, but this approach includes numerous subgroups, such as patients who do not meet the fibromyalgia guidelines but who nevertheless complain of similar symptoms. With regard to this issue, Mary-Ann Fitzcharles and Yunus have stated that they treat even patients who do not meet the diagnostic criteria for fibromyalgia listed in the guidelines as fibromyalgia patients, emphasizing not only the objective criteria set out in the guidelines but also the patient's own subjective complaints [5]. My hypothesis, on the other hand, emphasizes the patients' subjective complaints, and for phenomena classified as "chronic illness syndrome" with no objective signs such as test results, I infer the source of

nociceptive stimuli on the basis of careful medical interviews with these patients.

Yunus has defined central sensitization as the common mechanism underlying central sensitivity syndromes, and as described earlier, has set out factors that contribute to or trigger central sensitization. My hypothesis regards such psychosocial factors as exogenous or endogenous stimuli providing inputs, and explains it as the transformation by these inputs of the integrated biological regulatory system and individual and evolutionary adaptation. It can easily be conjectured that symptoms will thus vary by sex and age, and the effect of the environment surrounding an individual can also be readily inferred, enabling the appropriate treatment for each individual patient to be selected.

2 Hypothesis 2: Cephalic hypersensitivity syndrome can be explained in terms of the molecular biology of synaptic plasticity

Treatment for cephalic hypersensitivity syndrome has the goal of alleviating the pain of which the patient complains. Methods other than drug treatment are also important, such as the improvements in lifestyle and thinking described in Chapters 1 and 2, but it is important to identify the appropriate type of drug, dosage, and method of administration for each individual patient. Basic to this are the molecular biology of synaptic plasticity and pharmacological inferences. Many patients with cephalic hypersensitivity syndrome have long suffered from a range of forms of pain of unknown origin, and may also be suffering from symptoms that have undergone complex alterations as a result of the overuse of symptomatic painkillers or the wrong choice of medication. My hypothesis concerning synaptic plasticity disentangles such episodes of transformed pain, and is useful for increasing the chance of selecting appropriate medication.

In my encounters with patients with cephalic hypersensitivity syndrome, many patients have said that their motivation for coming to me was that they had visited several other hospitals and tried a variety of different medications, but their symptoms had worsened rather than improved. I have often also heard that they hadn't believed that medication at such low doses would be effective, and that although they had been surprised to find out that they were being prescribed antiepileptics, their symptoms had greatly improved (see Part 2). What this suggests is just how difficult it is to select the right type of drug and dosage. What first led me to the discovery of the concept of cephalic hypersensitivity syndrome was the fact that low doses of antiepileptics and antidepressants were effective treatments for a range of different chronic illness syndromes. These are drugs that act on excitation of the cranial nerves. Despite the fact that over the past 40 years, the molecular biology of the cranial nervous system has advanced rapidly, including gene analysis techniques, many aspects still remain unclear. Elucidation of their mechanisms is a task for the future, but here I shall describe current knowledge that backs up my hypothesis (although this is not a scientific review) and explain the thinking underlying my algorithm of treatment.

My inferences concerning ion channels and brain hormones

Ion channels are the basis of all cellular activity. This means that there are also several mechanisms for maintaining homeostasis in neurons. I have arrived at the following inferences on the basis of the shared pharmacological characteristics of the drugs I use to treat patients with cephalic hypersensitivity syndrome.

① Membrane potential-dependent ion channels may predominate in exogenous pain caused by stimuli such as touch and temperature, whereas ligand-dependent ion channels may predominate in endogenous pain such as emotional and intellectual pain.
② Some ion channels are believed to be associated with time-dependent brain hormones. This is evidence that night therapy may be effective for cephalic hypersensitivity syndrome.
③ Long-term potentiation of pain-related neurons involves a channel function system in which calcium ion inflow is predominant, and magnesium ions may be important in suppressing this system.

The choice of the easiest medication for individuals to take: Finnerup *et al.*'s work

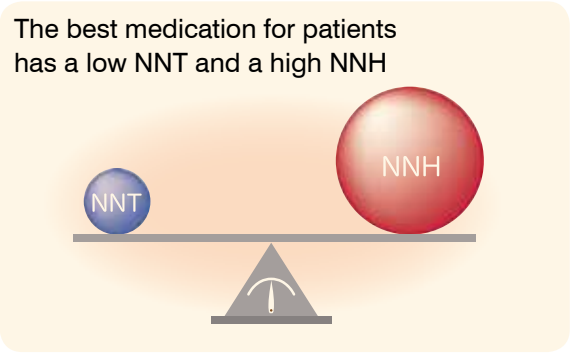
I have already discussed the significance of Yunus' proposed central sensitivity syndrome above. One thing that central sensitivity syndrome and my own proposed cephalic hypersensitivity syndrome have in common is that they are both disease concepts born out of our experience of clinical treatment with the goal of providing treatment that is easy for people to undergo. The work of Finnerup and her colleagues is extremely relevant as an effective approach to the selection of medication that makes it easy for people to undergo treatment[7,8]. Finnerup works in the Department of Neurology and the Danish Pain Research Center of Aarhus University Hospital, and uses pharmacoepidemiological techniques to investigate the balance between the effectiveness of various types of painkillers and their side effects, as well as the cost-benefit performance of development costs.

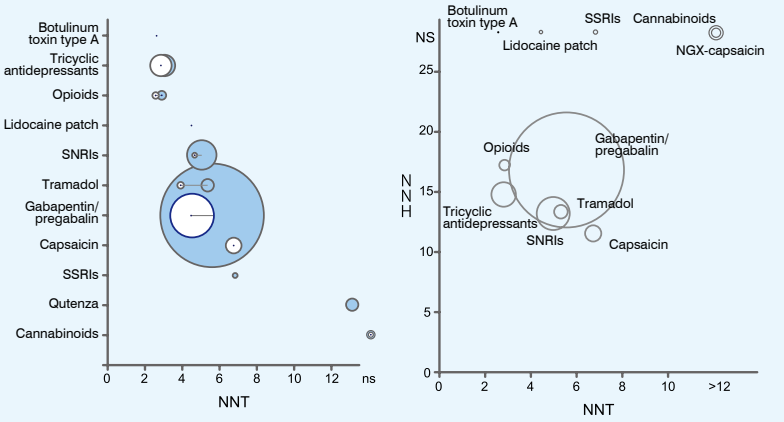
This is also an issue in Japan; the close relationships between doctors and pharmaceutical companies in clinical trials for drug development and the intensification of competition in drug development in many countries mean that

the basic nature of treatment is being overlooked. Despite the fact that the goal is the standardization of evidence-based treatment, drug development is at root carried out under political and economic pressure, far from the best principle for patients, who want low-cost drugs that are effective in low doses. As I mentioned earlier, Yunus has also raised this issue [2]. Finnerup and her colleagues analyzed painkillers, and as there is a large overlap between the drugs mentioned in their work and those used to treat cephalic hypersensitivity syndrome, their results are a useful reference from the viewpoint of drug selection, and I shall describe some of them here.

Number Needed to Treat (NNT) and Number Needed to Harm (NNH)

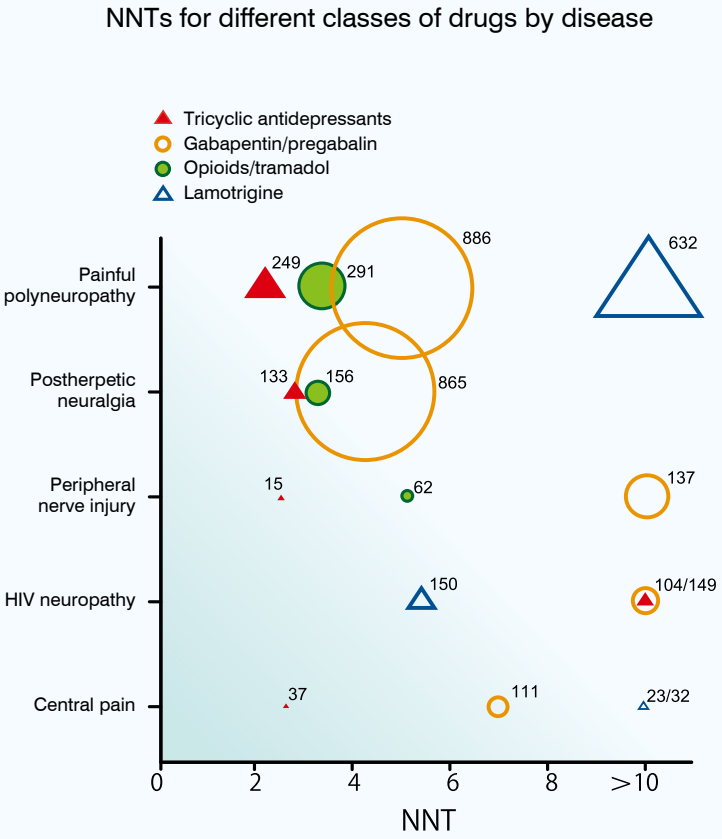
The number needed to treat (NNT) is an index of how many patients must be treated in order to achieve the effective treatment of a single case, and the number needed to harm (NNH) is an index of how many patients will be treated for an adverse event (side effect) to appear in a single case [9]. Generally speaking, if two medications have very similar mechanisms of action, the one with the lower NNT and higher NNH is chosen, as this is the best choice for the patient. The use of the NNT for evaluation has been criticized, but as an index for comparing studies carried out using different designs, it is a significant resource for deciding on which medication to use in clinical settings [7].





NNT and NNH for central and peripheral neuropathic pain, excluding trigeminal neuralgia
Left: The white circles show data from 2005, and the blue circles from 2010. The circle sizes indicate the relative number of patients who received active treatment drugs.
Right: 2010 data on the NNT and NNH for each class of drug. The placebo effect varied depending on the study design.
The circle sizes indicate the number of patients who received active treatment drugs.
Adapted from Figure 1.3 in Finnerup. NB., Sindrup. SH. & Jensen. TS. The evidence for pharmacological treatment of neuropathic Pain. 2010 Sep;150(3), 573-81.
Figure caption was omitted.

Reading the top figure from left to right, gabapentin and pregabalin are administered to large numbers of patients compared with other medications of almost the same pharmacological effectiveness. This tendency is particularly pronounced in comparison with tricyclic antidepressants (TCAs) and serotonin-noradrenaline reuptake inhibitors (SNRIs). The next figure shows that gabapentin and pregabalin have been the subjects of large-scale studies of polyneuropathy and postherpetic neuralgia, both of which cause severe pain, and that although they have also been shown to be effective against peripheral neuropathy and central pain, those were small-scale studies.



The symbol sizes indicate the relative number of patients who received active treatment drugs. Adapted from Figure 2 in Finnerup. NB., Sindrup. SH. & Jensen. TS. The evidence for pharmacological treatment of neuropathic pain. Pain. 150, (2010), 573-81.
Figure caption was omitted.

Both Finnerup and Yunus hold that the massive research costs involved in repeating a new clinical trial for every different disorder are reflected in drug prices and medical costs, and this is therefore not in the patient's best interest. There is a need to consider expanding the indications for effective drugs for diseases that have the same underlying mechanism, a process that does not necessarily require clinical trials that entail large amounts of money and time. It may also be possible to use the scientific and theoretical evidence obtained from the close observation of patients on an everyday basis and analysis, an attitude that is also common to the way of thinking that is key to the treatment I provide.

Medications for treating cephalic hypersensitivity syndrome and the molecular biology of synaptic plasticity

At the risk of repeating myself yet again, patients with cephalic hypersensitivity syndrome have a wide variety of complaints. I have inferred the mechanisms of these disorders from the commonalities of the drugs that treat them effectively. The table compares the medications for treating cephalic hypersensitivity syndrome described in Chapter 1 with the recommendations given in the guidelines for epilepsy, depression, chronic headache, fibromyalgia, and chronic pain, and summarizes their mechanisms of action. The table given as a reference was presented as the clinical pharmacological characteristics of antiepileptics, and what can be seen from these two tables is that many antiepileptics have an inhibitory effect on sodium and calcium ion channels.

Column

●The wisdom of older people

I have already mentioned Gerson therapy, the main pillar of which is a low-salt diet, in Chapter 1, but while reading Gerson's works, I suddenly remembered something. This was about pine trees. When I was a boy, my grandmother used to put bundles of pine needles tied up with string into the bath. "You should really use needles from pine trees that grow by the sea, but you can't get those here," she would say. Some decades later, I was making a business visit to Gengo Tsujita, Director of the Tuberculosis Sanitorium (the present-day Minami-Okayama Medical Center), when I noticed that the sanitorium was set within a dense pine wood. It offered its patients the benefits of a pine "forest bath."

The wisdom of our elders is a mighty thing, and this is not limited to pine trees. Today, a type of polyphenol extracted from pine needles and other sources is the focus of attention as being effective against menopausal syndrome and a range of lifestyle-related diseases, and research into its anticancer properties is also underway.

Yunus and Gerson were both clinicians as well as researchers. Since leaving the research laboratory at Okayama University, I too have been dealing with sick people to the best of my ability as a regular doctor. What I have felt over my long experience in everyday clinical practice is the universality of that phenomenon known as "sickness," and the wisdom of those people who have been faced with it. Drugs are useful, but most of them have been synthesized from natural medicinal plants or substances obtained as a result of our ancestors' experience. Substances that exist in the natural world will be easiest for people to use if they are taken in a form and at a dose close to their natural state. Yunus, Gerson, and I share similar ideas on this point.

I believe that a doctor's prescriptions and treatment policies should be based on a way of thinking that incorporates this viewpoint.

Overlap between medication for the treatment of cephalic hypersensitivity syndrome and drugs recommended in treatment guidelines, and their mechanisms of action

First-choice medication for cephalic hypersensitivity syndrome (Oota)	Guideline recommendations					Potential-dependent Na-channel blocking	Inhibitory neural potentiation by GABA concentration/function enhancement	Glutamate liberation, receptor blocking	Anion transfer blocking by carbonic anhydrase inhibitor in the brain	Membrane potential-dependent Ca-channel blocking	Reduced neurotransmitter release by synaptic vesicle protein binding	Blocking of serotonin/noradrenaline reuptake in the brain	Blocking of serotonin/dopamine reuptake in the brain
	① Epilepsy	② Depression	③ Chronic headache	④ Fibromyalgia	⑤ Chronic pain								
Tryptanol (amitriptyline)/Noritren (nortriptyline)		●	●	●	●							○	
Depakene (sodium valproate)	●	●	●				○	○					
Rivotril (clonazepam)	●		●			○	○						
Risperdal (risperidone)													○
Tegretol (carbamazepine)	●	●	●		●	○							
Lamictal (lamotrigine)	●	●	●			○		○		○			
Topina (topiramate)	●		●			○	○	○	○	○			
E Keppra (levetiracetam)	●				●						○		
Mystan (clobazam)	●					○	○						
Gabapen (gabapentin)	●		●	●	●		○			○			

① Japanese Society of Neurology (Editorial supervisor): Clinical Guidelines for Epilepsy Management 2010. Igaku Shoin. [In Japanese]
② Japanese Society of Mood Disorders Treatment Guidelines 2012. [In Japanese]
③ Japanese Society of Neurology/Japanese Headache Society (Editor): Clinical Guidelines for Chronic Headache Management 2013. Igaku Shoin. [In Japanese]
④ Japan College of Fibromyalgia Investigation (Editor): Fibromyalgia Guidelines 2013. Japan Medical Journal 2013. [In Japanese]
⑤ Japanese Society of Neurological Therapeutics (Editorial Supervisor): Standard Neurological Therapy: Chronic pain 2013. [In Japanese]

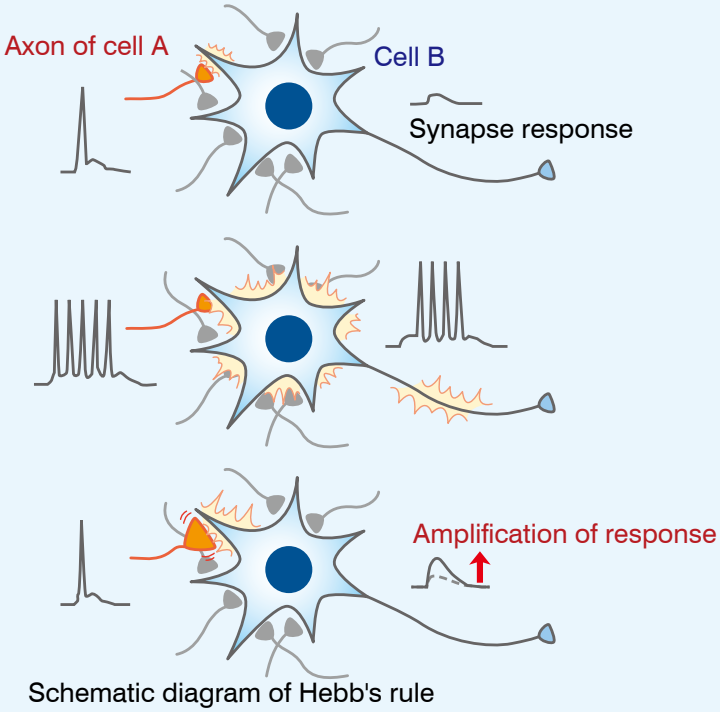
Reference: Clinical pharmacological characteristics of antiepileptics

