Guidelines for the Comprehensive Treatment and Care of Congenital Insensitivity to Pain with Anhidrosis (2nd Edition)

Grant sponsor: Health and Labor Sciences Research Grants for Research on Intractable Diseases, Ministry of Health, Labor, and Welfare.
Supervisor: Nobuhiko Haga

Greetings

We are pleased to present the second edition of the Guidelines for Comprehensive Medical Treatment and Care for Congenital Insensitivity to Pain with Anhidrosis. The first edition was published in March 2012 as a result of the work by the "Research to Understand the Current Status of Congenital Insensitivity to Pain and to Create Guidelines for Its Treatment and Care" group (FY 2009) and the "Research to Diagnose and Evaluate Congenital Insensitivity to Pain and to Create Guidelines for Its Treatment and Care" group (FY 2010 and 2011), both funded by Grants-in-Aid for Scientific Research on Intractable Diseases from the Ministry of Health, Labor and Welfare of Japan.

This second edition is based on the results of research on congenital insensitivity to pain (CIP) and congenital insensitivity to pain with anhidrosis (CIPA) conducted as part of the "Establishment of Medical Treatment Guidelines for Acute Encephalopathy and Convulsive Status in Children" (FY 2008, Representative: Dr. Masashi Mizuguchi) and the "Follow-up Study of Cross-Sectional Pathogenesis, Treatment, and Prognosis of Acquired Idiopathic Generalized Anhidrosis" (FY 2017 and 2018, Representative: Dr. Hiroo Yokozeki), which were funded by the Ministry of Health, Labor and Welfare of Japan. These guidelines summarize information on medical treatment and care that is currently considered standard.

The authors of these guidelines have been involved in the treatment of patients with these disorders for many years. In 1993, patients with CIPA and their families established the "Society for Congenital Insensitivity to Pain with Anhidrosis-Tomorrow," and the first symposium was held the following year. Since then, this symposium has been held every year, and medical professionals from various disciplines related to these diseases have held checkup sessions to collect data on a small number of patients with the aim of enabling experts to give appropriate advice to patients and their families based on the accumulated experience. However, only a limited number of patients and their families can participate in the symposiums. This guideline is intended primarily for health care professionals and is a collection of

information that may be useful in diagnosing, treating, and supporting patients. Although these diseases are rare, we believe this can be useful in the treatment of patients.

CIPA and CIP are both rare diseases, and there are very few studies with a high level of evidence. Therefore, these guidelines should not be considered medical guidelines based on exhaustive evidence, but rather a description by experts who have considerable experience with these diseases, based on the issues they have encountered. Therefore, these guidelines are not necessarily requirements for medical professionals to follow, but can use them as references for medical interventions.

November 2018

Nobuhiko Haga

Author List (in order of authorship)

Masaya Kubota, Division of Neurology, National Center for Child Health and Development Hospital, Department of Pediatrics, Shimada Ryoiku Medical Center for Challenged Children

Hideki Hoshino, Department of Pediatrics, Teikyo University Hospital

Yasuhiro Indo, Department of Pediatrics, Kumamoto University Hospital

Kikuko Ikeda, Department of Rehabilitation Medicine, Chiba Tokushukai Hospital

Naoko Baba, Department of Dermatology, Kanagawa Children's Medical Center

Makoto Nozaki, Wakaba Dermatology Clinic

Hiroshi Tanaka, Department of Orthopaedic Surgery, National Rehabilitation Center for Children with Disabilities

Nobuhiko Haga, Department of Rehabilitation Medicine, The University of Tokyo Hospital

Tomoko Kubodera, Chiba Dental Center, Tokyo Dental College

Shima Fukuoka, Omiya Hamada Eye Clinic, Department of Ophthalmology, The University of Tokyo Hospital

Toshiya Tomioka, Department of Anesthesiology, Saitama Red Cross Hospital

Kimiko Shirakawa, Pediatric Medical Center, Tokyo Nishi Tokusyukai Hospital

Fumiko Hamabe, Department of Nursing, Tokai University School of Medicine

Chizuko Tanaka, Department of Nursing, Faculty of Nursing, Kanagawa Institute of Technology

Table of Contents

Chapter 1: General Remarks

1-1 What is congenital insensitivity to pain with anhidrosis?

Congenital insensitivity to pain with anhidrosis (CIPA) is classified as hereditary sensory and autonomic neuropathy type 4 (HSAN-4) (Table 1-1-1) [1]. HSAN-4 is an autosomal recessive disorder characterized by the absence of temperature and pain sensations, sweating disorder, and intellectual disability (Table 1-1-1). The responsible gene was found to be the neuropathic tyrosine kinase receptor type 1 gene (*NTRK1*) located on chromosome 1 [2]. HSAN-4 is characterized by a selective loss of myelinated nerves (somatic C fibers and autonomic C fibers) and small myelinated fibers (A δ fibers), resulting in impaired temperature and pain perception and sweating (Table 1-1-2). In contrast, HSAN-5 is characterized by loss of temperature and pain perception, but is generally not accompanied by sweating disorders or intellectual disability, and is caused by mutations in the nerve growth factor beta (*NGFB*) gene and the sodium voltage-gated channel alpha subunit 9 gene (*SCN9A*). It is distinguished from HSAN-4 (CIPA) (Table 1-1-1). Therefore, HSAN-4 and HSAN-5 can be considered different pathological conditions, but they have also been reported as rare overlapping conditions. In Japan, the number of patients with HSAN-4 (CIPA) ranged from 130 to 210, and the prevalence (the ratio of the number of patients to the Japanese population) was 1 in 600,000 to 950,000, with the age range generally being between 5 and 40 years, although patients between 65 and 70 years of age were also observed [3]. The number of patients with HSAN-5 ranged from 30 to 60, which is less than of those with HSAN-4.

Table 1-1-1 Classification of hereditary peripheral nerve diseases

A. Hereditary motor-sensory neuropathy (HMSN)

B. Hereditary sensory autonomic neuropathy (HSAN)

- Type 1: Hereditary sensory radicular neuropathy
- Type 2: Congenital sensory neuropathy
- Type 3: Familial dysautonomia (Riley-Day syndrome)
- Type 4: Congenital insensitivity to pain with anhidrosis (CIPA)
- Type 5: Congenital insensitivity to pain (CIP)

(Adapted from Ref. 1)

Table 1-1-2 Sizes and functions of somatosensory and autonomic nerve fibers

Nerve fiber			Diameter (μ)	Conduction velocity (m/sec)	Function
Myelinated	**A**	A	12–20	70–120	Position sense proprioception
		B	5–12	30–70	Tactile and pressure sensation
		δ*	2–5	12–30	Pain (sharp) and temperature sensation
	B		1–3	3–15	Sympathetic preganglionic fibers
Unmyelinated	**C** *(somatic)		0.4–1.2	0.5–2.0	Pain (dull), temperature, and itch sensation
	C *(autonomic)		0.3–1.3	0.7–2.3	Sympathetic postganglionic fibers, sweating

*: Nerves that disappear or decrease in number in CIPA

(Adapted from Reference 7)

The first case of CIPA ever reported, that of a 15-month-old girl born to consanguineous parents, was by Nishida et al. in 1951.[4)] The child had no perinatal problems, but on the 17th day of her life, her body temperature reached 40.4 °C and she developed convulsive status, followed by high fever, anhidrosis, and dry skin in the summer. She had an ulcer on the tip of her tongue due to self-injury (biting) and the tip of her index finger was scarred, but she did not appear to be in pain. A femur fracture was not painful either. Her development was hypotonic, and she was capable of simple comprehension but unable to speak or grasp objects. Sweat tests were negative, and skin histopathology showed no abnormalities in sweat gland morphology. This report fully describes the initial signs and basic findings of CIPA.