Generic name	Mechanism of action	Indications	Normal dose		Biological half-life (hours)	Time to reach peak value (hours)	Time to reach steady-state (days)	Protein binding rate (%)	Therapeutic serum concentration range (μg/ml)	Main side effects
			Adult (mg/day)	Child (mg/kg/day)						
Phenobarbital (PB)	Ca, GABA, Glu, etc.	Ps, s-GTC, GTC	50~150	2~5	20~130	1~5	14~21	45~60	10~25	Sedation, drowsiness, disquiet, agitation, hyperactivity, rash, abnormal bone metabolism, low folic acid
Primidone (PRM)	Na, PB mechanisms	Ps, s-GTC, GTC	250~1,000	10~20	3~16	2~4	4~7	0~22	4~12	Sedation, drowsiness, weakness, ataxia, hyperactivity, double vision, dizziness / vertigo, rash
Phenytoin (PHT)	Na, Ca, etc.	Ps, s-GTC, GTC	100~300	3~10	7~42	2~12	4~10	80~95	10~20	Nystagmus, double vision, ataxia, gingival proliferation, hirsutism, rash, liver damage, immunosuppression, low folic acid, megaloblastic anemia
Carbamazepine (CBZ)	Na, Glu, etc.	Ps, s-GTC, GTC	200~1,200	5~20	3~26	2~8	3~7	65~85	3~12	Dizziness / vertigo, double vision, nystagmus, ataxia, drowsiness, rash, gastrointestinal disturbance, leukopenia, decreased folic acid, hyponatremia, liver damage
Zonisamide	Na, Ca, GABA, Glu, etc.	Ps, s-GTC, GTC, My; WS, LGS	200~600	4~10	24~60	2~6	10~15	45~50	10~30	Drowsiness, enervation, slowing of mental activity, loss of appetite, hypohidrosis, kidney/urinary tract stones
Sulthiame (ST)	Carbonic anhydrase inhibitor	Ps, s-GTC, GTC	200~1,000	5~10	2~10	1~5	-	-	6~20	Heavy-headedness, hyperventilation, loss of appetite, paresthesia, ataxia, drowsiness
Gabapentin (GBP)	Na, Ca, GABA, Glu	Ps, s-GTC, GTC	900~1,800	30~40	4~7	2~3	2	0~3	2~20	Drowsiness, dizziness / vertigo, headache, double vision, malaise, aggravated seizures, emotional instability, abnormal behavior
Topiramate (TPM)	Na, Ca, GABA, Glu, Carbonic anhydrase inhibitor	Ps, s-GTC, GTC, My, Ab; LGS	200~400	1~9	12~30	1~4	3~5	13~17	9~12	Drowsiness, dizziness / vertigo, decline in cognitive function, weight loss, kidney/urinary tract stones, metabolic acidosis, hypohidrosis
Acetazolamide (AZA)	Carbonic anhydrase inhibitor	Ab, My, GTC, s-GTC, Ps; WS, LGS	200~750	10~20	10~15	1~3	2~5	90~95	8~20	Dizziness / vertigo, paresthesia, headache, loss of appetite, polyuria, dry mouth, weakness
Ethosuximide	Ca	Ab, My	500~1,500	10~30	25~60	1~4	6~12	0~10	40~100	Gastrointestinal disturbance, drowsiness, abnormal behavior, hiccups, bone marrow suppression, rash, generalized erythematosus
Valproate sodium (VPA)	Na, Ca, GABA, Glu, etc.	Ab, My, GTC, s-GTC, Ps; WS, LGS	500~2,000	10~30	4~15	0.5~4 4~10 (sustained-release formulation)	2~4	84~95	40~100	Gastrointestinal disturbance, liver damage, coagulation disorder (low platelet count/fibrinogen), obesity, hair loss, diuresis, tremors, drowsiness, pancreatitis
Diazepam (DZP)	Na, Ca, GABA	Ab, My, GTC, s-GTC, Ps; WS, LGS	4~30	0.2~0.7	8~40	1~3	3~10	96~98	0.2~0.5	Sedation, drowsiness, decline in mental activity, ataxia, low muscle tone, salivation, excessive airway secretions
Nitrazepam	Na, Ca, GABA	Ab, My, GTC, s-GTC, Ps; WS, LGS	2~20	0.1~0.5	18~35	1~4	6~8	85~88	0.02~0.2	Sedation, drowsiness, decline in mental activity, ataxia, low muscle tone, salivation, excessive airway secretions
Clonazepam (CZP)	Na, Ca, GABA	Ab, My, GTC, s-GTC, Ps; WS, LGS	1~10	0.05~0.2	20~40	1~4	4~6	86	0.02~0.08	Drowsiness, decline in mental activity, ataxia, low muscle tone, abnormal behavior, sleep disturbance, salivation, excessive airway secretions
Clobazam (CLB)	Na, Ca, GABA, etc.	Ab, My, GTC, s-GTC, Ps; WS, LGS	10~30	0.2~0.8	10~30	1~4	6	83~85	0.1~0.4	Drowsiness, decline in mental activity, ataxia, low muscle tone, abnormal behavior, sleep disturbance, salivation, excessive airway secretions

Na: Na^+ channel inhibition; Ca: Ca^{2+} channel inhibition; GABA: γ-aminobutyric acid (GABA) activation; Glu: glutamate suppression; Ps: partial seizures; s-GS: secondary generalized seizures; GTC: generalized tonic-clonic seizures; Ab: absence seizures; My: myoclonic seizures; Ws: West syndrome; LGS: Lennox-Gastaut syndrome.
Source: Table 1 in Yamatogi, Yasuko. Drug treatment of childhood epilepsy. Journal of the Japanese Medical Association 136(6), P.i090. [In Japanese]

• **Synaptic plasticity**

Hebb's rule is a hypothesis postulated by Canadian psychologist Donald Hebb in 1949, which predicted that if the firing of neuron A results in the firing of neuron B, the connection between those two neurons will strengthen. This is the basic phenomenon in the brain that underlies learning. Today, the rule of synaptic plasticity proposed by Hebb, based on the theory that long-term changes at a synapse (the junction between two neurons) change the efficiency with which signals are transmitted, constitute the mechanism of learning, is known as Hebb's rule [10].



Schematic diagram of Hebb's rule

It has already been suggested that the mechanism of long-term potentiation in synaptic plasticity may be involved in the development of allodynia and hypersensitivity through somatosensory stimulation [11–14]. Many of the drugs on which I have focused as effective treatments for cephalic hypersensitivity syndrome, such as antiepileptics and antidepressants, act to block sodium and calcium channels. Work is still in progress on the molecular biological analysis of ion channels, including genetic factors, and the construction of a model that explains the entire picture may well not be a simple matter. Classically, cells possess ion channels, and the major principle that if their functions are not preserved then life cannot be maintained is true for every type of disease. The human body has developed systems for maintaining homeostasis that appear complex and elaborate at first glance, but the majority of the elements that compose amino acids, as well as the ions that are released and received at the synaptic terminals, belong to a limited range that are common on Earth: nitrogen, carbon, oxygen, hydrogen, calcium, magnesium, phosphorus, sodium, potassium, and a few others. When eukaryotic organisms first emerged around 2.2 billion years ago, the main elements available for them to use were potassium and magnesium. During the long process of evolution, cells came to store potassium and magnesium inside themselves while as far as possible excreting elements that subsequently became more common in the planetary environment, such as sodium and calcium, outside the cell, and these thus came to be used as the signals forming the intercellular network.

In this light, it is natural to focus on the metabolic functions and kinetics of Na^+, K^+, Ca^{2+}, Mg^{2+}, and other elements that account for the majority of ions, as well as amino acids, amines, and other neurotransmitters, when looking at the underlying mechanism of cephalic hypersensitivity syndrome. So far, the following discoveries have been made that may contribute to a molecular biological explanation of cephalic hypersensitivity syndrome.

- Among the neuronal Na^+ channel subunits, those associated with pain are Nav 1.3, Nav 1.7, and Nav 1.8, but currently there is no medication that acts specifically on those subunits [15–18].
- Nociceptive stimuli, including pain sensation, are transmitted via Type A δ and Type C fibers, with Type C being the main type associated with hyperalgesia.

High-voltage-activated calcium channels are involved in the occurrence of hyperalgesia and allodynia. Type A β fibers are also involved in allodynia [19].

- Long-term potentiation of pain-related neurons and synaptic plasticity are caused by calcium ion influx through NMDA receptors. NMDA receptor activation is blocked by magnesium ions at normal membrane resting potential, but if input by repeated impulses leads to the maintenance of depolarization by AMPA receptors and others, electrical repulsion causes the magnesium to dissociate, activating the NMDA receptors [20].
- When NMDA receptors are activated by depolarization, the calcium ion influx elevates the intracellular calcium ion concentration, activating Ca^{2+}/calmodulin-dependent protein kinase, protein kinase C, and the tyrosine kinase Fyn, inducing long-term potentiation [20].
- The magnesium ion blocking of NMDA receptors is essential for the induction of the expression of genes associated with long-term memory [21].
- The monoamine hypothesis: Monoamines are a class of neurotransmitters that include dopamine, noradrenaline, adrenaline, serotonin, and histamine. Hypotheses have been proposed for the involvement of the noradrenaline, serotonin, and dopamine systems in depression; the centrality of the dopamine system in bipolar disorder, with the additional involvement of noradrenaline and serotonin; the involvement of the serotonin system in anxiety disorder; and the centrality of the dopamine system in schizophrenia, with the additional involvement of NMDA-type glutamate receptors [22].
- The nervous system, immune system, and endocrine system are engaged in integrated biological regulation as an interacting complex system while maintaining the individual systems [23 24].

Nervous system–endocrine system: hypothalamic hormones–anterior pituitary hormones

Anterior pituitary-releasing hormones: growth hormone-releasing hormone, growth hormone-inhibiting hormone, prolactin-inhibiting hormone, thyrotropin-releasing hormone, corticotropin-releasing hormone, gonadotropin-releasing hormone

Posterior pituitary hormones: vasopressin, oxytocin

Nervous system–(endocrine system)–immune system: Hypothalamic–pituitary–adrenal system → immune system

Hypothalamic–pituitary–gonadal system → immune system
Hypothalamic–pituitary–thyroid system → immune system
Sympathetic nervous system–noradrenaline → immune system
Parasympathetic nervous system–substance P, dopamine, calcitonin gene-related peptide, corticotropin-releasing hormone, gonadotropin-releasing hormone → immune system
Vagus nerve–acetylcholine → immune system

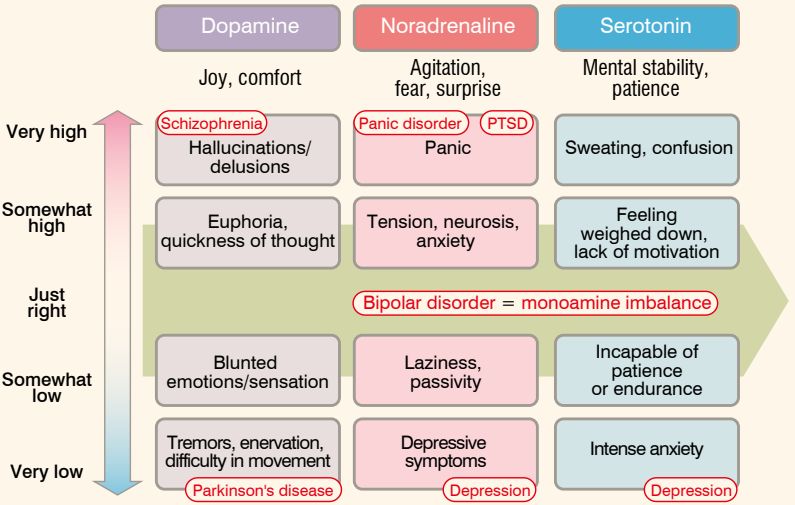
Vagus nerve → interleukin 1, interleukin 6, tumor necrosis factor α ← (inhibition) interleukin 4, interleukin 10, transforming growth factor β
Glial cells[25]/microglia, astrocytes, oligodendrocytes, etc. → immune system

From brain neurohormones to cephalic hypersensitivity syndrome: Commonalities with psychiatric and neurological disorders

I believe that it is the serotonin and dopamine systems that are generally involved with cephalic hypersensitivity syndrome. It may be that easily treated cases of cephalic hypersensitivity syndrome involve the serotonin system, whereas less easily treated, so-called intractable cephalic hypersensitivity syndrome, involves the dopamine system.

As I explained in Chapter 1, brain hormones comprise dopamine, noradrenaline, adrenaline, and acetylcholine, which work smoothly together thanks to serotonin, which plays a motherly role. Cephalic hypersensitivity syndrome does not develop if these hormones are in balance. What opens the door to cephalic hypersensitivity syndrome is not a potentially life-threatening major injury or illness, but rather the accumulation of everyday stress. Stiff shoulders and fatigue are the most obvious signs. The illustration shows the relationship between psychiatric and neurological disorders and an excess or deficiency of the three neurotransmitters apart from acetylcholine. Of course, in all cases, the real story is too complicated to be explained by a single substance, but depression is linked to the serotonin system, whereas schizophrenia and Parkinson's disease are linked to the dopamine system. Compared with schizophrenia, depression is

more strongly influenced by environmental than genetic factors and has a high rate of complete recovery if no other psychiatric disorders are present. Although the therapeutic environment for schizophrenia is far better today than it once was, it is more complex than depression, and complete recovery is difficult. In terms of its long-term prognosis, it will become severe in 10–20% of people, who will not recover [26]. New treatments are also being tried out for Parkinson's disease, which is a designated intractable disease. The same factors apply as with cephalic hypersensitivity syndrome. The latter can be better understood if it is broadly divided according to the serotonin system + noradrenaline system and the dopamine system. The serotonin type is characterized by depression, anxiety and tension, and hypersensitivity, and I earlier explained it in terms of



Monoamine neurotransmitters regulate emotions such as joy, fear, and anxiety and play a central role in the memory of emotions, and abnormalities in their metabolism or signal transmission are closely related to psychiatric symptoms and disorders.

Monoamine excess or deficiency and psychiatric and neurological disorders (Source: Report of the Brain Symposium in Nagoya 2013) [In Japanese]

the mechanism of the autonomic nerves, which are also the part of the nervous system that becomes hypersensitive to pain stimuli. Many patients with cephalic hypersensitivity syndrome who complain of headache and other pains or stiff shoulders are thus of the serotonin type. It is usually easy to build up a good doctor-patient relationship with this type, and as they also make an effort to follow the treatment plan, they recover comparatively more readily.

Patients with the dopamine type, on the other hand, do not complain of pain despite their entire body being stiff and tight, perhaps because they have become dulled to feeling pain.

I have the impression that the more a patient talks loquaciously about their own complaints, the less likely they are to be meekly persuaded by the doctor's explanation, and little can be expected of them in terms of cooperating with the treatment plan.

What action do these neurotransmitters exert on our "minds," and how can the relationship between the stress of interpersonal relationships caused by the activity of the "mind" and the development of an illness be explained in terms of molecular biology? Both of these questions have yet to be properly answered.

Acetylcholine, the key player in cephalic hypersensitivity syndrome: from chronic mental pain to chronic physical pain

Chronic pain that is purely physical does not lead to the development of cephalic hypersensitivity syndrome. It is mental chronic pain that opens the door. As I have mentioned before, a molecular biological hypothesis has been proposed in which depression and schizophrenia are caused by a disturbance in the balance of monoamine brain neurohormones such as serotonin, but I conjecture that a different key player, acetylcholine, is deeply involved in cephalic hypersensitivity syndrome. My hypothesis is that acetylcholine causes chronic physical pain from the chronic mental pain due to the disrupted balance in serotonin and dopamine in the brain via its action on the autonomic nerves, or that it amplifies existing physical pain via chronic mental pain and the autonomic nerves, leading to the development of intractable cephalic hypersensitivity syndrome.

In Parkinson's disease, there is insufficient dopamine and an excess of acetylcholine in the brain. This is manifested as cognitive and motor impairment. In Alzheimer's disease, the level of acetylcholine in the brain decreases, and cognitive impairment occurs. Aricept (donepezil), a drug developed as a treatment for Alzheimer's disease, increases acetylcholine via its cholinergic action and is believed to improve cognitive function. There is now growing evidence that the cause of myasthenia gravis, a disease characterized by diminished muscle strength, is that acetylcholine receptors are one of the target molecules for autoimmunity.

Acetylcholine was identified in the 19th century, and as such is the earliest neurotransmitter to have been discovered. Studies of acetylcholine receptors in the peripheral nerves, and particularly in neuromuscular junctions with muscles innervated by motor nerves, have progressed to the extent of determining their molecular structure [27]. The most important acetylcholine receptors are muscarinic and nicotinic receptors. These have different mechanisms, as muscarinic acetylcholine receptors are G-protein-coupled receptors, and nicotinic acetylcholine receptors are ligand-gated ion channels, but both play important roles in the intracellular and extracellular movement of K^+, Na^+, and Ca^{2+} ions. Acetylcholine has also been shown to enhance the long-term potentiation of memory in the hippocampus [28]. It has been suggested that noradrenaline may also promote this action [29], but many aspects of its joint action and properties together with other brain hormones in the central nervous system remain unclear. The importance of the wide-ranging functions of acetylcholine outside the neurons as a mediator of intercellular communication is gradually being recognized, but has yet to be fully explained. Koichiro Kawashima has stated that acetylcholine is also expressed in plants and eukaryotic organisms that do not possess a nervous system and proposed that it may have been used as a neurotransmitter when animals with a nervous system emerged in the process of animal evolution [30].

In Chapter 1, I explained that cephalic hypersensitivity syndrome is a disease that was predestined when humans acquired the ability to walk on two legs. Acetylcholine has existed on this earth long before the emergence of humanity and has played a role in biogenic activity. Without this premise of these properties of acetylcholine, it is impossible to explain the underlying mechanism of cephalic hypersensitivity syndrome.

In 2013, President Barack Obama of the United States announced the BRAIN (Brain Research through Advancing Innovative Neurotechnologies) initiative providing ten years of priority research funding. Almost simultaneously, Europe and Japan also allocated large amounts of funding to genetic and molecular biological studies of the brain and mind as priority research areas, and these studies are now proceeding.

To explain the mechanism of cephalic hypersensitivity syndrome, it will be necessary to elucidate the relationships between these brain hormones and the nervous system on the one hand and synaptic plasticity and long-term potentiation and depression on the other. This is truly cutting edge. Although a few related studies have been carried out, they are still at the level of animal experiments. Research on cranial neurons, even in other mammals, has in some cases apparently yielded completely contradictory results in animals such as rats and rabbits on the one hand and primates, which form complex social groups, on the other. The American research plan includes the development of neurologically related animal models ranging from nematodes to non-human primates. The brain, described in the Human Brain Project report as consuming "about 30W, the same as an electric light bulb, thousands of times less than a small supercomputer," is becoming better understood, and once studies on the fact that "sickness comes from the spirit," as the Japanese proverb puts it, are explained on the molecular biological level, the majority of my conjectures may well be validated.

3 Hypothesis 3: A biopsychosocial model is appropriate for the treatment of cephalic hypersensitivity syndrome

To repeat myself yet again, Yunus, Finnerup, and I all share a common concern for "treatment that is easy for people to undergo." Yunus in particular has pointed out the importance of the doctor-patient relationship in treatment, and at its root, this is a rejection of the "body–mind" and "disease–illness" dualisms [13]. Yunus frequently uses the term "biopsychosocial" coined in 1977 by George Engel [31] and raises the issue of doctors who make decisions on whether a patient has a "physical disorder" or a "mental disorder" on the basis of objective test results [3 32].

The biopsychosocial model

This model was put forward in 1977 by Engel, who was then Professor of Neurology at Rochester University in the United States. Engel pointed out the limitations of the biomedical model prevalent in the medical establishment by quoting Seymour Kety's 1974 study on the experience of illness by patients with diabetes and schizophrenia, stating that "The presence of the biochemical defect of diabetes or schizophrenia at best defines a necessary but not sufficient condition for the occurrence of the human experience of the disease, the illness. More accurately, the biochemical defect constitutes but one factor among many, the complex interaction of which ultimately may culminate in active disease or manifest illness" [31].