During neurogenesis in this disease, the thinnest myelinated Aδ fibers and both autonomic and somatic unmyelinated C fibers of peripheral nerves are selectively lost or reduced. As a result, the perception of temperature and pain, especially sharp pain, which is controlled by Aδ fibers, is impaired, as is the perception of dull pain and itching, which is controlled by unmyelinated C fibers (somatic) (Table 1-1-2). Aβ fibers are unaffected, and therefore the perception of touch and pressure on the skin is preserved (Table 1-1-2).

In addition, anhidrosis is thought to be due to a deficiency or decrease in autonomic C fibers (postganglionic sympathetic fibers, neurotransmitter acetylcholine) that regulate the function of the capillaries surrounding sweat glands, resulting in their inability to supply water and salts, the components of sweat, in a vasoactive manner. In addition, these fibers also innervate the erector pili muscle. The loss of these fibers results in the inability to get goose-bumps even when cold, as well as poor contraction of skin blood vessels and the failure to normally control the dissipation of heat. In other words, this disorder of body temperature regulation occurs in both high and low temperature environments. Thus, in addition to impaired sweating and temperature perception, the dysregulation of body temperature in this syndrome is also thought to be caused by impaired regulation of blood flow due to autonomic and vasomotor neuropathy.

In skin biopsies, the structure of the sweat glands themselves is found to be preserved, but the autonomic C fibers (postganglionic sympathetic fibers) that innervate the glands are missing. Peripheral nerve biopsy shows loss of Aδ and C fibers; autopsy of the spinal cord also shows loss of the Lissauer bundle, through which the Aδ and C fibers pass.

As a secondary consequence of decreased pain perception, affected infants have oral self-injuries (biting of the tongue, lips, and buccal mucosa), biting of the finger tips, recurrent fractures and joint injuries, and anhidrosis, which results in poor thermoregulation in hot environments and often recurrent fevers. Thus, high fever in newborns may be the first sign of the syndrome. Their sense of touch is often preserved (or even hypersensitive), and they respond well to tickling. Although the symptoms stem from the core pathology of the disease, early diagnosis (or suspicion) allows for appropriate care and promotes awareness of the disease concepts.

Motor function and language-related delays, autism, learning disabilities, and

attention deficit/hyperactivity disorder (ADHD) are often comorbid to varying degrees, with hypotonia being prominent in the early stages. These central nervous system symptoms may be primary, or secondary to environmental factors. Genetic mutations are thought to be involved, but the details remain unclear.

CIPA affects the whole body, and is not just a combination of impaired perception of temperature and pain and impaired sweating. It must be viewed comprehensively as a serious disorder that affects the health and well-being of the entire body of patients[6].

References

1) Dyck PJ, Klein CJ et al: Hereditary sensory and autonomic neuropathies. In: Noseworthy JH (ed). In: Noseworthy JH (ed) Neurological Therapeutics: Principles and Practice. CRC Press, London, p 2188, 2003.

2) Indo Y, Tsuruta M, et al: Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis. Nat Genet 13: 485-488, 1996

3) Haga N, Kubota M, Miwa Z: Epidemiology of hereditary sensory and autonomic neuropathy type IV and V in Japan. Am J Med Genet A 161: 871-874, 2013

4) Nishida G, Nomura M, Ueda M: General anhidrosis. (In Japanese) Saishin-Igaku 6: 1100-1104, 1951

5) Awaya Y: Congenital insensitivity to pain with anhidrosis. (In Japanese) Japanese Journal of Pediatric Medicine 28: 184-190, 1996

6) Nihei K: Congenital insensitivity to pain with anhidrosis. (In Japanese) Japanese Journal of Pediatrics 57: 121-126, 2004.

7) Erlanger J, Gasser HS: Electrical Signs of Nervous Activity. Univ. of Pennsylvania Press, Philadelphia, 1937

1-2 Laboratory Methods

Congenital insensitivity to pain with anhidrosis (CIPA) is often diagnosed clinically based on typical symptoms. The following tests are performed for differential diagnosis and objective symptom assessment.

1. Sweating tests

1) Minol test

This is a general test for sweating. After wiping the skin well and drying it, apply tincture of iodine (a mixture of 15 g iodine, 100 ml castor oil, and 900 ml anhydrous alcohol) to the whole body, and after it dries, apply starch over it. Then, induce a heat load by raising the room temperature or using a hair dryer, being careful not to burn the skin. If there is sweating, a purple color will be visible, indicating the presence of sweat glands (due to the iodine-starch reaction). In CIPA, very little or no color is observed. This test is suitable for systemic assessment of sweating sites, but it does not allow quantitative assessment of sweating volume. In the axilla and inguinal region, insensible perspiration may be trapped and a light purple color may be observed.

2) Sweat meter (Skinos)

A sealed cell is attached to the skin of the area where perspiration is to be examined, and the air in the cell is refluxed. The advantage of this method is that minute amounts of perspiration can be quantitatively measured over time.

3) Histamine erythema test

When 0.3 ml of 0.1% histamine is injected intradermally, a wheal appears at the injection site. The swelling is due to the direct action of histamine; the surrounding erythema is due to stimulation of the postganglionic fiber nerve endings of the sympathetic ganglia by histamine, as well as retrograde nerve excitation through axonal

reflexes. For this reason, in patients with CIPA, there is no or little erythema surrounding the lesion, even though a wheal may appear.

4) Acetylcholine test

Acetylcholine chloride (5–10 mg), is injected intradermally to observe if the receptors in the sweat glands and erector pili muscles work normally. Normally, perspiration and erect hair around the injection site are observed, but no response is seen in patients with CIPA.

5) Pilocarpine test

Pilocarpine, an alkaloid and a non-selective muscarinic receptor stimulant, excites the parasympathetic nervous system and promotes sweat secretion from sweat glands. When 1% pilocarpine (0.01–0.03 mg/kg) is injected subcutaneously, normally, sweating starts around 5 minutes after injection, and the whole body sweats in 30–40 minutes. It is not often performed in children because of the psychological burden.

2. Autonomic function tests

1) Sympathetic skin response (SSR) test

This is a physiological test that captures the changes in the electrical activity that occur in sweat glands simultaneously with sympathetic nerve activity induced by painful or emotional stimuli. In practice, the sensory branches of the median nerve are stimulated electrically, and potential changes, using a probe electrode positioned on the palm and the reference electrode positioned on the dorsum of the hand, are observed as a response. In CIPA, the SSR to sensory stimulation is decreased or absent.

2) Orthostatic test

Changes in heart rate and blood pressure are observed in the resting and standing positions. Normally, the heart rate increases and blood pressure is maintained, reflecting the increase in cardiovascular sympathetic nerve activity, but in some cases of CIPA,

the autonomic nerves do not work well, causing hypotension, bradycardia, and uncomfortable feeling.

3) Electrocardiographic R-R interval

After 15 min of rest, measure the R-R intervals of at least 100 consecutive heartbeats on the ECG and determine the mean and standard deviation. The normal CVR-R (coefficient of variation) in adults, calculated as standard deviation/mean x 100, 3–5, but in some patients with this syndrome, this value is reduced.

4) Cold pressure elevation test

One wrist is immersed in 4 °C water, and blood pressure is measured on the opposite arm that is not immersed in water. Under normal conditions, blood pressure rises compared to that before the cold stimulus because the warm and pain sensation becomes an afferent pathway, and skin blood flow decreases.

3. Skin biopsy

In a skin biopsy, a portion of skin is taken to examine the presence or absence of peripheral nerves and sweat glands using an optical microscope or electron microscope. Usually, the skin at the biopsy site is disinfected and anesthetized locally, and a small incision is made such that sutures are not necessary.

In this disease, there is no sweating, but sweat glands are present. It is characterized by a lack of nerve fibers surrounding the sweat glands. On the other hand, ectodermal dysplasia is characterized by the absence or hypoplasia of sweat glands, and can be distinguished from this syndrome.

4. Peripheral nerve biopsy

A biopsy of a portion of the peroneal nerve is usually performed, and light or electron microscopy reveals a decrease in unmyelinated fibers and small myelinated fibers.

5. Other tests

1) Peripheral nerve conduction velocity

Nerve conduction velocity and amplitude are measured for motor and sensory nerves. Electrical stimulation is usually provided in the upper limbs (median and ulnar nerves) and lower limbs (tibial and sural nerves). In this disease, the peripheral nerve conduction velocity is normal in principle, because the thin C and Aδ fibers are usually selectively damaged and the motor fibers and Aα and Aγ nerves are not damaged. However, in some cases of hereditary sensory and autonomic neuropathy (HSAN), abnormal conduction velocity may be observed, which is important for differentiation.

2) Electroencephalography

For patients with epilepsy, an EEG examination should be performed, but there are no known disease-specific EEG abnormalities. Since EEG recording is performed at rest, closing the eyes or sleep and sleep-inducing drugs may be required for patients with intellectual disability or infants who are unable to maintain rest.

3) Head CT/MRI

There are no characteristic findings in CIPA, but in cases of acute encephalopathy or severe intellectual disability, it is performed to investigate organic abnormalities in the brain.

4) Blood and urine tests

There are no characteristic blood or urine findings. In CIPA, sweating disorder tends to cause a heatstroke-like rise in body temperature, especially in summer, and this is necessary to distinguish it from infectious diseases. In severe heat stroke, rhabdomyolysis may occur, and attention should be paid to elevations in blood creatine

kinase (CK) and aldolase levels, disseminated intravascular coagulation (DIC), and myoglobinuria.

5) Radiography

In this disease, fractures and Charcot joints are often present. Radiographs of bones and joints are useful for diagnosis. Contrast-enhanced CT is useful for qualitative diagnosis of osteomyelitis and cellulitis.

6) Genetic testing

See the section on "Genetic mutations and pathogenesis".

References

1) Awaya Y: Congenital insensitivity to pain with anhidrosis. (In Japanese) Shoninaika 28: 184-190, 1996.
2) Terashima H: Congenital insensitivity to pain with anhidrosis. (In Japanese) Shoninaika 50: 1150-1154, 2018

1-3 Genetic mutations and pathogenesis

Hereditary sensory and autonomic neuropathy (HSAN) refers to a group of disorders in which the sensory and autonomic nervous systems are impaired due to genetic causes. HSAN has been classified into five types based on inherited factors, clinical phenotypes, and pathological findings. Not all types have both sensory and autonomic neuropathy. As the responsible genes have been identified, several new types have been added. Congenital insensitivity to pain (CIP) includes both HSAN type 4 (HSAN-4) and 5 (HSAN-5). HSAN-4 is called congenital insensitivity to pain with anhidrosis (CIPA) because it is associated with sweating disorders in addition to lack of temperature and pain perception. On the other hand, HSAN-5 does not involve sweating disorder and is called congenital insensitivity to pain (CIP). However, the disease concept of HSAN-5 is not clear from previous reports. Here, we first describe the causative genes of CIPA and then discuss the causative genes of other diseases.

1. Congenital Insensitivity to Pain with Anhidrosis (CIPA)

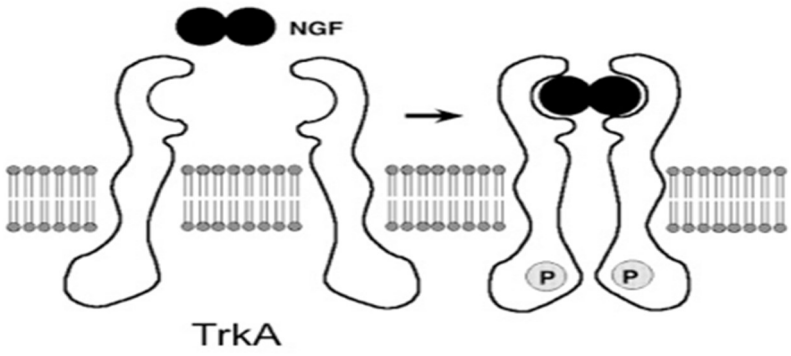
1) Causative gene

CIPA is caused by a loss-of-function mutation in a gene called *NTRK1 (*gene names are italicized). *NTRK1* is essential for the survival and maintenance of neurons that regulate sweating and temperature and pain perception during development and differentiation. The genetic information encoded by *NTRK1* is used by certain neurons to produce a protein called TrkA, a tyrosine kinase-type receptor for nerve growth factor (NGF) (Fig. 1-3-1). TrkA is a protein that penetrates the cell membrane once, and has a domain (region) that binds to NGF on the cell surface and an intracellular domain with tyrosine kinase activity. When NGF binds to TrkA, it activates the intracellular signaling system involved in neuronal growth, survival, and maintenance.

Figure 1-3-1

Nerve growth factor (NGF): A protein essential for the survival and maintenance of sensory nerves that transmit temperature and pain sensations and sympathetic nerves that regulate sweating during development and differentiation.

Tyrosine kinase-type nerve growth factor receptor (TrkA): A protein that located in the cell membrane of neurons and binds to NGF to transmit signals necessary for the survival and maintenance of neurons into the cell.



CIPA is an "autosomal recessive" disease according to Mendel's law of inheritance. *NTRK1* is located on the long arm of chromosome 1 (1q23.1). Humans have two copies of the *NTRK1* gene, one inherited from the father and one from the mother. The patient's father and mother, neither of whom show symptoms, have one mutated gene, which can cause the disease, and one unmutated gene. Such individuals, who have one mutated gene and do not show any symptoms of the disease, are called "genetic carriers". The frequency of the mutated gene varies from populations to population, but if the disease occurs in one in a million people, it is estimated that about one in 500 individuals in the entire population is a genetic carrier of the disease. If hereditary carriers of CIPA get married, their children have a 25% chance of inheriting the disease. In other words, there is a 75% chance that carriers will have a healthy child. These probabilities apply to every pregnancy.

In CIPA patients, TrkA encoded by the mutated *NTRK1* gene in some neurons does not function normally. This impairs the survival and maintenance of neurons, which depend on the NGF-TrkA system during fetal development. As a result, the patients lack temperature and pain perception as well as the ability to perspire.