Based on this, he proposed a new medical model in which the way in which illness is experienced by different patients and how this is reported is affected not only by biological factors but also by psychological, social, and cultural ones.

Cognitive behavioral therapy

As I have already described in Chapter 1, Oota-style cognitive behavioral therapy is included in one of the three arrows of my algorithm of treatment, "improving thinking." The cognitive behavioral therapy that now has a firm place in psychotherapy was in its narrow sense systematized by Aaron Beck in the 1960s, and its use along with drug treatment is now recommended in guidelines for the care of conditions including depression, chronic pain, fibromyalgia, and

headache. However, as Beck himself said, cognitive behavioral therapy is at its root a common sense-based approach, and the origins of the idea that people's perceptions are dominant over their feelings and behavior, and that conversely the way in which activities and behavior are carried out can affect thought patterns and feelings, can be traced back to Greek philosophy and Eastern thought. Beck's cognitive behavioral therapy may thus be regarded as a sophisticated methodology, but is not the be-all and end-all.

Cognitive behavioral therapy may be an ancient concept, but clinical studies of its use as a form of psychotherapy are comparatively recent. From the perspective of behavioral therapy, in the 1950s and 1960s, clinicians began to explore the possibilities of desensitization and relaxation training for phobias, based on Pavlov's famous classic conditioning experiments and Skinner's theory of operant conditioning. In terms of emotions and perceptions, Albert Ellis proposed rational emotive behavioral therapy, based on the idea that people make judgments in the light of beliefs rather than events, and that emotions are evoked as a result. It was Beck who first integrated these approaches from various different perspectives and systematized the theory of intervention for emotional disturbance.

Characteristic of the cognitive behavioral therapy developed by Beck is that it is a sophisticated combination of techniques for helping patients to notice their own internal thoughts associated with emotions such as depression, anxiety, and anger, and to correct them themselves. Normally patients undergo between five and 20 sessions lasting 45–50 minutes each. One feature is that it uses the Socratic method to enable patients to recognize and change their non-adaptive thoughts, by asking questions that stimulate their curiosity and intellectual appetite. Other techniques such as psychological education, role play, thought-change journaling, and task-based learning are also used to support patients in changing their own attitudes to rational ones [33].

In my own cognitive behavioral therapy, I do not demand anything difficult. Many of the patients who attend my clinics are already taking multiple medications and suffer from chronic pain and insomnia. Those with personalities that are almost pathologically earnest are not uncommon. They are the sort of

person that if they were told to perform breathing exercises for X minutes Y times a day, they would probably use a stopwatch. What is important is to tell them "It's all right. I'll make everything better," and "Just XX is enough." They have to be healed before they can change their behavior. Elastic band snapping therapy as a way of stopping automatic thinking and Magic Mirror therapy for release from negative thinking and self-affirmation are both effective for this purpose. Naturally these are used in combination with drug therapy.

Randomized comparative studies are in the process of demonstrating that cognitive behavioral therapy has some effect on the psychological aspects of patients with chronic pain or psychosomatic conditions, but studies from the neuroscientific or molecular biological perspectives are only just starting to take shape. As with studies on the mechanisms of pain, there have been a few reports of fMRI and other image analysis studies of changes in areas of the brain that handle emotions, perception, and memory. The day cannot be far off when my own algorithm of treatment, which is now a convincing inference, is accepted in clinical institutions as a matter of course.

Some of the patients who have undergone my treatment have previously been told at other hospitals that they "do not have a disease" and have had the experience of doctors becoming angry with them when they have repeatedly gone to be examined for their complaints. This is exactly the problem with doctors' thinking that was identified by Yunus. The diagnosis of central sensitivity syndromes and cephalic hypersensitivity syndrome is the salvation of patients who have been pigeonholed as suffering from a "frame of mind" or "mental illness" and for whom the wrong treatment has aggravated their symptoms. Its effect is not all a placebo effect, as at its root lies the algorithm of treatment that can be explained in biological, that is, scientific, terms.

At this stage, "standardization" that would enable the diverse range of chronic illness syndromes suffered by patients to be effectively classified and an accurate diagnosis reached has yet to be achieved. Recently, however, it has become possible to use some forms of diagnostic imaging for psychiatric disorders, and this has shown that chronic pain and stress result in atrophy of the hippocampus[14]. The day cannot be long in coming when it will be possible

to diagnose central sensitivity syndromes and cephalic hypersensitivity syndrome by means of an objective index.

Even if an objective diagnosis were to become feasible and treatment could be administered mechanically, however, cognitive behavioral therapy, in which the doctor listens to the patient's complaints about their suffering and enters into a dialogue with their feelings in order to treat them, will become even more important and should not be viewed lightly. It is the doctor's important role to elicit the patient's own biological capacity to heal and to encourage the switch from a vicious cycle to a positive circle of synaptic plasticity. Both Yunus and I are united in this assertion. That means that patients themselves must make an effort and cooperate in the course of their treatment. It is also important to take account of complex influences such as family and work, living environment, and economic circumstances. In this sense, the distortion generated by drug development requiring vast sums of money and the consequent economic competition that was suggested by Finnerup and her colleagues cannot be overlooked.

The table shows a summary comparison of the characteristics of the three of us. Yunus is not arguing about philosophical dualism, but is rather refusing to admit dualistic splits into treatment. I have always held a Buddhist worldview, as will be obvious throughout the cases described in Part 2. No small number of patients have been saved by hearing me speak the words, "I will definitely cure you." Of course, this is a "trick" based on long years of clinical experience. In order to heal and comfort people suffering from illness and pain, treat the innate human capacity honestly, in other words, scientifically. This is my message, and that of Yunus and Finnerup, to the next generation of doctors.

Footnote

Gerson therapy was developed 60 years ago in a very different era, and has therefore not been included in the comparison table. However, Gerson and I do have some things in common in terms of our breadth of vision, looking at the whole of natural science rather than merely medicine, as well as an honest analysis of patients' conditions without limiting the scope of disease. The Gerson therapy that he developed is based on the simple principle of

eliminating cancer cells by normalizing cells and the cellular environment. Although many aspects still remain unclear, this is also consistent with the assertion made by Mina Bissell of the Lawrence Berkeley National Laboratory that if in the right microenvironment, cancer cells are unable to proliferate and will normalize [34]. Gerson never spoke of the difficult position in which he was placed, but according to the biographies written by his daughter and grandchild, he was placed under unjustified pressure by colleagues who were jealous of his unending line of patients as well as by the American medical establishment. Although he never spoke in detail about his own worldview, he was praised by Albert Schweitzer as a true scientist "worthy of the Nobel Prize."

Characteristics of the thinking of Yunus, Finnerup, and Oota

	YunusF	innerupO	ota
WorldviewR	ejects dualism	Not mentioned	Buddhist worldview (non-dualistic)
Specialist field	Rheumatism, fibromyalgia	Neuropathic pain, traumatic neuropathy	Neurosurgery, epilepsy
Claims	Central sensitivity syndrome Developed disease classification and treatment method	Evidence-based pain treatment	Proposed cephalic hypersensitivity syndrome and developed treatment method
Treatment method	Combination of drug therapy and other treatments based on central sensitization	Pharmacologically based drug therapy	Combination of drug therapy and other therapies based on synaptic plasticity
Other	Advocated the importance of a biopsychosocial understanding in treatment	Emphasized the influence of the financial aspects of drug development on treatment, and mentioned the efficacy of treatment with multiple drugs rather than monotherapy	Advocates a general treatment method for symptoms formerly classified as chronic illness syndrome

Chapter 3

Quoted Sources

(1) Yunus MB. Central sensitivity syndromes: a new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. Semin Arthritis Rheum. Jun.37(6).339-52. 2008.
(2) Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin Arthritis Rheum. Jun.36(6).339-56. 2007.
(3) Yunus MB. The concept of central sensitivity syndromes In: Wallace DJ, Clauw DJ. Eds.; Fibromyalgia and other central syndromes. Philadelphia: Lippincott Williams & Wilkins. 2005. pp.29-44.
(4) Yunus MB. The prevalence of fibromyalgia in other chronic pain conditions. Pain Res Treat. 573-584. 2012. Epub. 2011. Nov 17.
(5) Fitzcharles MA. *et al*. The clinical concept of fibromyalgia as a changing paradigm in the past 20 years. Pain Res Treat. 184-835. 2012. Epub. 2011. Oct 29.
(6) Shimizu, Toshihiko *et al*. *Nō kabin syōkōgun*. Nihon Rinsho-sha. 70(1).145-150. 2012. [In Japanese]
(7) Finnerup. NB. *et al*. Algorithm for neuropathic pain treatment: An evidence based proposal. Pain. 118.289-305. 2005.
(8) Finnerup. NB. *et al*. The evidence for pharmacological treatment of neuropathic pain. Pain. 150.573-581. 2010.
(9) Guidelines for drug therapy of cancer pain 2012 version [In Japanese]
http://www.jspm.ne.jp/guidelines/pain/2010/chapter02/02_04_03_02.php
(10) Takahashi, Naoya. Ikegaya, Yuji. Matsuki, Norio. Hebb's Rule. Brain Science Dictionary [In Japanese],
http://bsd.neuroinf.jp/wiki/ ヘブ則 (2012) [In Japanese]
(11) Youn. D. *et al*. Ionotropic Glutamate Receptors and Voltage-Gated Ca^{2+} Channels in Long-Term Potentiation of Dorsal Horn Synapses and Pain Hypersensitivity. Neural Plasticity. 2013. ID 654257, http://dx.doi.org/10.1155/2013/654257
(12) Ohnami.S. *et al*. Effects of milnacipran, a 5-HT and noradrenaline reuptake inhibitor, on C-fibreevoked field potentials in spinal long-term potentiation and neuropathic pain. British Journal of Pharmacology. 167.537-547. 2012.
(13) Sandkuhler.J.*et al*. Hyperalgesia by synaptic long-term potentiation (LTP): an update. Current Opinion in Pharmacology. 12.18-27. 2012.
(14) Laferriere.A. *et al*. PKM ζ is essential for spinal plasticity underlying the maintenance of persistent pain. Molecular Pain. 7.99. 2011.
http://www.google.co.jp/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=0CB0QFjAA&url=http%3A%2F%2Fwww.molecularpain.com%2Fcontent%2F7%2F1%2F99&ei=hsL6U5T
4J83i8AXaxYCIBA&usg=AFQjCNGEqh4gUTSgviqkdjjrmj96TPBwRw
(15) Watanabe, Shuzo. Discovery of voltage-gated sodium-channel blockers for the treatment of neuropathic pain. Folioa Pharmacologica Japonica. 140.201-205. 2012. [In Japanese]
(16) Fischer.TZ. *et al*. Familial pain syndromes from mutations of the Nav1.7 sodium channel. Ann.N.Y.Acad.Sci. 1184.196-207. 2010.
(17) Chevrier.P. *et al*. Differential modulation of Nav1.7 and Nav1.8 peripheral nerve sodium channels by the local anesthetic lidocaine. British Journal of Pharmacology. 142.576-584. 2004.

(18) Vijayaragavan. K. *et al*. Gating Properties of Nav1.7 and Nav1.8 Peripheral Nerve Sodium Channels. The Journal of Neuroscience. 21(20).7909-7918. 2001.
(19) Koyama, Natsu. Fundamental knowledge of pain and pain relief. Volume 1: Fundamentals. Gijutsu-Hyohron Co., Ltd. 2010. [In Japanese]
(20) Kandel ER. *et al*. (Editors). Kanezawa I and Miyashita Y (Editorial supervisors of the Japanese version). Principals of Neural Science, pp.1429-1489. [Japanese translation]
(21) Miyashita. T. *et al*. Mg^{2+} block of Drosophila NMDA receptors is required for long-term memory formation and CREB-dependent gene expression. Neuron. 74.887-898. 2012.
(22) Inoue T. The Monoamine Hypothesis. Brain Science Dictionary [In Japanese]
http://bsd.neuroinf.jp/wiki/ モノアミン仮説 (2012) [In Japanese]
(23) Kojima I. Integrated biological regulation of the nervous system, immune system, and endocrine system. In Nagai R and Iriki A (Editors). Dynamics of biological homeostasis by inter-organ systems. Experimental Medicine (extra edition) 31(5).91-195. 2013. Yodosha Co., Ltd. [In Japanese]
(24) Miyake S. Mind over cytokines: Crosstalk and regulation between the neuroendocrine and immune systems. Clinical and Experimental Neuroimmunology. 3.1-15. 2012.
(25) Kudo Y. Glial Cells. Brain Science Dictionary [In Japanese]
http://bsd.neuroinf.jp/wiki/ グリア細胞 (2012) [In Japanese]
(26) Ministry of Education, Culture, Sports, Science and Technology. Report of the "Strategic Research Program for Brain Science" Brain Program Announcement Symposium in Nagoya. The mental mechanisms created by molecules: tracing the molecules and genes that govern brain function from the latest technology. 2013. [In Japanese]
http://brainprogram.mext.go.jp/media/publication/130914_report.pdf
(27) RIKEN. Press release documentation. Investigating the functional structure of molecules that control muscle movement: the structure and activation mechanism of receptors revealed by electron microscopic analysis. June 26, 2003. [In Japanese]
http://www.riken.jp/~/media/riken/pr/press/2003/20030626_1/20030626_1.pdf
(28) JST. Strategic Basic Research Program. Research Institute of Science and Technology for Society. Brain science and education: Investigating the factors affecting children's intellectual and behavioral development in Japan. "Elucidation of molecular *mechanisms* for post-birth development of *learning* abilities and its application to *learning*." Manabe, Shunya *et al*. November 2002–October 2005. Final study report. Published materials. [In Japanese]
http://www.ristex.jp/result/brain/program/pdf/int01.pdf
(29) Korchounov A.*et al*. Neuromodulatory Neurotransmitters Influence LTP-Like Plasticity in Human Cortex: A Pharmaco-TMS Study. Neuropsychopharmacology. 36.1894–1902. 2011.
(30) Kawashima K. Origin of acetylcholine and expression of non-neuronal acetylcholine. Biomedical Gerontology. 34(4).12-24. 2010 [In Japanese]
(31) Engel GL. The Need for a New Medical Model: A Challenge for Biomedicine. SCIENCE. 196(4286).129-136. 1977.
(32) Yunus MB. Psychological aspects of fibromyalgia syndrome: a component of the dysfunctional spectrum syndrome. Bailliere's Clinical Rheumatology. 8(4).811-837. 1994.
(33) Wright JH. Basco MR. Thase ME. Translated by Ono Y. Learning Cognitive Behavioral Therapy: An Illustrated Guide. Igaku Shoin, 2007, pp.1-30. [Japanese translation]
(34) Bissell M. Bissell Laboratory Research Focus.
http://www2.lbl.gov/LBL-Programs/lifesciences/BissellLab/research.html

References

Japanese Society of Neurology (Editorial supervisor): Clinical Guidelines for Epilepsy Management 2010. Igakushoin. 2010 [In Japanese]
http://www.neurology-jp.org/guidelinem/tenkan.html
Japanese Society of Mood Disorders Treatment Guidelines 2013 [In Japanese]
http://www.secretariat.ne.jp/jsmd/mood_disorder/img/120726.pdf
http://www.secretariat.ne.jp/jsmd/mood_disorder/img/120331.pdf
Japan College of Fibromyalgia Investigation (Editor): Fibromyalgia Guidelines 2013. Japan Medical Journal 2013. [In Japanese]
http://minds4.jcqhc.or.jp/minds/FMS/CPGs2013_FM.pdf
Japanese Society of Neurology/Japanese Headache Society (Editor): Clinical Guidelines for Chronic Headache Management 2013. Igaku Shoin. [In Japanese]
http://www.jhsnet.org/guideline_GL2013.html
Japanese Society of Neurological Therapeutics (Editorial Supervisor): Standard Neurological Therapy: Chronic Pain [In Japanese]
https://jsnt.gr.jp/guideline/mansei.html
Japanese Society of Neurological Therapeutics (Editorial Supervisor): Standard Neurological Therapy: Restless Legs Syndrome [In Japanese]
https://jsnt.gr.jp/guideline/restless.html
Japanese Society of Neurological Therapeutics (Editorial Supervisor): Standard Neurological Therapy: Vertigo [In Japanese]
https://jsnt.gr.jp/guideline/memai.html
Bear M. Connors B. Paradiso M (Editors). Kato H. *et al*. (Translation supervisors). Neuroscience: Exploring the Brain, p. 391. Nishimura Shoten 2007. [In Japanese]
Keio CBT Program (Editors). Cognitive Therapy/Cognitive Behavioral Therapy Manual for Depression 2010. [In Japanese]
http://jact.umin.jp/pdf/cognitive_medical.pdf
Kety SS. From Rationalization to Reason. Am J Psychiatry. 131(9).957-963. 1974.

Part 2. Treatment of cephalic hypersensitivity syndrome: case reports

Case 1 : A 46-year-old woman suffering from stiff shoulder for many years

I don't remember exactly when it started, but I had suffered from stiff shoulder for around 10 years. Both shoulders would swell up so much that it was difficult to turn my neck, and throbbing pain at the base of my neck affected my ability to work. I was examined at many hospitals and underwent thorough testing from neck X-rays to CT and MRI, but they couldn't find anything wrong. The drugs they prescribed were always the same, including Myonal (eperisone hydrochloride), Lioresal (baclofen), Celecox (celecoxib), and Loxonin (loxoprofen sodium hydrate). One time, I took the drugs as directed and they damaged my stomach, giving me stomach ulcers. My friend advised me to go to Myojinkan Neurosurgery Clinic. Dr. Oota listened carefully to everything I had to say and examined me thoroughly.

Dr. Oota explained that the term '*katakori* (similar to 'stiff shoulder' in English)' seems unique to Japanese language. What we call stiff shoulder is actually stiffness of the muscles supporting the head. After asking about my medical history all the way back to senior high school, he announced that I didn't have stiff shoulder and that I was actually suffering from headaches. I objected, as I had never had headaches, and he responded that my brain was likely mistakenly perceiving the headaches as stiff shoulder. He recommended we try some drugs to relieve my brain, which was convinced that my shoulders were stiff and hurting. He explained the drugs he was prescribing and the importance of managing my sleep and bowel movements. He also taught me techniques to help with working, such as the correct sitting position when working at a desk, the importance of the distance between the computer screen and the eyes, and one-minute stiff shoulder exercises that can be performed even while working. Speaking of which, there were also some stiff shoulder exercises posted on the Myojinkan Neurosurgery Clinic homepage. He told me that if I followed his advice for a month, my stiff shoulder would definitely get better. I stopped taking all painkillers and took only the drugs prescribed by Myojinkan Neurosurgery Clinic, and before even a month was up, my stiff shoulder quickly started to get better. I could turn my neck easily, and I was able to work without any problems. When I asked Dr. Oota what kind of drug he gave me, he told me that it was an antiepileptic. I was, and still am, amazed.

Case 2 : A 40-year-old man whose ability to work was affected by stiff shoulder and hand numbness

After undergoing surgery for hip osteoarthritis at a university hospital nine years ago, I experienced occasional numbness in my limbs. Then, about 18 months ago, my stiff shoulder, neck stiffness, right-hand numbness, and other symptoms got worse. On several occasions, when I went to turn on my computer after arriving at work, my right hand got stuck in a fist and I couldn't open it. Other times, when I tried to get up in the morning, my body felt like it was frozen stiff, and I was unable to move. I went from hospital to hospital and underwent various tests, but they could never find anything wrong. As my condition was cryptogenic, they advised me to see a psychiatrist. At the psychiatric hospital, they examined me and gave me a prescription, but the drug had no effect. I have a wife and child, and these lingering symptoms were affecting my work, so I was in a hurry to get well. I heard about Myojinkan Neurosurgery Clinic and went for an examination.

At my first appointment, Dr. Oota listened patiently to everything I had to say, and when he told me he could cure me, I was ecstatic. Until then, no matter what hospital I visited or which doctor had examined me, they had all turned me away saying they had no idea what was wrong. So, when Dr. Oota told me he would work with me, it made me happy and feel I could open up to him. He told me that my serious personality was at the root of my condition. That kind of cause hadn't even crossed my mind. However, after taking his advice to try not to do everything at home and work myself but to leave things to other people, I began to feel much less stressed. After following his instructions regarding walking every day, drinking enough water, and taking the prescribed Magmitt (magnesium oxide), I began to feel relief from the constipation I had suffered for many years. In the last two months, my stiff shoulder, head heaviness, and hand numbness have almost completely disappeared just by taking the prescribed drug once daily after my evening meal. None of the various tranquilizers and painkillers I tried before had any effect; however, once I changed to this drug, everything was totally different. I intend to continue trusting and receiving treatment from Dr. Oota.

From referral letter to the primary care doctor

Although somatoform disorder is also a possibility, this appears to be a case of cephalic hypersensitivity syndrome. In my opinion, the patient does not require

anti-inflammatory drugs. He has been prescribed carbamazepine, valproic acid, and amitriptyline to be taken once daily after the evening meal. Please continue his treatment for hypertension and other conditions unrelated to cephalic hypersensitivity syndrome.

Case 3 : A 70-year-old woman suffering from alleged depression for three years

My head felt heavy, I was irritable, I couldn't sleep at night, and people said I looked moody and seemed sluggish. Taking care of my grandchildren and cooking every day made me tired. Over the last two or three years, cooking had become a hassle, my grandchildren started to hate and rebel against me, and my previously dutiful daughter went through a divorce and also started to become hostile toward me, maybe because of her depression. I was examined at various hospitals, but they all recommended I see a psychiatrist.

At the psychiatric hospital, they diagnosed me with depression and tried various drugs. However, my head heaviness, dizziness, irritability, sadness, sluggishness, and other symptoms did not improve at all. I heard about Myojinkan Neurosurgery Clinic from an acquaintance and decided to give it a try.

After telling Dr. Oota all the details of my symptoms, as I had done many times before, Dr. Oota finally smiled and said, "You don't have depression!" When I asked him how he could know that just by looking at my face, he told me that my face did not look like the face of someone with depression; it was completely normal. He said it was easy to tell because the face is the mirror of the mind.

When I told him that my family situation was all bad — that my grandchildren called me an old hag and my daughter ignored me — Dr. Oota told me that my grandchildren rebelling against me was a sign that they were well brought up and that they were returning their favor in their own way.

"If this isn't depression, what do I have?" I asked him, and he told me that my brain had become hypersensitive to stress and that my symptoms indicated a state of 'stress response'.

When I asked him what I should do, he asked how I felt about stopping all of my antidepressants. I told him that would be disastrous and asked him to please give

me some drugs. He refused to give me any antidepressants because I didn't have depression but said he would give me something for the stress response. I was really nervous about decreasing my medication, but I trusted what he said, and after two weeks, my movements became lighter and my mood became brighter. After three weeks, I was able to do the cooking again. It's strange, but hearing Dr. Oota say, "Trust me. You do not have depression. You are completely normal." really helped me. I am also being careful about lack of sleep and constipation, which Dr. Oota told me were related to my symptoms. Thank you!

Case 4 : An 8-year-old boy unable to concentrate during lessons due to excessive daytime sleepiness

My son had fallen asleep as soon as he got home ever since he was in nursery. Even after starting elementary school, he got sleepy in the afternoons and would fall asleep in class. It was overlooked in the first grade, but once he started second grade, the teacher started telling him off for sleeping in class. Now he is in the third grade. His grades had dropped, and sometimes he handed in tests completely unanswered. At home, he would fall asleep watching television and sometimes even while eating. I became worried that it was interfering with his academic performance and school life and took him to Myojinkan Neurosurgery Clinic.

Dr. Oota diagnosed him with a condition called narcolepsy. I learned that narcolepsy can present as sudden weakness when the person experiences an emotional reaction such as laughing. Based on the results of genetic testing and the multiple sleep latency test (MSLT), Dr. Oota said it seemed to be narcolepsy. As drug safety in children has not been confirmed, he suggested we first try multiple naps during the day. However, after discussing it with the school, we realized that napping would be difficult; so, as a family, we decided that we wanted to try an adult narcolepsy drug. Now he has turned nine and has been prescribed a low dose of the adult narcolepsy drug, and he is much less sleepy during the day. Narcolepsy is apparently a hereditary disorder; as his parent, I feel responsible.

Case 5 : A 23-year-old woman whose daily life was affected by falling asleep during meetings even when she was standing and sometimes walking, who was unable to drive due to fear of falling asleep, and who became confused

From junior high school onwards, I used to feel very sleepy during class. In college, I sometimes fell asleep suddenly during lectures, even if I was standing up. I always felt sleepy no matter how much sleep I got at night, and when it was really bad, I was overcome by sleepiness even while standing or walking. This made me too afraid to get my driver's license, and it has affected my work.

I looked up my symptoms on the Internet and found they matched those of a condition called narcolepsy, and at the same time, I read about Dr. Oota. Because I was worried about the effect of my condition on my future work and life, I decided to visit Myojinkan Neurosurgery Clinic to be examined by Dr. Oota.

They wasted no time in administering some specialized tests. My EEG was normal, but I took the MSLT five times, and the results verified that I had narcolepsy. In the end, Dr. Oota told me I had narcolepsy with cataplexy. After looking at my sleep diary, he advised me to go to sleep earlier at night, and then gave me the long-awaited drugs. I instantly began to feel less sleepy at work. I stopped having nightmares, and I stopped becoming weak when I laughed. The drugs have no side effects, and I can go about my life with confidence.

Case 6 : A 12-year-old girl with symptoms of headaches and vomiting from infancy and recent tingling and numbness in the right hand

My daughter had suffered from headaches and vomiting from kindergarten age; the pain got better when she threw up. After starting elementary school, she would sleep in the nurse's office when she had a headache. When she was in the upper grades of elementary school, she started regularly having severe headaches, vomiting, and seeing flashing lights. Lately, she had been getting a pounding pain in the back of her head with tingling, numbness, and stiffness in her right hand. She was examined at a large hospital, but they said there were

no apparent abnormalities and gave her an injection to stop the vomiting. She took Bufferin (aspirin) about three times a week. She used to see flickering lights before she got a headache, and recently, even sunlight seemed to bring on a headache.

When she was examined at Myojinkan Neurosurgery Clinic, I was reassured to learn that the flickering lights were an aura preceding the headache called a 'scintillating scotoma,' and there was nothing wrong with her eyes. She was diagnosed as having light-sensitive migraine.

Since starting to take the prescribed drug, the headaches, nausea, vomiting, flickering lights, and numbness in her right hand have all disappeared. She still sometimes gets headaches, but when that happens, although it is a bit expensive, she takes a drug specifically for migraines rather than Bufferin (aspirin).

Case 7 : A 74-year-old man with confusional arousals who shouted and walked around at night

I was taking eight different drugs for atrial fibrillation and hypertension. I had trouble getting to sleep and often woke up in the night, making it difficult to sleep deeply, so I routinely took sleeping pills. Around two or three years ago, my family told me I was experiencing confusional arousals. I would often do things like roll out of bed, suddenly stand up on the bed, shout, and wander around at night. My family was worried, so I decided to get examined at Myojinkan Neurosurgery Clinic.

I didn't completely believe what my family said as I had absolutely no recollection of those things happening. Then, Dr. Oota performed an EEG while I was sleeping and recorded what happened while I slept using an infrared video camera. The video showed the strange things I did while I was asleep, such as standing up and rubbing the wall; I was totally shocked. I could also see that my legs frequently jerked.

I was diagnosed with REM behavioral disorder (RBD) and periodic limb movement disorder (PMLD), which Dr. Oota explained carefully to me. I didn't really understand what he was saying but just by taking one small tablet of Rivotril (clonazepam), a drug for epilepsy, before going to bed, my strange

nighttime behavior stopped, and I started to sleep well until morning. It was a strange illness, but I was cured thanks to the drug in the silver foil.

Case 8 : A 16-year-old girl with "monster headaches" that dramatically improved with a novel antiepileptic

I got 10-15 headaches a month that I self-treated with the over-the-counter drug Eve (ibuprofen) from when I was in junior high school. After starting senior high school, I increasingly had problems with relationships with other people, and that, combined with my introverted personality, prevented me from leaving my house. I was referred to a specialist clinic in another prefecture and was diagnosed with mild depression. I regularly visited the hospital for outpatient treatment, but my symptoms did not improve, and I was frequently late to or absent from school and spent a lot of time in the nurse's office. I often had headaches, and the school recommended I undergo brain testing. Thus, I visited Myojinkan Neurosurgery Clinic.

After Dr. Oota examined me, he told me that I snored all night, and my underlying migraines had become "monster headaches" because I had taken painkillers for such a long time. He started by prescribing various antiepileptics and antidepressants. However, nothing really worked, so he recommended that I have a tonsillectomy. After the surgery, it became easier to wake up in the morning, and I started to feel the effects of my new Topina (topiramate) prescription. My depressive mood got better, and my headaches improved until they were comparable with those of my twin sister.

Case 9 : A 10-year-old girl unable to sleep due to headaches and restless legs

Light and noise seemed to make my daughter's headaches worse. I get headaches too, but hers did not seem to be as bad as mine. She never had severe vomiting or anything like that. When she was thinking about things other than school and

studying, she stopped complaining about the pain. As a mother, I worried about her headaches, but I didn't think they were really that bad. However, she started to complain that her feet were restless from her ankles downward when she was lying in bed before she fell asleep, keeping her awake. I took her to a general hospital in another prefecture, and they gave her two kinds of drug that were supposed to be specific cures for restless legs syndrome, but they didn't seem to have any effect. I was worried because she couldn't sleep properly due to the headaches and restless feet, making her easily tired. Wanting to help my precious daughter, I took her as a walk-in patient to Myojinkan Neurosurgery Clinic.

Dr. Oota said that it didn't seem to be anemia, and it was strange that both types of drug for restless legs syndrome hadn't worked.

He said that we need to keep an eye on the restless feet before she falls asleep, as she is only 10. He prescribed an antiepileptic called Depakene (sodium valproate), which targets light sensitivity, and after she started taking it, the restless legs improved, and she started to sleep better.

Case 10 : A 34-year-old man who wanted to try subcutaneous injections after a diagnosis of cluster headache

For about eight years, I had been bothered by one headache attack a year that would last for one month. I got through that month by taking Bufferin (aspirin). I had a headache attack during a business trip to the Kanto region and went to the hospital. They tested me, but they said they couldn't find anything wrong and that it was probably cluster headache. They prescribed a migraine drug to be taken as needed. After a while, the headaches stopped. However, I then got a headache that lasted for a week. This time I went to a neurosurgical clinic, and they prescribed Maxalt (rizatriptan) to be taken as needed. Sometimes the drug would work depending on when I took it, but most of the time, it would have no effect. When I looked my symptoms up on the Internet, an article on the Myojinkan Neurosurgery Clinic homepage about the effectiveness of subcutaneous injections for cluster headache caught my eye, and I made an appointment.

After a detailed medical interview about my headaches, Dr. Oota said there

was no need for me to undergo any tests. He told me I showed typical cluster headache symptoms. Cluster headache is seasonal, but my headaches didn't clearly follow the seasons. Apparently, although cluster headaches often occur in the cold of winter and heat of summer, increasing numbers of people experience them regardless of the season. "Seems like both the earth and the people in it have become messed up" Dr. Oota said, laughing. Thanks to the Imigran (sumatriptan succinate) subcutaneous injections he prescribed, I can now work. I am very grateful.

Case 11 : A 41-year-old woman with repeated episodes of headaches that persist for one month then resolve as if they had never happened

I had suffered from headaches since senior high school and took over-the-counter Bufferin (aspirin). When I was 20, I was examined and tested at a neurology clinic, and they told me it was migraines caused by the blood vessels in my brain. They gave me Cleamine S (ergotamine tartrate/anhydrous caffeine/isopropylantipyrine), but it had very little effect. In recent years, I had been getting headaches for one month twice a year.

I would roll around in such pain that I could not keep still. I shocked my husband by pleading with him to cut my head off. I suffered from headaches for about one month last summer and one month this spring. I would take painkillers and push on through. Then after a month, the headaches would suddenly stop. This cycle kept repeating.

I was examined at Myojinkan Neurosurgery Clinic and underwent a medical interview about my headaches. Dr. Oota said that as my intraocular and blood pressure were normal and I had already undergone brain testing, there was no need for further tests. He told me my condition was called cluster headache. "Although standard migraine drugs can work, they aren't very effective," he informed me, and recommended subcutaneous injections. I was scared of the injections at first but they work really well and have helped a lot.

Case 12 : A 37-year-old woman effectively treated with oral drugs after a diagnosis of cluster headache, which is rare in women

My headaches started when I was in high school. At first they responded to over-the-counter painkillers, but over time, these started being less effective, and I went from two to four to six then eight tablets a day. Eventually, they stopped working altogether. I tried other drugs, but ended up having to take headache medication every day for a month. While I was at college, I always carried two boxes of headache drugs around with me in my pocket. After starting work, my headaches continued for two years. Then I moved to another prefecture, and strangely, the headaches suddenly stopped completely for four or five years. However, when I turned 27, they started again. They were concentrated within one to two months once or twice a year.

I was examined at Myojinkan Neurosurgery Clinic and underwent a medical interview about my headaches. Dr. Oota diagnosed me with suspected cluster headache, which is rare in women, and started me on oral drugs. He prescribed Vasolan (verapamil hydrochloride) and two kinds of antiepileptics to be taken in the mornings and evenings. These have made the headaches much better. I still have pain but it clears up quickly, and I am once again able to do the work I need to do, including housework, and to live a normal life. Previously, I had to foist housework and other work onto my family until the medication took effect, but the new drugs act quickly, making it easier for my family, too. The daily oral drugs and nasal drops both work well and have helped a lot. Dr. Oota said that both of the antiepileptics (Depakene (sodium valproate) and Topina (topiramate)) are working well.

Case 13 : A 59-year-old woman suffering from numbness in her limbs for four years

I had experienced numbness that extended down both arms right to my fingers since March four years ago. It started in my left arm and then spread to my right. Around May, I had lower back pain and visited an orthopedics

department where I underwent an MRI. I had neck traction and hot pack therapy for about one year, but there were no improvements. From around March last year, I experienced numbness down to both legs and feet and tingling pain from my knees to my toes. This gradually got worse, and I started taking Lyrica (pregabalin) painkillers. However, my symptoms continued to worsen, and increasing the Lyrica (pregabalin) dose had no effect. My legs were numb from the moment I woke up. It was terrible when I sat down, but lying down didn't help. If I woke up in the night, the numbness and tingling stopped me from getting back to sleep, and I had to start taking sleeping pills. The numbness didn't stop me from walking or and did not majorly get in the way of my daily life, but when it was bad, I couldn't cook or do the laundry or vacuuming. I had to spend increasing amounts of time lying down resting. One month ago, my regular orthopedist told me that as my MRI results showed my herniated disc had resolved and there were no other abnormalities, there was no need for further treatment, and he discontinued my Lyrica (pregabalin) and Depas (etizolam) prescriptions.

Although I still had numbness and pain in all my limbs, I was now not receiving any treatment. I was so anxious and didn't know where to turn, and then I heard about the cephalic hypersensitivity syndrome hotline. I called them and ended up going in to see Dr. Oota. By that point, the numbness was so bad that I could not fall asleep, so I was taking Lendormin (brotizolam). Dr. Oota noted that I had previously undergone a lot of testing and said that they didn't need me to take any more tests at that point. My blood work showed low platelet and white blood cell counts, and some other counts were slightly outside the normal range. Thus, he told me I might need treatment in coordination with an internal medicine specialist. In the meantime, he put me on close to a pediatric dose of an antiepileptic and four kinds of antidepressants combined with vitamin supplements to be taken at 8 pm daily and said they would continue to monitor my blood work. "You will absolutely get well," he told me. The numbness improved within two or three days of starting to take the drugs. After four weeks, the numbness and tingling pain has decreased to about a two on a scale of one to ten. I am mentally feeling much better and am very grateful. I can do housework. Sometimes I overdo it and get tired and get the numbness, and then my right leg starts to feel heavy, but it's not so bad I can't put up with it or deal with it myself. I haven't noticed any particular side

effects. I haven't felt sleepy or sluggish during the day. I am sleeping well and am considering stopping the Lendormin (brotizolam). I am trying to follow Dr. Oota's instructions regarding sleeping, walking, and avoiding becoming constipated. He said that feelings of trying too hard cause stress, so I am trying to relax and stop being a perfectionist about everything. My oral drugs are listed as Selenica (sodium valproate) 100 mg granules, Noritren (nortriptyline) 5 mg, Rivotril (clonazepam) 0.25 mg powder, Risperidone (risperidone) 0.25 mg, Cinal (ascorbic acid/calcium pantothenate), and Gasmotin (mosapride citrate hydrate).

Case 14 : A 43-year-old man with cluster headache originally misdiagnosed as trigeminal neuralgia (facial neuralgia)

About once a year, I would get sharp pains running down the left side of my face that sometimes caused me to jump up in the night. About six years ago, I started experiencing dizziness and occasional numbness and the inability to move my left hand. The pain was so bad that I desperately wanted help, so I got examined at Myojinkan Neurosurgery Clinic.

After a medical interview about my headaches, Dr. Oota told me it was more likely that I had cluster headache than trigeminal neuralgia. He predicted that the pain got worse when I drank alcohol and that it felt like behind my left eye was being gouged out. He was totally right. I told him I had no money but I wanted something to be done, and he said that oxygen was the cheapest treatment option. After inhaling oxygen for 15 minutes, my headache instantly got better. "It is a sorry state of affairs when a man has the money to gamble on pinball but cannot pay for medical care" he said with a wry smile but loaned me an oxygen tank. I thank God, Buddha, and Dr. Oota.