2) Pathogenic mechanism

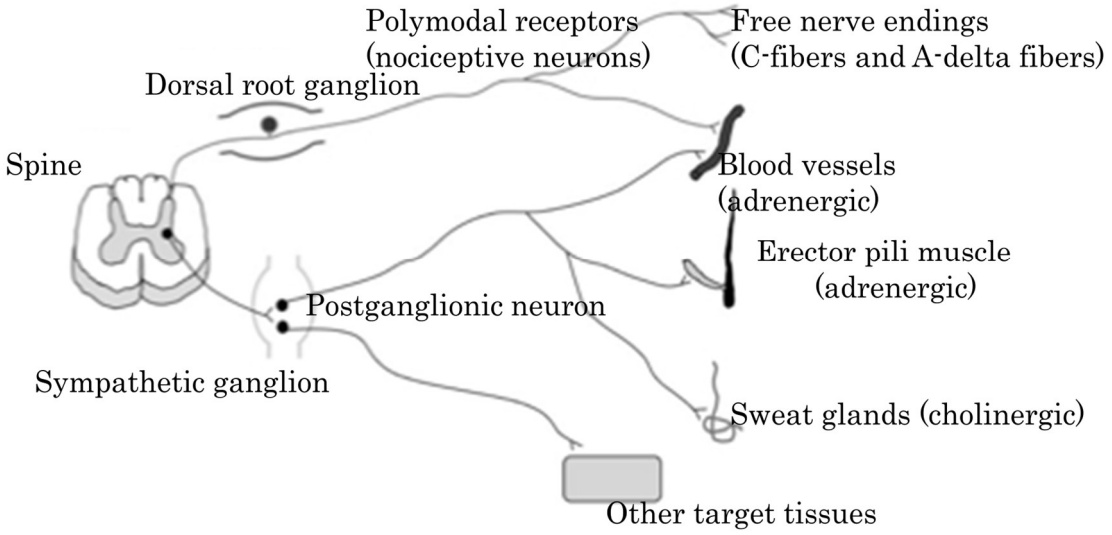
To understand the pathogenic mechanism of CIPA, it is necessary to know the function of NGF. NGF is one of the proteins known as neurotrophic factors (neurotrophins). It is known that there are four types of neurotrophic factors in humans,

and that they are indispensable for the survival and maintenance of neurons during the process of development and differentiation. The types of neurons on which NGF acts include sensory nerves that convey temperature and pain and autonomic nerves that regulate sweating. NGF acts specifically on these neurons via the TrkA protein. Thus, neurons whose survival and maintenance depend on the NGF-TrkA system during fetal development are called "NGF-dependent neurons". The NGF-dependent neurons in the peripheral nervous system are NGF-dependent primary afferent neurons and sympathetic postganglionic neurons (Fig. 1-3-2).

Figure 1-3-2

The sensory nerves that transmit the sensations of temperature and pain are "polymodal receptors". They respond to more than one stimulus, including temperature, mechanical stimuli, metabolic changes, cell damage pathogen invasion, immune cell activation, and endocrine signals.

The sympathetic nervous system is an autonomic system that, along with the parasympathetic nervous system, provides regulatory responses to the body.



Sensory neurons that convey the sensations of temperature and pain are included in the NGF-dependent primary afferent neurons. On the other hand, the neurons that convey the sensation of touch are not NGF-dependent. Therefore, although the senses of temperature and pain and touch are grouped together as somatosensory sensations, they

are thought to have different functions. Neurons are specialized cells with long wire-like neuronal projections (axons) emerging from their cell bodies (Fig. 1-3-2). In the case of NGF-dependent primary afferent neurons, the cell bodies are located in the dorsal root ganglion near the spine, and the axons extend to the tips of hands and feet. The axons of NGF-dependent primary afferent neurons are either fine myelinated fibers (A δ fibers) wrapped in a membrane called myelin, a layered membrane composed of lipids and proteins, or unmyelinated fibers (C-fibers) that are not wrapped in myelin. In adults, some axons can reach one meter in length. The reason we feel pain when we injure our legs, for example, is because there are receptors that respond to painful stimuli at the end of axons (free nerve endings) that extend from cell bodies located in the lumbar region to the toes. NGF-dependent primary afferent neurons include nociceptive neurons, but also respond to a variety of bodily changes and stimuli other than nociceptive stimuli. This is why they are sometimes called "polymodal receptors" (Figure 1-3-2). The lack of temperature and pain sensations in CIPA patients is due to the lack of NGF-dependent primary afferent neurons.

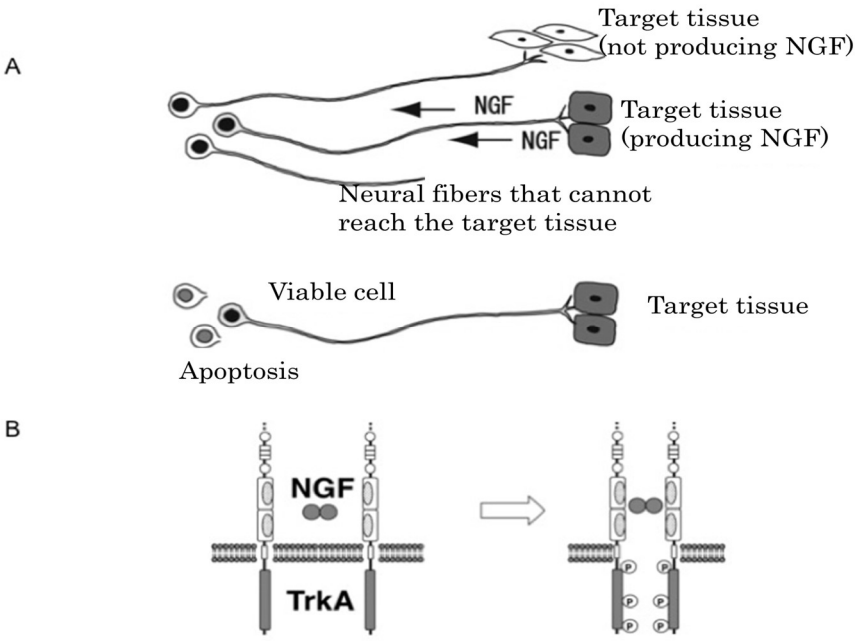
On the other hand, sympathetic postganglionic neurons in the autonomic nervous system are also NGF-dependent neurons in the peripheral nervous system. Sweating is regulated by the sympathetic nervous system. Sympathetic postganglionic neurons are directly involved in the regulation of the functions of various internal organs and tissues. Their cell bodies are located in the sympathetic ganglion near the spine (Fig. 1-3-2). The axons of these neurons are unmyelinated fibers (C-fibers), and patients with CIPA have sweating disorders because of the loss of sympathetic postganglionic neurons that innervate the sweat glands.

NGF is synthesized and secreted by cells in various tissues, including the skin. For this reason, NGF-dependent neurons are distributed in various parts of the body. NGF and its receptor TrkA are necessary for NGF-dependent neurons to extend their axons to various tissues during development and for their survival and maintenance. During fetal development, NGF-dependent neurons extend their axons to NGF-producing cells (target cells) (Fig. 1-3-3A). In this process, neurons are produced in excess, but the amount of NGF synthesized and secreted by target cells is limited. Therefore, NGF-dependent neurons compete for NGF. Neurons that have axons extending to cells that do not synthesize or secrete NGF do not receive NGF. Only those neurons that receive NGF from target cells via TrkA can survive. Neurons that do not receive NGF

from target cells do not survive because they undergo selective cell death, known as apoptosis. Through this process, a specific relationship between surviving neurons and the target tissues is established (Fig. 1-3-3A). Thus, the survival and subsequent maintenance of NGF-dependent neurons requires the normal functioning of both NGF and TrkA.

Figure 1-3-3

Specific relationship between surviving neurons and the target tissues.



TrkA is produced in the cell bodies of NGF-dependent neurons and is integrated into the cell membrane, and when NGF binds to TrkA, it transmit signals into the cell that are essential for the survival and maintenance of neurons during development (Fig. 1-3-3B). At this time, two TrkA molecules are combined (dimerized) and their intracellular tyrosine kinase domains interact with each other, resulting in the phosphorylation of a specific amino acid (tyrosine) in TrkA. In this way, the intracellular signaling essential for the survival and maintenance of NGF-dependent neurons is activated. In addition, there is a pathway in which information is transmitted by a complex consisting of NGF and TrkA (the NGF-TrkA complex) that is taken up from nerve endings and transported along long axons to the cell body, where it results in the activation of various genes in the nucleus.

Because children with CIPA have mutations in *NTRK1*, the product of this gene, the TrkA protein, does not function properly. As a result, the survival and maintenance of NGF-dependent neurons is impaired, resulting in the loss of all these neurons. Patients with CIPA also show symptoms suggestive of brain dysfunction, such as intellectual development and hyperactivity, but the cause of these symptoms is still unclear. NGF-dependent neurons are found not only in peripheral nerves but also in the central nervous system of the brain, which is presumed to be related to this.

2. Phenotypes of CIPA

The phenotypes (symptoms) observed in patients with CIPA are diverse. For this reason, each patient may appear to have a different phenotype, even though the disease is based on mutations in the same gene. In some other inherited diseases, this can be explained solely on differences in genetic mutations. However, in the case of CIPA, phenotype differences due to differences in secondary tissue damage must also be considered. This point is also relevant to the correlation between genetic variants and phenotypes in CIPs other than CIPA.

When considering the phenotypes of CIPA, it is easier to distinguish between phenotypes caused by genetic abnormalities and phenotypes caused by interactions with the environment. The basic genetic abnormality phenotype is the loss of NGF-dependent neurons. This is common to all CIPA patients. This is easier to understand if we consider the disease mechanism described earlier: loss of NGF-dependent neurons leads to a lack of temperature and pain sensation and impairment of sympathetic nerve function. On the other hand, the environmental interaction phenotype includes secondary complications and sequelae of trauma or infection. Therefore, it may not be present in all patients. Secondary complications include nerve damage due to trauma or fracture (including motor deficits and sensory deficits other than those related to temperature and pain), and damage to various organs and tissues. Encephalopathy due to heat stroke and its sequelae may also be a secondary complication. Gastrointestinal symptoms such as ileus due to peritoneal adhesions secondary to infections such as peritonitis should also be considered a secondary complication.

Thus, when considering the phenotype of CIPA, it is important to distinguish between the phenotype caused by genetic abnormalities and the phenotype caused by

interactions with the environment, in order to consider the pathogenesis and pathological mechanisms.

3. Differences in the underlying genetic mechanisms of CIP and CIPA

1) CIP is due to mutations in the *NGF* gene

Two types of diseases caused by mutations in the *NGF* gene (also known as the *NGFB* gene) have been reported so far. In 2004, it was reported that a missense mutation in this gene was the cause of Norrbottnian congenital insensitivity to pain (NCIP) in a large family in Norrbotten, a region in the northernmost part of Sweden. Patients in this family have impaired pain and temperature perception, but no intellectual development-related or sweating disorders. Repeated skin trauma was unremarkable and self-injurious behavior such as biting the tongue was absent. Some patients had joint damage in the lower extremities (Charcot joints) since childhood. However, others developed mild feet and knee joint-related symptoms only in adulthood. Histological examination of peripheral nerves showed that the numbers of both unmyelinated fibers (C fibers) and fine myelinated fibers (A-delta fibers) are reduced, but the reduction in unmyelinated fibers is more marked. Genetic analysis of this family revealed that the gene responsible for NCIP is *NGF*.

To understand the pathogenesis of NCIP, it is necessary to understand the process of intracellular synthesis and secretion of NGF protein based on genetic information. Proteins, which are synthesized by linking various amino acids based on the genetic information defined by the DNA sequence of the corresponding gene, have an N-terminus and a C-terminus. NGF protein is first synthesized in the cell as a precursor (proNGF) with an amino acid sequence called a signal peptide attached to its N-terminus. This signal peptide is required for the extracellular secretion of NGF, and is detached when proNGF is converted to mature NGF. Through this process, NGF is secreted into the extracellular space (although some proNGF is also thought to be secreted in its native form).

The gene mutation detected in patients with NCIP is a missense mutation (R211W) in which arginine (Arg), the 211th amino acid of the proNGF protein, is replaced by tryptophan (Trp). This results in a substitution of the 100th amino acid in the mature NGF protein, which is thought to prevent it from functioning properly. In addition, this protein with the R211W mutation exists intracellularly as proNGF, but the amount of

NGF secreted extracellularly is reduced compared to normal. These results suggest that in patients with NCIP, the function of NGF protein is affected due to its structural abnormality, and its amount is also reduced.

Patients with NCIP do not have intellectual disabilities or sweating disorders. For this reason, NCIP was initially reported as HSAN-5. However, when the association between patients and the mutation was investigated, it was found that not only homozygotes for the R211W mutation but also heterozygotes had symptoms. In homozygotes, joint-related symptoms associated with insensitivity to pain appear from childhood. In heterozygotes, on the other hand, joint-related symptoms appear in adulthood and are not as severe as in homozygotes. Nerve biopsies also show that the degree of nerve fiber loss appears to be less than in homozygotes. This suggests that NCIP is not inherited as an autosomal recessive trait, but as a dominant trait (strictly speaking, an incomplete dominant trait). Thus, there are some objections to classifying the disease in this family as HSAN-5.

In 2011, a case of CIP due to a loss-of-function mutation in *NGF* was reported in an Arab family. Five out of six children born to parents in consanguineous marriages were affected. The disease seen in this family has also been reported as HSAN-5. However, since the patients in this family had anhidrosis and intellectual disabilities in addition to insensitivity to pain, it seems more appropriate to classify their disease as HSAN-4 (CIPA). A mutation with a single nucleotide substitution and the deletion of two nucleotides was detected in the patients' *NGF* gene. This results in a frameshift (V232fs) that shifts the reading frame of the gene sequence at the codon corresponding to the 232nd amino acid (valine) of the proNGF protein. In addition to this, the original amino acid sequence of the C-terminus changes. Thus, the structure and function of the mutated protein differ distinctly from those of the normal one, and it is not secreted by the cell. Therefore, it is presumed that this NGF protein cannot act on the patients' NGF-dependent neurons, and the survival of these neurons is impaired. There is no description of the peripheral neuropathology findings of patients in this family. The parents in this family are heterozygous for the frameshift mutation (V232fs) and are not symptomatic. Therefore, the mode of inheritance is autosomal recessive.