Case 15 : A 10-year-old boy with sleep apnea syndrome originally misdiagnosed as attention deficit hyperactivity disorder (ADHD)

My son was often restless, irritable, and prone to temper tantrums, and was treated as a problem child at school. He found it difficult to get up in the mornings and was often late for school, even though he didn't hate school and there was no sign that he was trying to avoid going. His temper tantrums were sometimes really bad, so I thought something might be wrong and had him examined at Myojinkan Neurosurgery Clinic. At the pediatric department, they had given me lifestyle advice for attention deficit hyperactivity disorder (ADHD). He couldn't get to sleep easily and ended up finally falling asleep at 10 or 11 pm for days on end.

He underwent a medical interview about his sleep habits, and I told Dr. Oota that my son snored really loudly for a child. On examining him, Dr. Oota found that both of his tonsils were enlarged. Home polysomnography showed few signs of apnea, but there were indications of shallow breathing, and his blood oxygen saturation level while sleeping dropped to 62%.

Dr. Oota said that his breathing problems while he was asleep meant that he wasn't getting enough sleep at night to recover from tiredness built up during the day. In order to turn him back into a normal kid, he said the first priority was to cure the snoring.

He immediately made an appointment for us with the ENT department at the general hospital. Dr. Oota said that it was dangerous for him to sleep on his front until after the tonsillectomy, and told my son to sleep on his side using a body pillow he loaned us. I was surprised to learn that Myojinkan Neurosurgery Clinic has sleep and pillow counseling. After the tonsillectomy, my son's snoring completely stopped. He is sometimes still irritable and has temper tantrums, but far less than before. He is doing better in school and is as pleased about the improvements as I am.

Case 16 : A 66-year-old woman unable to carry a shoulder bag due to tingling mid- and upper back pain

I had suffered from chronic lower back pain for about 30 years. Based on my X-rays, the doctors told me I had lumbar spondylosis deformans, and I received treatment for many years. I had tried many different painkillers, but nothing really worked. About three or four years ago, I started getting tingling pains around my shoulder blades. I was examined at a local dermatology clinic, but they couldn't find anything wrong. Then, about two years later, I started getting the same kind of tingling pain from my back across my side when I lay down in bed. I was waking up many times in the night and couldn't sleep. It was even painful when just the seams of my clothes touched my skin, so I went to the dermatology department of the general hospital. I told them that I couldn't carry a bag on my shoulder due to the pain, and that when I lay down, I felt a tingling pain in the areas of my body bearing my weight. But once again they said they couldn't find anything wrong and recommended I see a neurologist.

When I went to Myojinkan Neurosurgery Clinic, I asked Dr. Oota to examine me thoroughly from my neck down to my lower back. I underwent a perception test, pinprick test, and neck and lower back MRI. The results showed a mild herniated disc at T12/L1 but no associated nerve compression, and the level of spinal deformity was appropriate for my age and wasn't pathological. "If that is the case, what's wrong with me?" I asked and was told that my brain had become hypersensitive and was causing tingling pains in different parts of my body. Dr. Oota gave me a drug to take once a day after my evening meal and told me that would ease my symptoms. He told me to take it for the time being as if it were a dietary supplement. When I asked what kind of medicine it was, he told me it was a pediatric antiepileptic! At first I was angry, thinking "You are kidding me, right? Giving a drug for kids to an old lady who looks after her grandchildren?"

However, maybe his words had a hypnotic effect because within a week of starting the drug, the tingling pain began to improve. It was still there, but I was able to sleep and do the housework better. I stopped being bothered by the seams of my clothes and was able to carry a shoulder bag again. I will never forget Dr. Oota's face as he laughingly told me, "You have cephalic hypersensitivity syndrome. Your brain has been playing tricks on you!"

Case 17 : A 46-year-old woman with generalized pain diagnosed as fibromyalgia that was refractory to treatment

I started having seizures when I was about five years old. After catching mumps, I ended up with generalized seizures that progressed to status epilepticus. Testing at a university hospital revealed brain wave findings similar to those for cerebral palsy, and they gave me antiepileptics. About eight years ago, I became unable to sleep on my back or side due to back and shoulder pain and I had to sleep on my front every night using a stomach-sleeper pillow. My buttocks hurt when I sat down, and I had pain in both elbows and knees, the front of my hip bones, both ankles and wrists, the second knuckle of every finger on both hands, both sides, and where my lumbar support belt touched my body. My entire body hurt, and I sought help at every hospital I could find. At one general hospital, they treated me as if I had indefinite complaints, and the doctor ended up yelling at me and telling me not to bother coming back. At another general hospital, they suspected connective tissue disease but told me it was not rheumatism despite the presence of rheumatoid factors. They prescribed me drugs as a stopgap measure, but these had absolutely no effect. I was also examined at a hospital specializing in cranial nerve disease, but the treatment had zero therapeutic effect. At a general hospital in another prefecture they said that I met the tender point criteria for fibromyalgia, but I had to discontinue the treatment due to side effects. I tried every imaginable test and treatment but nothing worked. After years of worrying, I finally visited Myojinkan Neurosurgery Clinic.

Dr. Oota told me that the fact that all those tests had come back normal and all those drugs had been ineffective was the clearest manifestation of my condition. I asked him if there were any drugs that would work. Taking into consideration my history to date and after noting that I was negative for fibromyalgia and hysterical seizure and didn't meet the criteria for a definitive diagnosis of connective tissue disease, he recommended treatment for cephalic hypersensitivity syndrome. He prescribed another two antiepileptics in addition to the antiepileptic Tegretol (carbamazepine) that I was already taking. At first, I didn't notice much effect, but then I gradually began to lose weight and had less pain. A year and a half later, I have returned to work and am taking care of my mother who is disabled with psoriatic arthritis. My mother appreciates my help, and I want to take care of her as she took care of me.

Case 18 : A 46-year-old woman suffering from headaches for nearly 20 years who was astonished when they resolved

I had suffered from headaches since junior high school. At that time, if I took an over-the-counter painkiller, the headaches would disappear in a day. However, around the age of 28, after having my third child, the headaches became more frequent and started lasting for two or three days. I would spend one of those days feeling nauseous and vomiting and unable to eat or move. These awful headaches would occur once or twice a month. They seemed to happen particularly around my period and ovulation. My whole head throbbed, I got stiff shoulder, and couldn't stand bright lights or loud noises. These severe headaches forced me to lie prostrate and prevented me from living a normal life, so I visited Myojinkan Neurosurgery Clinic.

After a medical interview regarding my headaches, Dr. Oota told me I had a type of migraine common in women that was related to menstruation and sensitivity to light and sound. When I asked if it could be cured, he said he could make me completely well! He told me to stop taking all over-the-counter painkillers, go to sleep at 10 pm, make sure I got to bed and got up early every single day, and only take drugs once a day in the evening. I told him that it wasn't that easy as my headaches weren't normal headaches and that I was really worried about limiting my medication to once a day. In response, he agreed to prescribe me pediatric doses to take twice a day in the morning and evening. The drugs he prescribed were Depakene (sodium valproate) 100 mg tablets and Topina (topiramate) 25 mg tablets. I was worried about the low doses, but after taking the drugs for a while, the headaches that used to unfailingly come on once every two weeks completely stopped. I was astonished.

Now, I sometimes forget to take the drugs, but I no longer get any headaches. When I was young, I visited many hospitals, but all they did was prescribe me painkillers and tell me there was nothing else they could do if the drug had no effect. I'd given up and assumed the drugs wouldn't work this time either, but amazingly, my headaches have gone.

Case 19 : A 75-year-old man unable to sleep due to recurrent stomach pain that did not resolve despite treatment at various hospitals

Last spring, I had just sat down at the table to eat my evening meal when I suddenly felt unwell with sharp abdominal pains, nausea, and bloating. I rushed to the night clinic but they couldn't diagnose what was wrong, and I went home, still in pain, with a prescription for painkillers to be taken as needed. The next day I went to the local hospital, and they gave me an intravenous injection (IV), but my symptoms didn't change. On another visit, I had an abdominal X-ray, but it didn't show anything wrong, so they referred me to a larger hospital. I was admitted for three weeks, during which time I underwent head-to-toe testing, including X-rays, CTs, and gastroscopy, but everything came back normal. Meanwhile, the abdominal pains, nausea, and bloating continued, so they recommended I see a psychosomatic medicine specialist as well. I was getting weaker by the day and had lost over 10 kg. I was worried but kept attending my wife's regular hospital and getting IVs and injections, although my symptoms still did not change. I was acutely aware of various movements in my abdomen. I spent most of my time lying down at home; every day was hard, and at one point I even thought about taking my own life. However, I still continued receiving treatment at the psychosomatic clinic.

Then an acquaintance told me about someone they knew who had also visited many hospitals to no avail, but who got better after visiting Myojinkan Neurosurgery Clinic. My wife and I got straight on the train.

Even though it was my first visit, I was fortunate to be examined by Dr. Oota. He listened quietly to everything I had been through, and finally told me, "I will definitely make you well". On hearing that, it was as if a weight had been lifted, and I felt half-better already.

Before the examination, I underwent a detailed medical interview, based on which Dr. Oota prescribed me some drugs. I was very grateful. On our way home, my wife and I talked about how happy we were to have met such a good doctor. According to my wife's notes, about three days later, I became able to help her a little about the house. Then I started to sleep properly. I was able to drive to Fukuyama to renew my driver's license. I started walking 30 minutes daily, which I still do to this day. Here is how much I walked this August compared to last August:

Last August: Overall steps per day, 4,503 (4,340 walking, 163 running)
This August: Overall steps per day, 7,636 (5,688 walking, 1,770 running)

At the beginning of this year, I started organizing my books. I am putting the ones I no longer need up for auction. It takes a lot of time, but I'm enjoying myself. My children and sister-in-law are happy to find me active and cheerful. Last September, I tested myself by taking our family car and visiting our three family gravesites in Sera District. I was able to drive 100 km! During Golden Week this May, I spent three days driving the Shikoku Pilgrimage route, visiting 23 out of the 88 temples. Thanks to Dr. Oota, I have made a rapid recovery. I hope he doesn't mind, but I intend to continue seeing him!

Case 20 : A 69-year-old woman suffering from diverse symptoms that prevented her from even doing the cooking

I hadn't been in good health for a while, but since giving up my job as a cleaner last June, my condition got progressively worse. I had headaches most days with throbbing pain in my temples and at the back of my head that was particularly bad from around noon until the evening. I also had severe stiff shoulder and nausea and became highly sensitive to light and odors. I would wake up soon after falling asleep at night, after which I would only doze on and off. I wasn't sleepy during the day, but I always felt like I wasn't getting enough sleep. From the beginning of this month, my left cheek and the area around my lips felt numb when I got up in the morning. The numbness disappeared within about 30 minutes but recurred throughout the day. I also had a lumbar herniated disc, and my legs and feet were constantly cold and numb. My head hurt every day; my eyes were bleary and irritated; my limbs felt numb; my body was cold; and my lower back was painful. I couldn't cook and spent all day lying down in my pajamas. I didn't want to see anyone or even open my eyes. I stopped being able to taste my food and rapidly lost my appetite. I was sure there was something seriously wrong with me, so I spent about six months going to various hospitals with my daughter. However, there was no change in my symptoms, the number of drugs they prescribed kept increasing, and I became more and more worried. Suspecting that something was definitely going on in my brain, I visited Myojinkan Neurosurgery Clinic.

Dr. Oota listened to everything I had to say and reassured me by saying, “Don’t worry, I will cure all your symptoms”. I returned home feeling much brighter, all my uncertainty gone. It was the first time I had heard of cephalic hypersensitivity syndrome, but the symptoms matched mine exactly, and I knew that was what I had. I went from taking huge quantities of drugs to a single, nightly dose of the drugs prescribed by Myojinkan Neurosurgery Clinic. My symptoms have noticeably improved, my sense of taste and appetite have returned, and I have put on five kilograms. My headaches are also better, and I am able to do the cooking and other housework like I could before I got sick. I used to hate going out, but now I go shopping, to concerts, and out to eat with my friends. I also look after my grandchildren for my daughter while she works.

I never thought this day would come. The period of time when I would pray for my dead mother to come for me and take me away from my suffering seems like a dream. I am so grateful to have found Dr. Oota, to whom I would like to say the following:

Thank you! Death can wait; I want to live for many years yet.

Case 21 : A 68-year-old man struggling with tinnitus for over a decade

Beginning about 16 years ago, I have been suffering from constant tinnitus of high-pitched ringing and popping sounds in both ears at night. When it was quiet after turning off the television, I would suddenly start to hear these sounds in my ears and couldn’t sleep. After a while, I started to notice the same sounds during the day as well. I went to see an ENT specialist at the general hospital, and after undergoing various tests, I was given some tranquilizers. However, nothing had changed after taking them for a week, and I spent the next six months undergoing outpatient treatment and trying drug after drug. Two years later, I was prescribed Myslee (zolpidem tartrate) at the local internal medicine clinic. That helped me sleep a bit better, but apart from that, I didn’t notice much improvement. I went to nearly all the hospitals in the prefecture, including the university hospital. However, they all just gave me the same tests and the same drugs. Meanwhile, the tinnitus sounds got louder. I came to the conclusion that my tinnitus could

not be cured and decided that alcohol might help me sleep better, so I started drinking two glasses (360 cc) of *shochu* every evening as a nightcap. However, a doctor once told me that nightcaps were bad for sleep, so I made sure I stopped drinking by nine pm.

Around April last year, I was examined at the city psychiatric hospital and started taking four pills every evening to help me get to and stay asleep. I took the drugs for 11 months but suffered from side effects such as eye discharge, decreased concentration, and feeling spaced out. It affected my daily life, making me worry about things like the fact that I was now more prone to accidents while driving, but that I wouldn't be covered by insurance. My symptoms did not improve even after attending the psychiatric hospital, and worried about the increasing amounts of drugs I was taking, I went from one hospital to another trying to find a drug that would work better. A relative of mine had previously undergone brain surgery and he told me about his surgeon, so this March I visited Myojinkan Neurosurgery Clinic and met Dr. Oota for the first time.

Dr. Oota told me that tinnitus is a sign that my brain is alive and that I would have to learn to get along with it for the rest of my life. He warned me against fighting against it too hard. "The moment your heart stops, the tinnitus will stop, too," he laughed. He mixed me a powder containing small doses of various drugs to take one hour before sleeping. At first, I was very nervous. After being overprescribed sleeping pills until then, would this single packet of powdered drug really help me sleep?

To my surprise, I slept really well! I asked what was in the mixture, and he showed me my chart, which listed the drugs as Depakene (sodium valproate) 200 mg, Tryptanol (amitriptyline) 10 mg, Rivotril (clonazepam) 1 mg, and Risperidone (risperidone) 0.5 mg. It had been a long time since I had woken up feeling that good. Until then, I had only been sleeping around four hours a night, but the drugs Dr. Oota prescribed enabled me to sleep soundly. After a while, he reduced my dose by half, but my motivation and appetite are still good, and everything is easier. My appetite and energy have returned, and I want to go and play golf. I have put on about five kilograms. I have spent over 15 years of my precious life worrying about tinnitus. Now, strangely, I don't notice it. What were the last 10 or so years all about? My wife laughed. I am so thankful every day.

I would like to finish up by expressing my gratitude. I intend to keep coming in for treatment.

Case 22 : A 62-year-old woman suffering from whole-body pain

I had been troubled for some time by slight headaches that persisted throughout the day, and I never felt completely well. Three years ago, I underwent a head MRI at a general hospital, but it came back normal, so they just prescribed me Loxonin (loxoprofen sodium hydrate). Although the pain decreased for a while, I still got the headaches. Then I started having lower back pain and numbness in both legs and feet, and I went to a doctor again. A lumbar MRI showed the early stages of a herniated disc, and they gave me prescriptions for more Loxonin (loxoprofen sodium hydrate) and a gastrointestinal drug. From around September last year, I began to experience pain in both upper arms as well as numbness in both legs and feet. I went to the general hospital again and underwent a head and neck MRI. The results showed straight neck, a herniated disc between C5 and C6, and cervical spinal stenosis due to thickening of the ligamenta flava. They gave me various drugs, but nothing helped the pain. It was at that time that a friend introduced me to Myojinkan Neurosurgery Clinic.

After examining me, Dr. Oota said that the disc herniations in my neck and lower back were only mild and were not directly related to the numbness and pain in my limbs. He carefully explained cephalic hypersensitivity syndrome to me, and I was really surprised to hear that it was my brain arbitrarily causing my condition. Dr. Oota taught me how to sit in a chair correctly to help my straight neck and gave me some exercises for stiff shoulder that I have incorporated into my daily routine. He reduced my drugs, and I am currently taking half a blue pill as if it were a dietary supplement. I feel much better than before, and I have found a way to co-exist amicably with my few remaining symptoms. Thank you, Dr. Oota! I intend to keep coming to see you for treatment.

Case 23 : A 71-year-old woman troubled by severe headaches that did not respond to even powerful drugs

I wasn't really troubled by headaches when I was young. Then one morning in August, I woke up with nerve pain from the back of my neck to the back of my head. Sometimes I would get sharp, shooting pains in the left side of my head

that continued throughout the day. I was examined by a local neurologist and had a head MRI, but they couldn't find anything wrong. Thinking that stiff shoulder might be the cause of the pain, I started having massages, but it didn't get better. I went to a local internal medicine clinic, and they prescribed me the painkiller Kentan (loxoprofen sodium hydrate). The pain got a bit better, but the doctor was concerned about the risks of dependence with long-term use as Kentan (loxoprofen sodium hydrate) is so strong, so they changed me onto a different painkiller, which didn't really work. It was around then that a friend of mine went to hear a lecture by Dr. Oota and strongly advised me to go and see him.

For the first two months or so, the antiepileptic Dr. Oota prescribed didn't have any effect but after changing to Paxil (paroxetine hydrochloride hydrate) 10 mg and Risperidone (risperidone) 0.5 mg at the start of the third month, I gradually started to see an improvement, and the pain got much better. Housework and other things used to be too much trouble, but I am much happier now that the pain is now significantly less, and I no longer have to worry about the headaches. I'm not 100% better, but I am just pleased to be about 98% well. Thank you, Dr. Oota!

Case 24 : A 48-year-old man with severe rotational vertigo and tinnitus

I had been experiencing dizziness two or three times a month for over 10 years, but these episodes would quickly resolve if I lay down. Then, about seven years later, I suddenly started having severe symptoms including tinnitus, rotational vertigo, nausea, and vomiting about three or four times a year. The symptoms were really bad, so I went to the ENT department at the general hospital and underwent a CT and MRI, but the results came back normal. They ruled out Meniere's disease but couldn't tell me what was actually wrong. The tinnitus was present every day.