Thus, although the disease is caused by mutations in the same gene (*NGF*), the inherited forms in CIP caused by loss-of-function mutations and NCIP caused by missense mutations are different.

2) CIP caused by mutations in the sodium channel gene (*SCN9A*)

After the cause of CIPA was identified, it became known that there were patients with CIP, which is distinctly different from CIPA. In CIP patients, there is no sweating disorder, no intellectual disability, and no obvious morphological abnormality in the biopsy of peripheral nerves. As a result of genetic analysis of such patients' families, a case of CIP caused by a mutation in a sodium channel gene was reported in 2006.

This hereditary disease is also called channelopathy-associated insensitivity to pain. The responsible gene, *SCN9A*, located on the long arm of chromosome 2 (2q24), was identified in patients from northern Pakistan with three families of consanguineous marriage. This gene encodes the alpha-subunit of a voltage-gated sodium channel (Nav1.7) that is expressed in nociceptive neurons. In each family, three nonsense mutations (which refers to codons corresponding to amino acids being replaced by stop codons) were detected. The Nav1.7 protein encoded by *SCN9A* with these nonsense mutations is a shorter protein than normal. This makes it a loss-of-function mutation. Patients were homozygous for these mutations, and both parents were heterozygous. Since both parents have no symptoms, the inherited form of the disease is autosomal recessive.

When nociceptive neurons receive a painful stimulus, an electrical phenomenon called depolarization occurs in their cell membranes, producing an action potential that transmits electrical impulses from the body to the central nervous system (afferent). Nav1.7, a voltage-gated sodium channel, is located at the ends of nociceptive neurons and is thought to amplify the depolarization of the neuronal membrane. In fact, the mutated Nav1.7 protein detected in patients has been shown to fail to function properly. At about the same time, other research groups also reported cases of CIP caused by the same mutation.

In summary, these results indicate that CIPA patients lack pain sensation due to the lack of NGF-dependent neurons. On the other hand, CIP patients with the *SCN9A* mutation lack pain sensation because the sodium channels specifically expressed in these neurons do not function properly, even though NGF-dependent neurons are present.

3) Other case reports

Patients with HSAN-5 do not have autonomic neuropathy such as sweating disorders, nor do they have intellectual disability. However, the number of reported cases is small, and there is no consensus among experts about the disease concept. For example, in 2001, a British research group analyzed the *NTRK1* gene in a patient they determined to have HSAN-5. They found a mutation in this gene in the patient, and reported that CIPA and HSAN-5 were caused by mutations in the same gene, differing only in phenotype. However, it was pointed out by another research group that they may have analyzed CIPA patients (not those with HSAN-5).

In November 2004, the case of a five-year-old girl was reported in the US mass media. Initially, her disease was clinically diagnosed as CIPA; later, after a detailed investigation, it was found in 2011 that her disease was CIP caused by a mutation in the above-mentioned sodium ion channel gene *SCN9A*. This case was also introduced on a US TV program in 2010, and further introduced on a Japanese commercial TV program in 2011. At that time, there seemed to be some confusion about the name of the disease and its pathogenesis. Her disease is not CIPA, but actually channelopathy-related insensitivity to pain.

In addition to CIP caused by mutations in the *NTRK1*, *NGF*, and *SCN9A* genes mentioned above, there have been reports of cases caused by mutations in other genes, although these are very rare. However, a detailed elucidation of the pathogenesis of CIP remains a challenge for the future.

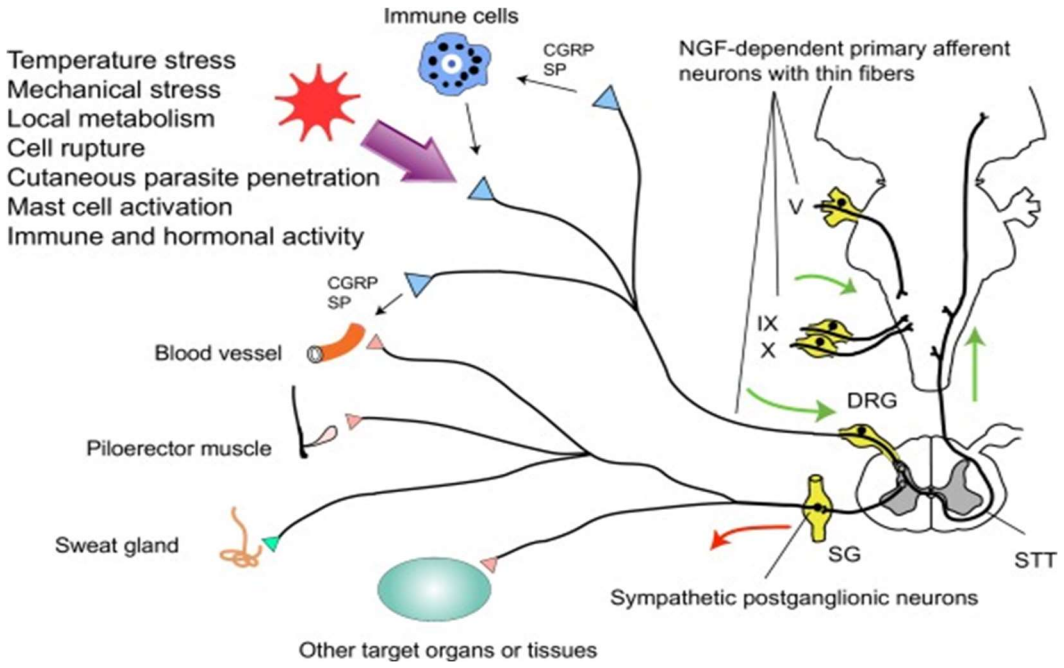
4. The concept of interoception and sympathetic nerve function

1) NGF-dependent neurons

The nervous system can be divided into the central nervous system and the peripheral nervous system. The central nervous system includes the brain and spinal cord. The peripheral nervous system, on the other hand, includes motor and sensory nerves, as well as the autonomic nervous system. For example, motor nerves transmit signals from the brain and spinal cord centrifugally (from the central nervous system to the body) to stimulate muscles to contract. Moreover, sensory nerves transmit sensory stimuli applied to the skin, muscles, joints, and internal organs in an afferent direction (from the body to the central nervous system) through the spinal cord to the brain. In addition, as one of the autonomic nervous systems, the sympathetic nervous system regulates the functions of blood vessels, erector muscles, and sweat glands in the skin,

as well as internal organs and tissues. In this way, sympathetic nerves are centrifugal neurons, and as detailed above, patients with CIPA are deficient in NGF-dependent primary afferent neurons and sympathetic postganglionic neurons in the peripheral nervous system (Fig. 1-3-4).

Figure 1-3-4 Patients with CIPA lack NGF-dependent primary afferent neurons with thin fibers (NGF-dependent primary afferents) and autonomic sympathetic postganglionic neurons. CGRP, calcitonin gene-related peptide; DRG, dorsal root ganglia; SG, sympathetic ganglion; SP, substance P; STT, spinothalamic tract.
(Indo Y. Neurosci Biobehav Rev 87: 1-16, 2018)



2) NGF-dependent primary afferent neurons and sympathetic postganglionic neurons

The cell bodies of sensory nerves are located in the dorsal root ganglion near the spine, and they transmit various sensations by extending nerve projections (axons) to each region of the body they innervate. NGF-dependent primary afferent neurons, which also respond to nociceptive stimuli, have thin axons with free nerve endings (Fig. 1-3-4). As mentioned earlier, NGF-dependent primary afferent neurons are classified into those with thin myelinated fibers (A-delta fibers) whose axons are covered with myelin, and those with thinner unmyelinated fibers (C-fibers). The speed at which sensations such as pain are transmitted is faster in the former than in the latter.

The cell bodies of sympathetic postganglionic neurons are located in the sympathetic ganglion near the spine (Fig. 1-3-4). These neurons have unmyelinated fibers. The sympathetic nervous system, together with the parasympathetic nervous system, is an autonomic nervous system that regulates the functions of internal organs and tissues of the body. In patients with CIPA, the sympathetic postganglionic neurons are defective, resulting in the failure of the sympathetic nervous system to regulate various body responses. This is why there is a lack of perspiration and thus fever in hot environments, a lack of erector pili muscle reflexes (no goose bumps), a lack of vasoconstriction and thus hypothermia in cold conditions, and impaired pupillary dilation.

In clinical neurology, Horner's syndrome is known to be associated with mild eyelid drooping, tendency of pupillary constriction, and dysregulation of facial sweating, and is caused by a variety of congenital and acquired causes. It is also observed in patients with CIPA and is due to the loss of sympathetic postganglionic neurons innervating the head and face. In these cases, the Horner syndrome is bilateral.

3) NGF-dependent primary afferent neurons (polymodal receptors), the concept of interoception, and the function of sympathetic nerves

NGF-dependent primary afferent neurons not only transmit the sensations of temperature and pain, but also respond to various other stimuli (Fig. 1-3-4). In the field of neuroscience, new ideas regarding sensation have been proposed. NGF-dependent primary afferent neurons monitor various biological responses occurring in the human body and continuously transmit this information to the brain. This includes information regarding various mechanical loads, temperature changes, chemical changes, metabolic processes, and levels of hormones and cytokines (intercellular transmitters of immune responses) in the skin, muscles, joints, teeth, blood vessels, and internal organs. The details of the various stimuli mentioned in Figure 1-3-4 are as follows. Temperature stress refers to a change in temperature, such as heat or cold. This includes non-painful sensations of warmth and coolness. Mechanical stress may include stretching of smooth muscle and baroreception. Local metabolism includes acidic pH (increased hydrogen ions), hypoxia, hypercapnea hypoglycemia, hypo-osmolality, and hyperlactatemia. Cell rupture releases ATP, glutamate, etc. Invasion of parasites into the skin causes an increase in histamine levels; activation of mast cells releases molecules such as

serotonin, bradykinin, and eicosanoids (various prostaglandins, thromboxane, leukotrienes). Immune and endocrine activity also increases the levels of cytokines and somatostatin. Thus, NGF-dependent primary afferent neurons are polymodal receptors that respond to a variety of stimuli.

Some stimuli sensed by NGF-dependent primary afferent neurons, such as pain, are perceived as warning signals, and may induce defensive response behaviors. However, most of them are unconsciously transmitted to the brain and work to maintain constancy in the body. This condition, also called homeostasis, is the state of the body in which many physiological functions are coordinated and regulated. In other words, it is a state in which the dynamic equilibrium of the body is maintained. For example, the body temperature (core temperature) is maintained at a constant level because of homeostasis mechanisms in which the monitoring of body temperature by NGF-dependent primary afferent neurons and the regulation of sweating by sympathetic nerves play important roles.

When humans feel pain, it can be interpreted as a warning to the brain that nociceptive stimuli are being delivered to the tissues of the body, and that there is an abnormality in the homeostasis of the body. The brain uses this information to maintain homeostasis through the sympathetic nervous system. CIPA patients not only lack these warning signals, but also have impaired homeostatic mechanisms. As a result, they constantly face major problems in sustaining a normal life.

NGF-dependent primary afferent neurons transmit interoception-related signals by monitoring various biological changes, including those related to temperature and pain. In contrast, exteroception is the ability to perceive objects outside the body. The sense of touch is included in the external senses, along with other senses such as sight and hearing.

The brain and body contribute to overall vital activities by exchanging both centrifugal and afferent information via NGF-dependent neurons in the peripheral nervous system. The afferents corresponding to the autonomic nervous system have not been clearly described. Based on the concept of interoception, NGF-dependent primary afferent neurons are thought to be afferents from the body to the brain, corresponding to the autonomic nervous system. If the concept of interoception becomes widely accepted in the future, the concept of somatosensory perception may also change.

In summary, NGF-dependent primary afferent neurons and sympathetic

postganglionic neurons in the peripheral nervous system form a neural network connecting the brain and the body and play an important role in maintaining homeostasis in the body.

4) Disorders of homeostasis mechanisms integrally controlled by the brain

The essential role of the autonomic nervous system, including the sympathetic nervous system, is to maintain homeostasis in the body. The autonomic nervous system fulfills this role in close association with the endocrine and immune systems, especially through the brain. In humans, it is also closely related to processes related to cognitive and psychological functions.

In CIPA patients, the thermoregulatory reflex and the defense-response autonomic reflex, which are homeostatic mechanisms integrally controlled by the brain, are impaired due to the lack of NGF-dependent neurons. Because of the lack of the former, core temperature homeostasis cannot be maintained, resulting in fluctuations in body temperature depending on the environmental temperature. The latter is the so-called "fight-or-flight response," which allows animals to defend themselves when exposed to dangerous situations. It is similar to the way a cat reacts when it meets a dog—in this process, a specific organized behavior involving autonomic responses and movements occurs; specifically, sympathetic excitatory reactions such as increased pulse rate, elevated blood pressure, erect hair, and dilated pupils, as well as responses such as rounding of the back and raising of the tail are observed. A similar reaction occurs in humans when they feel pain or fear, although it is not as obvious. These emotional experiences, which involve activation of the sympathetic nervous system, are memorized by the brain and lead to the body protecting itself in the future.

From the time we are born, we learn to protect ourselves from harm in our daily lives. The ability to learn to relate daily unpleasant emotional experiences to the situation around us is essential to this. However, CIPA patients lack NGF-dependent primary afferent neurons and sympathetic postganglionic neurons, so they not only fail to perceive danger to their bodies, but also fail to activate their sympathetic nervous system in response to danger. In other words, the emotional responses that are reflexively triggered by unpleasant experiences such as pain or memories of such experiences are absent. In addition, it becomes difficult to remember the surrounding situations related to the unpleasant emotional experiences, and to learn how to avoid

danger in advance when encountering a similar situation again. As a result, they are constantly exposed to danger even in their daily lives.

Recently, the idea that mental activities such as "emotions and feelings" are dependent on the interactions between the brain and the rest of the body has been proposed. From the perspective of biological evolution, such mental activities are closely related to the maintenance of homeostasis and defense mechanisms of the body, which are integrally controlled by the brain. Based on this idea, NGF-dependent neurons may be involved in the neurobiological basis of emotions and feelings.