Once every three or four months, I had severe tinnitus and vertigo followed by vomiting that continued for around three hours, and sometimes I had to take time off work. Over time, the gaps between episodes shortened until they were happening once every two months and continuing for five or six hours. Once, I

was taken to hospital by ambulance.

I attended a specialist otological hospital for about two years as both an inpatient and an outpatient. I tried various IVs and drugs and participated in a clinical trial but nothing changed. About two years ago, I stopped smoking, but my condition was getting gradually worse, with daily tinnitus and occasional episodes of mild vertigo and vomiting. I learned about cephalic hypersensitivity syndrome from the Myojinkan Neurosurgery Clinic website and paid them a visit.

I was examined by Dr. Oota. He told me that the tinnitus was not part of my condition, saying, "Tinnitus is something that arises as a result of brain activity and will stop when your heart stops. You will have to learn to get along with it." However, he categorically told me that he would cure my rotational vertigo, nausea, and vomiting. The first drug he gave me was meant to suppress the tinnitus, vomiting, and vertigo, but it made me really sleepy, and my speech became slurred, making it difficult for me to drive and go about my daily life. When I told Dr. Oota about the side effects at my next appointment, he halved the dose. The tinnitus is still there, but the rotational vertigo and nausea, vomiting, and headaches have all gone, and I haven't had to take any more time off work. The severe monthly vertigo didn't happen the month after beginning treatment and still hasn't come back six months later. I am so grateful.

Case 25 : A 61-year-old woman unable to keep her balance

I suffered from headaches, menstrual pain, and stiff shoulder for a period of time when I was young, but since then, I have been relatively healthy. However, recently, I had been feeling shaky and unable to walk in a straight line. I would suddenly feel like I wasn't in control of my own body, become dizzy and unable to keep my balance, and would have to sit down. It felt like the back of my head was being squeezed while the front of my head felt heavy. I was too scared to walk around, so I spent most of my time at home asleep. I knew I couldn't carry on like that, so I went to Myojinkan Neurosurgery Clinic for a thorough examination.

The results of my MRI showed no sign of a stroke or abnormality that could be causing dizziness. During the medical interview, Dr. Oota listened carefully

to my symptoms and then asked me about the headaches, menstrual pain, stiff shoulder, and lower back pain that I experienced when I was young. Then he told me about a condition called cephalic hypersensitivity syndrome. He prescribed me two low-dose drugs to take in the mornings and evenings, and my dizziness has disappeared. I have no strange sensations, and I feel completely well. It's as if nothing ever happened.

Case 26 : A 38-year-old woman unable to sleep at night for two years due to restlessness

Every evening since about two years ago, I had been feeling relentless itching, pain, restlessness, and crawling skin on the soles of my feet, calves, thighs, and around my lower back. When it was really bad, it would even affect my arms and mid- and upper-back. This malaise was severe and persistent. I would wake up many times a night due to my restless legs, so I wasn't getting enough sleep. That made me so sleepy during the day that it affected my work. I found myself nodding off at work, and looking at bright lights made me lightheaded and sleepy. I would suddenly be overcome by sleepiness when I was driving, which made me scared to get behind the wheel. I didn't know what was causing the restlessness and resorted to buying over-the-counter drugs from the drug store and getting anti-itch creams and oral drugs from dermatology and internal medicine clinics, but nothing worked.

I happened to find some people on the Internet who had the same symptoms as me and learned that they were receiving outpatient treatment for something called restless legs syndrome. Apparently, some doctors don't really understand restless legs syndrome and end up diagnosing something completely different. I searched online for a local hospital where I could be seen by a specialist, but I couldn't find one anywhere. I did, however, find Myojinkan Neurosurgery Clinic in the neighboring prefecture that deals with this condition.

At my first appointment, I told Dr. Oota about my symptoms, and he told me that he would definitely make me well. Just hearing that, I started to feel better. Even after all the worrying, I might actually recover! I started taking the drugs Dr. Oota prescribed, and by the second day, the unpleasant symptoms I had been

experiencing had nearly disappeared. I started to sleep deeply at night and was able to work without any problems. It was exactly as Dr. Oota had said! It is about a three-hour round trip, but I am so pleased to have found a doctor I can trust.

I intend to keep visiting Myojinkan Neurosurgery Clinic. Public awareness of restless legs syndrome needs to be raised so that more people who are suffering from this condition can get well.

Case 27 : A 50-year-old woman suffering from headaches for over 20 years causing her to finally take leave from work

I started having headaches regularly when I was in high school, and somewhere down the line, I found that 20 years had gone by and I was in pain every day. I took painkillers three times a day as a matter of course, and in hindsight, had become completely dependent on them, although I was unaware of it at the time. If the drugs didn't work, I would rush to the hospital for an injection. That was my normal way of life. The turning point came when I got transferred at work. I went from a commute of 15 minutes by car to a workplace nearly two hours away, requiring a complete change of daily routine. I found I was taking painkillers five or six times a day. All the drugs I was taking, including the specific migraine drugs, stopped having an effect, and I ended up taking a leave of absence from work and became housebound. Staying at home just reduced the number of times a day I took the drugs, but it didn't solve anything. An acquaintance strongly recommended I try Myojinkan Neurosurgery Clinic. I visited there, although I felt it would be useless to visit such a place up until then.

When I told Dr. Oota my symptoms, he immediately said, "Don't worry, I'll quickly make you better! You will be completely well". To be honest, that made me feel a little strange. Until then, most of the hospitals I had visited treated my headaches by giving me Terranas (lomerizine hydrochloride) and traditional Japanese medicine just to give me some measure of comfort. However, at Myojinkan Neurosurgery Clinic, Dr. Oota carefully explained my symptoms. When I understood that the drugs prescribed here are for tackling the cause of the pain, I began to believe I might be freed from the pain, and I cried.

For the first two weeks, I stopped taking all the drugs I had been prescribed from other places and only took what Dr. Oota gave me. Soon after beginning treatment, I reduced the frequency at which I took the drug from once a day, to once every other day, to a two-day gap, and then to a three-day gap, and I felt a positive effect. However, I also felt really sleepy. I explained that to Dr. Oota at my appointment two weeks later, and he changed me to a different drug and told me to take that for one month. At first, there wasn't much change, but by the second half of the month, I no longer needed to take the drug.

I never believed this day would truly come. I am just full of gratitude. I hope that this treatment for cephalic hypersensitivity syndrome soon becomes widely known for other people suffering in the same way. Thank you so much.

Case 28 : A 46-year-old woman with vertigo with dizziness and wobbliness that affected her ability to work for six years

Around the time I turned 40, I suddenly started experiencing rotational vertigo with vomiting. I had many unpleasant days where my head was dizzy and the lower part of my field of vision was wobbly. The vertigo happened more frequently when the seasons changed, particularly as it became winter. During the winter, I visited the internal medicine clinic once every 7 to 10 days for an injection. Thinking that the vertigo was more frequent in the winter because of stiff shoulder, I also saw a chiropractor. The internal medicine clinic said I had hypertension and kept me under observation for a week, but there was no improvement so I started taking antihypertensive drugs. However, the vertigo symptoms did not improve at all. Sometimes I had vertigo when I was at work and would break out in a sweat and vomit. When work was busy, there were often days when I was unable sleep. I would lie in bed thinking about one work-related thing after another and couldn't get to sleep. Because I was worried about the vertigo, I turned down things like business trips during the winter.

When I was examined at Myojinkan Neurosurgery Clinic, Dr. Oota told me to stop taking the vertigo drug that I had been receiving from the internal medicine clinic for all that time. He also told me that the antihypertensive drugs and thyroid medication may have been causing the vertigo and that we should adjust those

while keeping an eye on my blood pressure and blood work. He also wrote me a referral letter for the internal medicine specialist.

Since starting the drugs prescribed by Myojinkan Neurosurgery Clinic, I haven't had vertigo once. The dizziness and wobbliness have also disappeared. I had been seeing a white cloud at the bottom of my field of vision, but that has also gone away, and my field of vision is wider. I haven't even had vertigo in the winter, when it used to be most frequent, and I was able to have a completely stress-free New Year for the first time in years. I was astonished. What have the last few years been about? I worry less about work when I am at home and am sleeping better. In February, I had to stay in a hotel for three days for a business trip, but I was able to sleep well and didn't experience any vertigo.

Case 29 : A 42-year-old woman whose headaches and vertigo improved beyond expectations

I had had headaches since I was in high school. When they affected my day, I took over-the-counter headache drugs (mainly Bufferin (aspirin)), to stop the pain. Because the headaches got better after I slept and didn't affect my daily life, I didn't need to take any painkillers when I was at home. Even after turning 40, I still got headaches once or twice a month, which I dealt with by taking headache drugs. However, from about 10 months ago, I also started to be bothered by vertigo, so I got examined at the ENT department. However, they couldn't give me a satisfactory explanation, and even though they gave me some drugs, I reached the stage where just moving my head from side to side made me feel faint. Nothing I did helped; the headaches gradually increased from once or twice a month to the point where my head was pounding every morning when I got up. It wasn't so bad I couldn't put up with it, but I had constant mild throbbing, and I became convinced there was something wrong with my brain. I visited the Myojinkan Neurosurgery Clinic hoping to get thoroughly checked out with an MRI or CT.

I promised Dr. Oota I wouldn't take any over-the-counter painkillers or painkillers from other hospitals. Instead, he gave me a pediatric dose of two other drugs to take every day after my evening meal. (I took them before I went to sleep

at night, instead.). Strangely, the pounding, throbbing headaches disappeared the next day. I still feel like a headache is coming on. But, I am amazed! After taking the drugs for three weeks, the vertigo hasn't completely disappeared, but it is much better than before, and if I don't do anything out of the ordinary, it doesn't interfere with my daily life. If I move my head from side to side, I still feel faint; for example, when I check for other vehicles while I am driving. It stops after a few seconds but I'm hoping to somehow get rid of the vertigo for good. After talking to Dr. Oota, he increased the frequency of my dose to twice a day in the mornings and evenings, and I'm looking forward to seeing if that helps. At Myojinkan Neurosurgery Clinic, they show me my chart without being asked; they even advised me to show it to my regular doctor.

Case 30 : A 38-year-old woman unable to ride in a car or on a bicycle

About a year and a half ago, I started to get a bit dizzy when I was out shopping or in crowded places, and sometimes it would get really bad. I took my concerns about my dizziness symptoms to a neurosurgical clinic, but they couldn't find anything wrong. I then tried the ENT department and underwent many tests, but they couldn't give me a definitive diagnosis either. Then, about 10 months ago, I became weak over all, felt lightheaded, and got really dizzy while I was driving and couldn't drive anymore. After that, I started to get so dizzy I couldn't walk properly. I felt nauseous and unsteady even when I was sitting down. When I lay down because I felt ill, it felt like everything was spinning. I got examined again at my local clinic, and they told me it was stress, fatigue, and lack of sleep and prescribed me Merislon (betahistine mesilate) tablets, Adetphos Kowa (adenosine triphosphate disodium hydrate) granules, Nauzelin (domperidone) tablets, Tsumura Yokukansan Extract (yokukansan) granules, and Rize (clotiazepam) tablets. I took these five drugs for about six months to no avail. In everyday life, it became difficult for me to stand up straight or walk outside alone, thereby affecting my ability to work and worrying my family, who recommended I try Myojinkan Neurosurgery Clinic. Thorough dizziness / vertigo, eye pressure, hearing, and other tests all came back normal as did my neurological test results. I filled out a medical interview form about my sleep

habits, and Dr. Oota seemed interested in things like my sleep talking, periodic leg movements, and mild daytime sleepiness and took particular note of the fact that my dizziness was especially bad in crowded places and when driving in rush hour; I told him about everything. He gave me a drug to be taken once a day after my evening meal to treat the sleep talking, periodic leg movements, and crowd-related dizziness. He told me I would get better just by stopping all the other drugs I had been taking up until then and to "trust this drug and take it once daily". I kept my promise to do as he said, and after taking the drug for about a week, I gradually began to be able to stand still and walk. I still got slightly dizzy when walking long distances or if I felt under a lot of pressure or tired, but this settled down over time, and after taking the drug for a month, I was able to work again. I am so pleased. I really regret taking so many drugs. As a final push, I am making an effort to get enough sleep and have started walking in the mornings. After cutting back on my beloved coffee and taking Magmitt (magnesium oxide) and Pursennid (sennoside A•B) with three cups of water after my evening meal, I now have regular morning bowel movements and no longer feel backed up. Recently, people around me have been commenting that my whole demeanor has changed. I'm so grateful. I wish I had come here earlier so that I could have gotten better sooner. I intend to keep visiting Myojinkan Neurosurgery Clinic for treatment.

Case 31 : A 76-year-old man nearly gave up driving

I retired when I was 60. From around that time, I sometimes experienced dizziness and felt nauseous. Around three years ago, I started feeling dizzy and sick and had strange sensations in my abdomen when the screen changed while I was watching TV. From that time onwards, I became unable to stand the light and the lights from the TV, and road tunnels when I was driving caused me a lot of distress. I noticed there were times when I was driving in tunnels that I nearly went over the center line, and I became very anxious. I visited various hospitals, but my symptoms didn't improve at all. I rushed to the hospital in a taxi three times because of the pain in my upper stomach and how bad I felt. I suffered with these symptoms for about 15 years. I routinely took tranquilizers and received

treatment at my local hospital for hypertension, chronic gastritis, and headaches. The biggest problem was the severe anxiety I experienced when driving. Even when I tried really hard, there were times when I nearly crossed the center line. That never used to happen to me before. I knew if I carried on like that I would no longer be able to drive. My condition was affecting my daily life, and I was struggling to cope.

I underwent a medical interview and was shown to Dr. Oota's office. After various tests, I still clearly remember him saying, "Great, I know what's wrong." He only prescribed me one drug: Depakene (sodium valproate) 100 mg. I had to take one tablet every morning and evening. My headaches disappeared in the first two weeks, but light and sound still caused me problems. He upped my dose to Depakene (sodium valproate) 200 mg tablets and told me to try driving on the highway. I tried and was amazed. It was like I had been reborn. I drove 300 km. I thought I would never drive again, but that gave me back my courage. Now, I hardly notice the lights even when I am driving on the highway, and I no longer get headaches in the same way. I also don't need to take tranquilizers any more.

From referral letter to the primary care doctor

Brain wave responses to light stimulation were normal, and no epileptic discharge was observed. I have prescribed valproic acid monotherapy for the light sensitivity to avoid interference with the 10 drugs the patient is currently taking as prescribed by your institution.

Case 32 : A 74-year-old woman unable to greet others or cross the road

My head felt heavy, and I would experience dizziness if I bent down, so I couldn't bow in greeting to other people. Looking side to side to check for cars before crossing the road made me dizzy, so it was hard for me to use pedestrian crossings. I also had headaches, for which I took Bufferin (aspirin). Concentrating seemed to bring on a headache, so I preemptively took painkillers about twice a day. Lately, the Bufferin (aspirin) had stopped having an effect, so I started taking Loxonin (loxoprofen sodium hydrate). I was examined at an ENT

clinic and various other medical institutions, but I didn't get any better. I told the hospital where I had lung cancer surgery that I was suffering from headaches and dizziness, and they referred me to Dr. Oota at Myojinkan Neurosurgery Clinic.

The heavy-headedness and dizziness were so bad that I couldn't bring myself to do anything. I couldn't unpack after moving to a new house, and I couldn't be around other people. My head felt heavy from the moment I got up every day, and I was at a loss for what to do.

Dr. Oota told me that the underlying problem was sound-sensitive migraine and said if I followed his instructions exactly, I would be completely cured in one month. He asked me to promise to stop the painkillers I had been taking every day; then, we could start treatment. He explained cephalic hypersensitivity syndrome to me and told me that my migraines had transformed due to inappropriate treatment and had become chronic daily headaches. He prescribed me one drug to be taken daily after my evening meal and pediatric doses of two kinds of drugs to take every morning and evening. After a month of expectantly taking the drugs, the lightheadedness I used to experience when bowing my head to people in greeting and when I turned to the side when riding my bicycle was gone. I still can't be around other people, but I can now look carefully from side to side and cross the road. I can also cook again. I have started walking for 20 to 30 minutes and am gradually getting my things tidied away in my new house. I still get mild headaches if I am worried about something, but under normal circumstances, I am headache-free, and things are much better. It feels untrue that I can wake up in the morning with a clear head. It is now possible for me to have happy days. I am getting better. Thank you, Dr. Oota.

Case 33 : A 70-year-old man suffering from lack of sleep due to 20 years of restless legs

I had been experiencing restlessness in the summers, making it difficult to get to sleep for about 20 years. In the winter, my toes were always hot at night, and I would keep my feet out from under the blankets for about 10 minutes, move them in when they felt cold, and then stick them back out after about two or three minutes when they got hot again, even in mid-winter. Repeating this, I would

turn over every four or five minutes or so and didn't get to sleep until about four o'clock in the morning. I felt like I was only sleeping for about two hours a night, and this situation went on and on. I was checked out by a local doctor, but they couldn't find the cause, and a neurological checkup showed no abnormalities. I went to Myojinkan Neurosurgery Clinic on the recommendation of my son, who is a radiologist at a general hospital, and daughter, who lives in Fukuyama City. Dr. Oota gave me a detailed explanation of the causes of the abnormal restless legs symptoms, telling me about things like neurotransmitters and receptors in the brain. He told me that sleeping pills and tranquilizers wouldn't help and started my treatment by dealing with my brain's hypersensitivity to neurotransmitters.

After my appointment, I took one tablet of the drug Dr. Oota prescribed, and from that night onwards, I have been falling asleep easily. The sleeplessness I had been suffering from disappeared as if it had all been a bad dream, and I am now able to sleep through until morning. The drug gave me mild abdominal pain, and when I told Dr. Oota, he halved the dose, and the pain stopped. I am still sleeping well. I am free of my sleep disorder for the first time in 20 years and am so relieved.

The only thing I am still worried about is how long I should keep taking the drug. After discontinuing Topina (topiramate), the abdominal pain has stopped, and I am still sleeping well.

From referral letter to the primary care doctor

In addition to restless legs, the patient presented with transformed stiff shoulder migraine. To treat both conditions as part of his cephalic hypersensitivity syndrome, I have prescribed combination treatment with clobazam and valproic acid. Marked improvement has been observed in the quality of his daily life with a single daily low dose, so I have instructed him to view the drugs as a dietary supplement that can be occasionally missed. I am prescribing two-month courses of the drugs but he is only attending appointments every three months. His progress is good.

Case 34 : A 40-year-old man with probable dysthymia initially suspected to be cephalic hypersensitivity syndrome

I had been in poor health with symptoms such as momentary dizziness for about 10 years. I was examined and diagnosed with depression at multiple hospitals and had been taking various drugs, but my symptoms did not improve. In particular, for the last three months, I had been momentarily blacking out as I was finishing work, and always felt somewhat run-down. I would frequently experience the same kind of symptoms once I got home and wouldn't be able to sleep until one o'clock in the morning. If I started to dwell on the fact that I couldn't get to sleep, my heart would suddenly race and I would feel panicked. I started drinking alcohol to get to sleep. I thought the cause was tiredness because of my job, but the symptoms never got any better. Wanting to do something, I went to Myojinkan Neurosurgery Clinic.

On the day of my first appointment, I underwent a thorough medical interview that covered everything including my momentary blackouts, my feelings of sleep deprivation, daytime sleepiness, alternating diarrhea and constipation, the fact that my symptoms manifested from the evenings through to the mornings, and details of my job.

Based on the results of an EEG, Dr. Oota prescribed me the antiepileptic Depakene (sodium valproate), and my blackouts immediately stopped; however, the drug made me dizzy. At my appointments, I chat freely with Dr. Oota. I tell him about my problems with palpitations, tinnitus, and sleeplessness, and about my job and family. He then adds to or changes my prescription accordingly. I am still taking Depakene (sodium valproate). At one point, I was still in bad shape, so I decided to try and stop taking my drug without consulting Dr. Oota. That made me worse, so I started taking it again. Even with the same drug, I was sometimes better and sometimes worse. I told Dr. Oota all my worries: that I was constantly depressed and unmotivated, so I thought there was something unusually wrong with me and that I might die. Dr. Oota always listened patiently. After a while, Dr. Oota referred me to a psychiatrist who diagnosed me with epileptic personality disorder and depression. I looked them up on the Internet and found the symptoms include indecisiveness, inability to concentrate, lack of appetite, lack of confidence, feelings of despair, and being easily tired. These are the same symptoms as those described to me to by the psychiatrist and match my

symptoms exactly. It was a relief to finally have names for my condition. I am currently still taking Depakene (sodium valproate) while trying to improve my daily life. I don't want to rush my recovery.

Case 35 : A 66-year-old man suffering for five years from sleeplessness and bizarre climbing motions while sleeping

I started experiencing insomnia five years ago and tried various sleeping pills, but nothing really worked. My feet would get cold while I was sleeping, making it even more difficult for me to stay asleep. It started to affect my daily life, so about three years ago, I got examined at my local general hospital. They prescribed me Tryptanol (amitriptyline) and Gabapen (gabapentin), which helped a bit, so I have continued receiving these drugs for the last two years from my regular doctor who is an internal medicine specialist. My regular doctor prescribed me nine types of drug for my diabetes mellitus, hypertension, and hyperlipidemia, and together with these two drugs prescribed by my general hospital, I was taking a total of 11 different kinds of drug. Even with the drugs, I still couldn't sleep because my feet felt cold. Last year, when I was climbing Mount Yari, my roommate asked, "Are you trying to climb the mountain while you sleep?" I asked him what he meant and he told me that I was kicking my legs in my sleep as if I were climbing a mountain. When I heard that, I realized I had also noticed my legs making small jerking movements. My feet were even colder than usual, and I had to wear the thickest mountain-climbing socks I could find, even in the middle of summer. Still unable to sleep, I would finally switch on the TV as the sound from the TV made it comparatively easy to fall sleep. When my feet were particularly cold, I would get up and walk around, which seemed to warm them up. I spent every night in this manner, suffering from sleeplessness. It was around this time that I spotted an advertisement on the side of a building for the Research Foundation Sleep Research & Support Center. Assuming that a place that researched sleep would be knowledgeable on the topic of sleep, I paid them a visit.

When I exited the elevator on the third floor, I was greeted by a sign for the Sleep Laboratory. I was examined in the examination room on the floor below

and had the opportunity to describe my condition in detail. Dr. Oota told me they needed to run some tests and attached many devices to my head, fingers, and feet, and I stayed overnight for testing. Based on my polysomnogram, Dr. Oota said I had the severest form of periodic limb movement disorder with restless legs syndrome. I had never heard such disease names and thought them odd. They showed me a video of myself while I slept, and I was surprised to see that I really did kick both legs as if I were climbing a mountain. Dr. Oota told me that he could completely cure me. I only half believed him, but I replaced my one Tryptanol (amitriptyline) 10 mg tablet, three Methycobal (mecobalamin) tablets, and two Gabapen (gabapentin) 200 mg tablets with one Rivotril (clonazepam) 0.5 mg tablet and one BI Sifrol (pramipexole hydrochloride) 0.5 mg tablet before bed, and from that day, I was able to sleep well. I stopped kicking my legs while I slept and was able to swap my mountain-climbing socks for regular socks.

I no longer feel sleepy during the day, and my life is transformed.

Case 36 : A 58-year-old man suffering from 20 years of chronic lower back pain, 10 years of sleeplessness and constipation, and six years of stomach and mid- and upper back pain, and anorexia

I had been suffering from chronic lower back pain for 20 years, but the pain started getting worse last October. I started to feel additional pain in my right thigh and numbness from my knee downwards, making it impossible for me to stand for longer than 10 minutes at a time and forcing me to sit down. I couldn't walk for more than 30 minutes in one go. I got examined at various orthopedic clinics, but as MRI testing showed no abnormalities, they said my condition was cryptogenic, and all we could do was keep an eye on it. I had also been suffering from chronic gastritis for five or six years. In February of this year, I started to feel a heavy pain around my stomach and the area of my back behind my stomach as if I were being squeezed. That pain became constant and was worse after eating compared to when my stomach was empty. I was examined by a gastroenterologist and underwent gastroscopy, which showed that my gastritis was getting worse. They started me on six tablets a day of two kinds of drugs,

but after one month, my symptoms hadn't improved at all. The doctors thought it might be stress-induced gastritis or an autonomic nerve problem and referred me to a psychosomatic medicine specialist. After examining me, one doctor prescribed Cercine (diazepam) 5 mg, Reslin (trazodone hydrochloride) 25 mg, Lexapro (escitalopram oxalate) 0.5 mg, and Ascomarna (triazolam) 0.25 mg, but my stomach pain did not improve at all, and they increased the dose of the drugs prescribed by the gastroenterologist.

I had always had a small appetite, which may be partly to blame for my weight dropping to 44 kg. I had also been suffering from insomnia and constipation for 10 years, so when I found out about the Myojinkan Neurosurgery Clinic outpatient sleep clinic, I paid them a visit. After a pre-exam, I was shown to Dr. Oota's office, and Dr. Oota asked me even more details about my condition. As well as telling him about my suffering related to my illness, I also told him about my difficulties with managing the church. He told me I needed to be brave and stop all of the drugs I had been taking up to that point. As those drugs had had no effect despite the many years I had been taking them. I wasn't too bothered and didn't object. On the fourth day of taking the drugs prescribed by Dr. Oota, the heavy pain in my stomach felt a bit better, and the pain in my mid- and upper back disappeared. My stiff shoulder also got somewhat better. Dr. Oota told me to take my drugs at 8 pm and then go to bed at around 10 pm. After trying that, I now fall asleep easily and don't wake up until about 5:30 in the morning. I feel refreshed, like I have slept well. My bowel movements have also improved. The pain and numbness in my right leg and foot has not yet resolved, but I am continuing to take the drugs, as I believe they will work with time. I intend to make sure I have a constant, almost structured, daily routine. Dr. Oota told me that internal conflict was at the root of my condition and that this cause is also known as 'over-seriousness disorder' or 'hypercritical disorder". Although I can't help my personality, I will keep trying to change my mindset as much as I can.

[Letter detailing condition and treatment plan]

XX XX, 2014

Dear Mr. XX,

I would like to explain my approach for your ongoing treatment.

In addition to suffering from chronic lower back pain for the last 20 years, you have had leg pain and numbness for the last six months, causing you distress when standing and walking. You have been receiving treatment for chronic gastritis for the last six years and have been suffering for the last three months from heavy pain around your stomach and the area of your back behind your stomach as if you are being squeezed. Thorough testing, including gastroscopy and MRI, revealed no abnormalities, and you were told that the cause of your condition was unknown, sending you into a state of considerable anxiety. You have been examined by various specialties, including internal medicine, psychosomatic medicine, and orthopedics, resulting in prescriptions for around nine types of drugs a day. Doctors have told you that they do not know the cause of your complaints so all you can do is keep an eye on your condition. This often happens in cases of chronic illness syndrome. The very fact that you have a chronic illness syndrome is hard for you. It is also troubling for doctors who are unable to identify any underlying findings to support a diagnosis. You have three drugs from the psychosomatic medicine department to take before bed, and six from the internal medicine department; this is more than normal. The fact that you are taking all these with no improvement in your condition is effectively the same as taking no drugs at all. I recommend you be brave and stop taking all 15 tablets of all nine drugs.

One more important point is that you seem to be caught up in your obligations: the things you think you must or are supposed to do. You obviously can't be irresponsible, but convincing yourself that things have to be a certain way is tying your mind up in knots and making life very hard for you. Self-generated stress is also known as endogenous stress. Treatment has to begin by you freeing yourself from medical drugs and changing your mindset to break away from 'musts' and 'supposed tos'.

As you have been taking all these drugs for such a long time, it is unwise for you to suddenly stop. You will undergo 'night therapy', which involves taking the five drugs that I have prescribed you at 8 pm every day and then turning out the lights at 10 pm. You will take the minimum possible number of tablets;

specifically, a total of 4.5 tablets covering all five drugs. Although my night therapy does not involve any standard painkillers or sleeping pills, I anticipate improvements in your pain and stomach condition. The first step of the treatment is you trusting in the night therapy and me as your doctor. The Bible says that those who believe will be saved. I feel a little intimidated talking about the Bible to a Christian missionary such as yourself, but it's important so I would like you to hear me out.

I also have an illness and am currently researching laetrile therapy (apricot seed therapy), which I would like to try. The main component of laetrile therapy is amygdalin, a constituent of apricot and peach kernels. The late Mutsuyuki Kochi was a researcher who studied amygdalin at RIKEN Institute in Tokyo, which is now the subject of attention by the news related to Haruko Obokata. He apparently got the idea for his research from 2 Kings 20:20-7 in the Old Testament. These verses read as follows:

20:1: In those days Hezekiah, became ill and was at the point of death. The prophet Isaiah son of Amoz went to him and said, "This is what the Lord says: Put your house in order, because you are going to die; you will not recover."

20:2–3 Hezekiah prayed to the Lord. "Remember, Lord, how I have walked before you faithfully and with wholehearted devotion and have done what is good in your eyes." And Hezekiah wept bitterly.

20:4–5: The word of the Lord came to the prophet Isaiah: "Go back and tell Hezekiah, the ruler of my people, 'This is what the Lord, the God of your father David, says: I have heard your prayer and seen your tears; I will heal you. On the third day from now you will go up to the temple of the Lord.

20:6 I will add fifteen years to your life. And I will deliver you and this city from the hand of the king of Assyria. I will defend this city for my sake and for the sake of my servant David.'"

20:7 Then Isaiah said, "Prepare a poultice of figs." They did so and applied it to the boil, and Hezekiah recovered.

While reading from the Old Testament, Kochi noticed that figs seemed to be able to cure death. When he gave a fraction of liquid fig extract to cancerous mice, they became well as written in the Old Testament. Working with the RIKEN Institute, Kochi investigated the constituents of figs, and in 1975, he identified the active ingredient as benzaldehyde, a breakdown product of amygdalin. A

report on benzaldehyde therapy was published in the American scientific journal, Anticancer Research. Thirty years later, benzaldehyde therapy is still in use. Kochi believed what was written about dried figs in 2 Kings in the Old Testament and arrived at an anticancer treatment: benzaldehyde therapy. I think you believe in the Lord. Borrowing from the words of the prophets, the Bible talks of many people who have been saved by believing in the Lord. I will cure you. The drugs I prescribed today have no side effects. Believe that you will be healed and along with taking these drugs, try and adopt a more flexible mindset. 'Must' and 'supposed to' are contrary to the Lord's great teaching of forgiveness. Try and change your expectation that "things should be a certain way" to "any way is fine" and maintain an attitude of forgiveness towards everything. That will make things much easier for both your mind and body. I hope that you will start to believe in and be proud of the body that the Lord gave you. The Lord respects your feelings. We were made by the Lord and are therefore close to Him. Believe in the Lord, believe in yourself, and try and give yourself praise.

After receiving the Lord's forgiveness, King Hezekiah's illness was cured in three days and he went on to live for another 15 years. If you believe in the Lord, you too, will undoubtedly be saved. I am not a prophet, but I believe that healing your body will come after healing your mind.

Case 37 : A 55-year-old man who began behaving strangely in his sleep after taking a drug for trigeminal neuralgia

According to my wife, I had long been waving my hands, kicking my feet, and talking in my sleep. In the mornings, I felt like I hadn't slept well and was exceedingly sleepy during the day. I heard about the Sleep Center and went for an examination. Dr. Oota gave me a prescription for Rivotril (clonazepam), and my condition got much better after taking just one tablet before going to bed. A few years later, I experienced increasing pain in my lower right teeth and I received treatment for cavities, but the pain did not improve at all, so the dental clinic referred me to the oral surgery department of the general hospital. They put me on two tablets of Tegretol (carbamazepine) twice a day, and the tooth pain got much better but did not completely disappear. The pain sometimes kept me

awake at night. At that time, I was no longer taking the drugs I had received from Myojinkan Neurosurgery Clinic two years earlier.

Then, about one month ago, in addition to the sleep talking, I apparently started engaging in other strange nighttime behaviors such as getting up and urinating in the room rather than the toilet or opening the refrigerator and getting something to drink. I took my wife's advice and got re-examined at Myojinkan Neurosurgery Clinic, where Dr. Oota told me that the pain in my teeth originated in the mandibular division of the trigeminal nerve. On reflection, the strange behaviors I was unknowingly engaging in while I was sleeping began after I started taking Tegretol (carbamazepine). Dr. Oota recommended I keep taking the Tegretol (carbamazepine) for the trigeminal neuralgia but gave me an additional prescription for Rivotril (clonazepam). After I started taking the Rivotril (clonazepam), all the strange nighttime behaviors stopped, including the sleep talking.

Case 38 : A 67-year-old man with a sensation like mice running round in his stomach, no appetite, and who was unable to sleep

I started having problems with insomnia about eight years ago. It was particularly hard for me to fall asleep, and I was examined at the neurology department where they prescribed me sleeping pills, which helped me get some sleep. However, my poor appetite and indigestion did not resolve, so I was examined at the gastroenterology department. They performed various tests, including blood tests, X-rays, ultrasound, CT, and gastroscopy, but everything came back clear. I was still taking gastrointestinal drugs, but the stomach pain, indigestion, and feeling of pressure had continued for the last four years, and I was unable to get rid of the strange sensation that mice were crawling around in my stomach. My appetite decreased, and my weight dropped from 60 to 54 kg. Due to my poor health, I was unable to work for long hours at a time or repeatedly stand up and sit down. I was exhausted and spent most afternoons lying down. It felt like mice were running round inside my stomach, to the extent that I wanted someone to cut me open and clean my insides out. Recently, I had been doing an hour or so of farming in the morning then spending the rest of the

day lying down inside. My neighbor couldn't stand to see me like that any longer and recommended that I go to Myojinkan Neurosurgery Clinic.

Dr. Oota there told me to stop taking and wean my body off all 19 tablets of the drugs I had been on for so long (six tablets of two kinds of stomach drugs, three Gasmotin (mosapride citrate hydrate) tablets, three Solanax (alprazolam) tablets, two Dogmatyl (sulpiride) tablets, two Depromel (fluvoxamine maleate) tablets, one Halcion (triazolam) tablet, one Desyrel (trazodone hydrochloride) tablet, and one Lendormin (brotizolam) tablet). He then gave me guidance regarding things like mirror therapy and how to improve my daily life and mindset. I was reluctant to stop all the sleeping pills at once, so he gave me four weeks to discontinue them gradually. It made me really nervous that Myojinkan Neurosurgery Clinic only gave me a prescription for 3.5 tablets: half a tablet of Tryptanol (amitriptyline) 10 mg, one tablet of Depakene (sodium valproate) for children, one tablet of Rivotril (clonazepam) 0.5 mg, and one tablet of Risperidone (risperidone) 0.5 mg. But I trusted Dr. Oota and kept taking the drugs, and in less than a month, the sensation of mice in my stomach disappeared, my appetite returned, and I was able to sleep without taking any sleeping pills. I am now able to focus on my farming, which gives me a great deal of pleasure.

Commentary

Until the patient's lifestyle or environment changes, his or her condition will not fully recover. Happiness can be achieved only during the brief periods of amelioration that occur within the cycles of exacerbation and remission. Drug therapy is mostly ineffective due to his obsessive, highly anxious personality, which remains unchanged despite his age. Patient, careful guidance is required to help him improve his mindset. Treatment effectiveness depends on the doctor's strength and drive and the time he or she can devote to consultations. I would like to see a family-based counseling system become standard in Japan's regional towns and cities.

Case 39 : A 61-year-old man suffering from unpleasant sensations in the throat and tongue and numbness around the tip of the tongue

About two years ago, the inside of my mouth started to feel salty, and my tongue became numb. At first, it just felt like there was a strange taste inside my mouth, but gradually, my tongue became numb, and my throat became scratchy. After a while, the tip of my tongue and the area around it were constantly numb. I forgot about the numbness while I was asleep but noticed it soon after getting up in the morning. As my symptoms got gradually worse, it became harder for me to fall asleep. I would lie in bed awake, and when I finally fell asleep, I used to wake up because my throat was dry. No other part of my body was numb, so when I went to be examined at the general hospital, they initially sent me to the ENT department and then to the oral surgery department. They started me on zinc and vitamin supplements, but my throat scratchiness and tongue numbness did not improve at all. I didn't know where to turn. I heard about Myojinkan Neurosurgery Clinic through word of mouth and went for an examination.

When I opened my mouth to be examined by Dr. Oota, he commented that I had severe bruxism. He asked me various questions, such as if I dreamed a lot, talked in my sleep, or had hot flashes in my feet, all of which fit my symptoms exactly. He gave me lifestyle guidance, including advice to avoid drinking alcohol, and a prescription for one Rivotril (clonazepam) tablet. Just by taking that one tablet, the bitter taste and numbness in my mouth that had bothered me so much disappeared. The next week, Dr. Oota reduced the dose of Rivotril (clonazepam) to a half tablet, but even with just that, I am now able to sleep through until morning.

Case 40 : A 60-year-old man suffering from generalized pain for many years

I had been suffering from lower back pain for 14 or 15 years and had undergone testing at various hospitals, but no one could find the cause. I was hospitalized in a specialist pain clinic for 45 days and given an epidural block. The pain eased

for the first 10 days, then the injection stopped being effective. CT, MRI, and bone scintigraphy performed at a general hospital all came back normal, and the doctors there did not mention anything about the spondylosis that had been pointed out at a previous hospital. I went to a hospital in Kurashiki and had a nerve block injection, but it had no effect at all, and I was referred to a psychosomatic clinic in Kurashiki. The doctor there diagnosed me with depression. I was hospitalized in the psychosomatic medicine department in a university hospital in Kansai for a total of 11 months, but I didn't get any better. If I leaned forward even slightly, sharp pains ran down my entire back, and I could barely walk.

I called the cephalic hypersensitivity syndrome hotline and went for an examination at Myojinkan Neurosurgery Clinic. Dr. Oota asked me detailed questions about my life, such as my personality, family and work relationships, and about any differences between my daytime and nighttime symptoms. I told him about my wife, three sons, and four grandchildren; that I have an inflexible personality but make sure my work is done right; that I played baseball until I was in my 40s, so I am confident in my physical strength; and that I have had a bad relationship with my brother for a long time. Dr. Oota told me to discontinue the seven types of drugs I had received from the hospital in Kansai and that I could stop taking the cholesterol drug I was on because my cholesterol levels were not that high. He said I was causing the pain myself —that my muscles were stiff due to stress and that the stiffness was causing the pain. He told me that because my chronic pain was stress-related, drugs would be of no use if I didn't find a way to relieve my stress. He told me that my brother and I are separate individuals; therefore, I should put our sibling relationship to one side and be practical about our respective work-related responsibilities. He told me there was absolutely no need for me to be on bed rest and that I was actually in very good health. Everything he said made sense.

I had previously been examined at many different hospitals, but Dr. Oota was the first to have the insight to ask me about my work relationship with my brother. Dr. Oota told me that I didn't need to take any drugs, but I needed to gradually wean myself off some of the ones I was on. He prescribed me one Tryptanol (amitriptyline) 10 mg tablet, one Rivotril (clonazepam) 0.5 mg tablet, and one Risperidone (risperidone) 0.5 mg tablet to be taken once daily; and two Paxil (paroxetine hydrochloride hydrate) tablets. Within one month, I was no longer kept awake by the pain. I had no need to call for an ambulance to take me

to hospital because of severe pain as had repeatedly happened before. My wife was surprised, and said it was as if I had been exorcised of whatever demon spirit had possessed me. My relationship with my brother has not improved, but Dr. Oota told me that my brother isn't concerned with me and that the problem is with my mind. I can't fix the problem by staying at home, so I am going to my workplace and doing what work I can. Recently, I have started coming round to the idea that the company should be managed according to my brother's policies, as it is his company.

Commentary

This patient had cephalic hypersensitivity syndrome arising due to psychological stress and underlying lower back pain. Although there was no static muscle load or other physical contributing factors, his body became stiff because his mind was set on not wanting to go to work, and his mental pain became physical. This is a typical case of stress-related overactive pain memory.

Case 41 : A 38-year-old woman with epilepsy complicated by hysterical seizures whose convulsive seizures, from which she had suffered for many years, resolved after receiving a diagnosis of just epilepsy (with no mention of hysteria), making it easier for her to get married

From 'My epilepsy outpatient clinic: an introductory handbook' by Dr. Kosuke Oota

The patient had had seizures since the age of 15. A 24-h EEG and imaging testing at a university hospital all came back normal. Her pediatrician ruled out epilepsy based on normal results on EEGs carried out a few dozen times, including an overnight EEG, and said there was no need for her to take antiepileptics. When she went to Canada to study at 19 years old, she took a referral from her pediatric neurologist stating that her seizures were not epilepsy. She recalls having seizures twice while driving and twice while eating when in her twenties. When she was 30, she had a generalized seizure while eating and was emergently admitted to

our hospital. An EEG and MRI showed no abnormalities, and the neurologist prescribed Depakene (sodium valproate). When she was referred back to her original pediatric neurologist, she again rejected a diagnosis of epilepsy and discontinued the drug. However, she subsequently had mood-related mini- and generalized seizures and was repeatedly rushed to the hospital. Based on her family's strong demands, her pediatric neurologist prescribed antiepileptics, and she stopped receiving outpatient treatment at our hospital. The following year, when she was 31, she stopped taking the drug for a year and apparently had no seizures. Then, when she was 32, she collapsed while doing office work and had a generalized seizure. Her seizures subsequently became frequent, and her sister worriedly brought her in to see us.

The patient has a meticulous, nervous personality and complained strongly of stress at home and work. Based on her test and treatment history to date, I suspected cephalic hypersensitivity syndrome. According to what her sister had witnessed, the seizures were particularly prevalent after the patient was excited or had taken a few bites of food at meal times. Mini-seizures presented as strange movements of her mouth and lips, whereas large seizures involved her falling to the floor and making groping movements with her hands. Her face turned to the right. During a seizure, she didn't breathe, her face would turn blue, and she would making chewing motions and lick her lips. During a recent attack in August, her left hand was clenched and her right hand was stretched out. Once or twice, she suffered from incontinence. After a seizure, she would complain of muscle soreness and sometimes found she had bitten the inside of her mouth. Her boyfriend's description of her seizures was similar to that of her sister.

Both the patient and her sister told me about her ongoing feud with her mother. When asked about her relationship with her mother, her face paled and tightened, her lips quivered, and she became agitated. Mental excitement is well known to induce epileptic seizures. It was difficult to determine whether she was suffering from epileptic or psychogenic nonepileptic seizures. While talking with the patient, it came out that her mother verbally abused her, accusing her of female hysteria. Although it appeared that she was suffering from epilepsy complicated by hysterical seizures, which are psychogenic nonepileptic seizures that resemble epileptic seizures, I chose to tell her instead that I believed she did not have hysterical seizures and that it was simply epilepsy without an abnormal EEG. On hearing this, her face immediately brightened and she looked

satisfied with the diagnosis. During the subsequent four years, she has taken Tegretol (carbamazepine) 400 mg and Mystan (clobazam) 20 mg daily and has experienced no seizures. The doses are such that there would be no risk of fetal deformity if she became pregnant, thus making it easier for her to get married. I have effectively acted as matchmaker for many women with epilepsy, who have all gone on to have healthy babies! When I explained this to her, she went on to marry her long-term boyfriend and moved to Tokyo six months later. She seemed very happy.

Commentary One

Epilepsy cannot be definitively ruled out solely on the basis of a normal EEG. On the other hand, it is not possible to categorically state that all seizures without abnormal brain electrical discharges are hysterical seizures (a type of psychogenic nonepileptic seizure). In this case, I decided that it did not matter if the seizures were epileptic or hysterical as long as the diagnosis would reduce the patient's feuding with her mother. Once she married and moved out of the home, the incidence of seizures dramatically decreased. The matchmaking role I chose to play was the best choice from the perspective of the seizures and her age.

Commentary Two

Micturition and defecation syncope are common vagal reflexes. Some vagal reflexes occur at times of intense fear or anxiety and result in generalized seizures with loss of consciousness that resemble epileptic or hysterical seizures. Neural reflexes occurring outside the patient's conscious control should not be denounced as "female hysteria".

Case 42 : A 55-year-old man suffering from feeling unsteady and slurred speech for five years

About five years ago, I started to become unsteady on my feet. Luckily, I work at a desk, so it did not affect my ability to do my job; however, I was unable to walk in a straight line down the hall, and when I moved around the workplace, I bumped myself against my colleagues' desks. The biggest problems were my inability to walk down the stairs without holding the handrail and that I was stumbling over my words, preventing me from talking clearly in meetings and other work situations. As a mid-level manager, I was often expected to lead meetings, and my inability to talk was making me depressed. My boss told me repeatedly to get thoroughly checked out by a doctor, so I went to various hospitals and underwent multiple CTs and MRIs, but wherever I went, they told me there was nothing wrong with me. I was feeling increasingly stressed due to my unsteadiness, slurring, poor performance at work, and other problems and started to suffer from chronic insomnia.

I received various drugs from the psychosomatic medicine department, but they just made me feel sluggish, and it became even harder to talk. Meanwhile, I was diagnosed with depression by the psychiatric hospital, and they increased my drugs. I knew I had to do something, so I took my colleague's advice and went to Myojinkan Neurosurgical Clinic. They performed equilibrium function testing and told me the results clearly showed cerebella ataxia. I underwent a detailed medical interview covering my history to that point, including the time I had intense pain in the right side of the back of my head for about two weeks five years ago for which I was examined at a neurosurgery clinic. A thorough repeat MRI showed right vertebral artery stenosis, which was affecting the posterior inferior cerebellar artery. The neurosurgeon at Oota Memorial Hospital diagnosed dissecting aneurysm with stenosis. He performed endovascular treatment involving surgical placement of a stent in the stenosed region to restore the blood flow, and the unsteadiness and slurring I had suffered from for years miraculously disappeared.

Commentary

The non-hemorrhagic dissecting aneurysm in this patient presented as a hole in the internal elastic lamina of the vertebral artery, resulting in extravasation of blood into the vessel wall, formation of a false lumen, and compression of the original vessel lumen, causing stenosis. The vertebral artery comprises a left and right branch, which anastomose to form the basilar artery. The patient was missing a bypass vessel linking the vertebral-basilar and carotid systems and had stenosis of the origin of the normal contralateral vertebral artery. Treatment comprised stent dilatation of both the origin of the left vertebral artery and the portion of the right vertebral artery stenosed due to the dissecting aneurysm. This case was an unusual find in the cephalic hypersensitivity syndrome outpatient clinic.

Afterword

About the cephalic hypersensitivity syndrome hotline

I have long wanted to write a book about cephalic hypersensitivity syndrome. The opportunity finally presented itself when I found myself with too much time on my hands during my stay in Koriyama City, Fukushima Prefecture when receiving particle radiotherapy for my cancer.

The talented secretaries who have supported my work over the last 20 years took dictation over the phone, and the outline of the book quickly took shape. Patient testimonials remain largely unaltered from the original wording in thank-you notes I have received over the years. This book is a culmination of 40 years of experience with outpatient treatment for cephalic hypersensitivity syndrome.

The 42 case reports substantiate the need for my approach better than any paper in a scientific journal. Readers suffering from the symptoms listed in this book will undoubtedly find a case that echoes their own experiences.

This book is not the end of the story. Important work still remains to comparatively analyze cases that did and did not respond to antiepileptics and antidepressants. I have established a toll-free direct cephalic hypersensitivity syndrome advice hotline (Tel 084-959-2920) for patients suffering from symptoms resembling cephalic hypersensitivity syndrome.

People who call for advice will receive a response from me. Those who would like me to examine them can make an appointment. If I cannot treat them, I will refer them to a suitable doctor, and we will make an appointment on their behalf based on that doctor's outpatient care schedule. Calls to the hotline are fielded by an experienced nurse, and we aim to build a hotline you can rely on.

About the author: who is Kosuke Oota?

On reading Part 2 of this book, it soon becomes clear that Dr. Oota has many fans: male and female, young and old. They are charmed by Dr. Oota's electric personality, deep compassion, and perceptive sensitivity, and like-minded people tend to be devoted to him for life. Even people who do not hit it off with him are unable to forget him after just a single meeting. Dr. Oota profoundly affects people's lives. His professional accomplishments are too numerous to list, but I would like to take this opportunity to explain why Dr. Oota's personal qualities make him so popular.

Perceptive sensitivity

From Oota Memorial Hospital, Myojinkan Neurosurgery Clinic, and the Oota Gramophone Museum, to his three holiday homes in Utsumi, Sanwa, Ishigaki, and his personal home in Okinogami, Dr. Oota has been involved in the design and building of numerous facilities. This is the architect side of Kosuke Oota. Although all the buildings are simultaneously beautiful and functional, Oota Gramophone Museum is the masterpiece. Wooden ships hang from the ceiling, and the acoustics are sublime. According to Dr. Oota, his designs are based on intuition rather than careful calculations.

Dr. Oota himself admits that his strengths do not lie in book learning. However, his brilliance as a doctor and the foresight evident in his published papers, medical equipment development, and hospital management policies are universally acknowledged. This is the neuroscientist side of Kosuke Oota. Dr. Oota has the knack of seeing right to the heart of the matter. He often downplays his abilities, saying his theories are based on deductions and assumptions, but these theories are always borne out. His work on cephalic hypersensitivity syndrome as laid out in this book is a case in point. According to Dr. Oota, as ion channels are the basis for biological mechanisms, it must be possible to explain cephalic hypersensitivity syndrome by electrical circuits. On first hearing, this sounds questionable, but if you read the latest English research papers, that "?" becomes a "!". Although the medical community has yet to catch up, "Bayesian inference is perfectly suited to medical statistics" is another Oota theoretical 'prophecy'. He is able to see and verbalize the true nature of things that are at first glance 'absurd' or unfathomable in the light of current wisdom. Insight is essential

for scientists. Many scholars bury themselves under mountains of papers and repeat experiments to finally, after a great deal of time, achieve something like insight. However, even insight acquired in this way is better than the alternative: many scholars go no further than simply compiling vast amounts of data. Even for the gifted Dr. Oota, scientific insight does not arrive in the form of a voice from the heavens, attained without any effort. His success reflects his constant attention to the world around him, his sincere focus on patients' complaints, and the perpetual working of his brain to expose pharmacological and pathological truths. This book by Dr. Oota thus presents the essence of simple knowledge.

Profound compassion

The depth of Dr. Oota's compassion is without doubt. His late wife, Dr. Shoko Oota, supposedly said, "he is almost generous to a fault". However, men like Dr. Oota, who put others before themselves, are few and far between in modern Japanese society. Dr. Oota tells people what they need to hear for their own good. For the person on the receiving end, his words often contain many home truths that they would prefer to avoid, making it difficult to immediately emotionally accept what he says. However, after thinking calmly, they come to realize that everything he has said is right on the mark, and for those who want to improve their lives, his advice is welcome.

Dr. Oota's compassion expects nothing in return. Repaying kindness is undoubtedly a matter of social courtesy, but aside from that, Dr. Oota's compassion represents unconditional love for others. This is a truly difficult attitude to maintain. It is possible to be confused by his words as he talks about many things, but if you look at his actions and results, these are based in thought for the other person, and it is clear that he expects no reward. In consequence, those who understand Dr. Oota's depth of compassion are deeply devoted to him in return.

Electric personality

Finally, I would like to introduce the charismatic side of Dr. Oota. He resembles the actor Yujiro Ishihara in appearance — he is unarguably good looking. On the inside, he remains forever young. He is full of curiosity and does not get caught up in the notion of obligations. He is always seeking new things and overflowing

with new ideas. I always picture him as a James Bond-type — taking his gleaming white boat *Isokaze* and sprinting across the Ishigaki horizon between the blue of the sea and the sky. When it comes to his brilliant deductive skills, his character is more closely matched to that of a villain in a Kogoro Akechi or Sherlock Holmes movie entangled in political scandals, intrigue, and ambition. Despite his clear-headedness, competence, and easy-on-the-eyes appearance, he never puts on airs, is as carefree as a child, and remains unchanged by the passing years. The only downside is that you are unlikely to meet anyone better. I fervently hope he remains with us for many years yet.

Nami Kobayashi
May 2014

Brief Author Bio

Kosuke Oota graduated from Okayama University Medical School in 1964 and completed his doctorate at Okayama University Graduate School in 1969. After working as Chief of Neurosurgery at National Fukuyama Hospital (now called National Hospital Organization Fukuyama Medical Center), in 1976, he established Oota Hospital, now known as the Brain Attack Center Oota Memorial Hospital. In 1986, he developed a wide-area emergency medical network using Oota CT image data transmission devices in coordination with medical facilities in isolated islands and remote mountainous areas without on-site neurosurgeons. He is a recipient of the Japan Medical Association's highest merit award as well as a Congress of Cell Transplant Society prize for his active work in kidney and cornea donation from deceased donors. In his roles as clinical professor at Okayama University Medical School and primary researcher at the Shibuya Longevity Health Foundation, his research interests cover cerebrovascular disease, sleep disorders, and cephalic hypersensitivity syndrome.

Publications

MR angiography: basics to clinical application. An easy to understand guide. Axel Springer Japan Publishing (1991)

My epilepsy outpatient clinic: an introductory handbook. Fukuyama Transporting Shibuya Longevity Health Foundation (2012)

Increasing incidence of cephalic sensitivity dizziness / vertigo at my dizziness / vertigo outpatient clinic. 2nd edition. Fukuyama Transporting Shibuya Longevity Health Foundation (2012)

Cephalic hypersensitivity syndrome is on the rise: testimonials from 36 people finally cured of this condition. Shibuya Longevity Health Foundation (2013)

Cephalic hypersensitivity syndrome

Toll-free advice hotline

An advice hotline for people whose daily lives are affected by conditions such as headaches, dizziness / vertigo, tinnitus, insomnia, restless legs, numbness in a limb, and pain.

Stress can lead to autonomic nervous system imbalance, which in turn can cause brain hypersensitivity. By relieving this hypersensitivity, patients can be freed from the chronic headaches, dizziness / vertigo, and other symptoms affecting their daily lives, thereby improving their quality of life.
Myojinkan Neurosurgery Clinic runs a toll-free advice hotline for people troubled by cephalic hypersensitivity syndrome. A specialist nurse will take careful note of your symptoms and then return Dr. Oota's comments to you shortly after. Please don't hesitate to call.

Hours

Mon–Fri: 9:00–11:00 and 14:00–16:00

Tel: 084-959-2920
(dedicated number)

*** Please allow at least 30 minutes for your call to allow time for a detailed medical interview.**

Cephalic hypersensitivity syndrome:

A revolutionary approach to healing chronic illness syndrome

First edition: March 1, 2015
English edition : November 7, 2015

Author: Kosuke Oota
Publisher: Shibuya Longevity Health Foundation
3-12-16 Okinogamicho, Fukuyama City,
Hiroshima Prefecture 720-0825, Japan
Tel.: 084-922-9757
Fax: 084-922-9758
http://www.zaidan-shibuya.com

Illustrations: Yasuhisa Kimura
Layout: Tsutomu Otsuka
Printer: One Write Co. Ltd.
English translation: FORTE Science Communications

- In case of misprints, please send to the address above.
  A new copy will be provided at our expense, including postage fees. Please note that we cannot provide replacements or accept returns in response to customer requests for any reason other than misprints.

- Any reproduction, reissue, or posting online of all or any part of this book without prior consent constitutes infringement of the author's and publisher's rights. Please contact us to obtain permission beforehand.

- Any unauthorized reproduction of this book (such as copying or scanning) is prohibited except for personal use and other circumstances allowed under copyright laws. It is illegal to transfer or sell reproductions or scanned data to other parties.