References

1) Ahmad S, Dahllund L, et al: A stop codon mutation in SCN9A causes lack of pain sensation. Hum Mol Genet 16: 2114-2121, 2007

2) Carvalho OP, Thornton GK, et al: A novel *NGF* mutation clarifies the molecular mechanism and extends the phenotypic spectrum of the HSAN5 neuropathy. J Med Genet 48: 131-135, 2011

3) Cox JJ, Reimann F, et al: An *SCN9A* channelopathy causes congenital inability to experience pain. Nature 444: 894-898, 2006

4) Craig AD: How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci 3: 655-666, 2002

5) Damasio AR: Descartes' Error: Emotion, Reason, and the Human Brain. Putnam and Sons, New York, 1994

6) Damasio A, Carvalho GB: The nature of feelings: evolutionary and neurobiological origins. Nat Reve Neurosci 14: 143-152, 2013

7) Drenth JP, Waxman SG: Mutations in sodium-channel gene *SCN9A* cause a spectrum of human genetic pain disorders. J Clin Invest 117: 3603-3609, 2007

8) Einarsdottir E, Carlsson A, et al: A mutation in the nerve growth factor beta gene (*NGFB*) causes loss of pain perception. Hum Mol Genet 13: 799-805, 2004

9) Goldberg YP, MacFarlane J, et al: Loss-of-function mutations in the Nav1.7 gene underlie congenital indifference to pain in multiple human populations. Clin Genet 71: 311-319, 2007

10) Indo Y, Tsuruta M, et al: Mutations in the *TRKA*/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis. Nat Genet 13: 485-488,

1996
11) Indo Y: Molecular basis of congenital insensitivity to pain with anhidrosis (CIPA): mutations and polymorphisms in *TRKA (NTRK1)* gene encoding the receptor tyrosine kinase for nerve growth factor. Hum Mutat 18: 462-471, 2001
12) Indo Y: Nerve growth factor, interoception, and sympathetic neuron: lesson from congenital insensitivity to pain with anhidrosis. Auton Neurosci 147: 3-8, 2009
13) Indo Y: Nerve growth factor, pain, itch and inflammation: lessons from congenital insensitivity to pain with anhidrosis. Expert Rev Neurother 10: 1707-1724, 2010
14) Indo Y: Nerve growth factor and the physiology of pain: lessons from congenital insensitivity to pain with anhidrosis. Clin Genet 82: 341-350, 2012
15) Indo Y: Neurobiology of pain, interoception and emotional response: lessons from nerve growth factor-dependent neurons. Eur J Neurosci 39: 375-391, 2014
16) Indo Y. *NTRK1* Congenital Insensitivity to Pain with Anhidrosis. 2008 Aug 5 [Updated 2020 Apr 30]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1769/ [2021.11.1 access]
17) Indo Y: Nerve growth factor, interoception and the autonomic nervous system: lessons from the molecular pathophysiology of congenital insensitivity to pain with anhidrosis. (In Japanese) The Autonomic Nervous System 52: 36-40, 2015
18) Indo Y: Nerve growth factor and the physiology of pain: The relationships among interoception, sympathetic neurons and the emotional response indicated by the molecular pathophysiology of congenital insensitivity to pain with anhidrosis. (In Japanese) No To Hattatsu 47: 173-180, 2015
19) Indo Y: Nerve growth factor-dependent neurons in the peripheral nervous system: an update of basic scientific research on the autonomic nervous system. (In Japanese) Neurological Medicine 87: 54-61, 2017
20) Indo Y: Congenital insensitivity to pain with anhidrosis. Japanese Journal of Perspiration Research 24: 46-51, 2017
21) Indo Y: NGF-dependent neurons and neurobiology of emotions and feelings: lessons from congenital insensitivity to pain with anhidrosis. Neurosci Biobehav Rev 87: 1-16, 2018

22) Larsson E, Kuma R, et al: Nerve growth factor R221W responsible for insensitivity to pain is defectively processed and accumulates as proNGF. Neurobiol Dis 33: 221-228, 2009

23) Mardy S, Miura Y, et al: Congenital insensitivity to pain with anhidrosis: novel mutations in the *TRKA (NTRK1)* gene encoding a high-affinity receptor for nerve growth factor. Am J Hum Genet 64: 1570-1579, 1999

24) Minde J, Toolanen G, et al: Familial insensitivity to pain (HSAN V) and a mutation in the *NGFB* gene. A neurophysiological and pathological study. Muscle Nerve 30: 752-760, 2004

25) Miura Y, Mardy S, et al: Mutation and polymorphism analysis of the *TRKA (NTRK1)* gene encoding a high-affinity receptor for nerve growth factor in congenital insensitivity to pain with anhidrosis (CIPA) families. Hum Genet 106: 116-124, 2000

26) Schon KR, Parker APJ, Woods CG: Congenital Insensitivity to Pain Overview. 2018 Feb 8 [Updated 2020 Jun 11]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK481553/ [2021.11.1 access]

27) Staud R, Price DD, et al: Two novel mutations of *SCN9A* (Nav1.7) are associated with partial congenital insensitivity to pain. Eur J Pain 15: 223-230, 2011

28) Toscano E, Simonati A, et al: No mutation in the *TRKA (NTRK1)* gene encoding a receptor tyrosine kinase for nerve growth factor in a patient with hereditary sensory and autonomic neuropathy type V. Ann Neurol 52: 224-227, 2002

Chapter 2: Pathophysiology and Care

2-1 Basic Symptoms

The basic symptoms in congenital insensitivity to pain with anhidrosis (CIPA) or without anhidrosis (CIP), common in the pediatric population, are outlined by age.

1. Infancy

Insensitivity to pain may be noticed if care is taken when blood is drawn for testing for congenital metabolic abnormalities in the newborn, but it may be difficult to detect unless there are comorbidities such as fever of unknown origin. Subsequent vaccinations are also likely to be painless, but are often overlooked. Thus, insensitivity to pain is rarely detected early. Because of the sweating disorder, the child is dependent on ambient temperature and is prone to hyperthermia, which may be noticed in the incubator or fever-induced convulsions in early infancy (even at less than 1 month of age)[1)]. In cases of patients with febrile convulsions, 70% had a higher-than-normal body temperature of 40–42 °C[1)]. On the other hand, in cold environments, peripheral blood vessels contract poorly and goose-bumps do not occur, making the patient prone to hypothermia. Thus, both hot and cold environments result in problems in thermoregulation.

In addition to motor and language development delays with hypotonia, mood swings, sleep disturbances, difficulty in feeding, and poor weight gain are associated with the above-mentioned impaired temperature control. In addition, at around 6 months of age, as the teeth emerge, painless bites to the tongue, lips, and fingers are constant, as well as deformities of the fingers and nails, and subsequent self-injury, such as by head banging, may also occur. This often leads to a vicious cycle of new mood disorders, sleep disorders, and feeding problems. Early dental care (use of protective plates) and the establishment of a healthy sleep-wake rhythm are important for avoiding self-harm and sleep and feeding disorders during this period.

The reason why patients continue to bite their mouths and fingers when there is no pain is unclear, but they may do so because of the absence of pain, or to confirm tactile sensations or sensations of tenderness (functions of the remaining Aβ fibers). The

patient’s sense of touch is rather hypersensitive, and the senses of taste and smell are almost preserved.

When the child is able to move around, he or she will touch anything, but will not know if it is hot or cold because of the lack of heat and cold sensations, which increases the possibility of burns (on the hands, feet, and in the oral cavity, including cold burns), so extreme caution is needed in this regard.

2. Early childhood

The above self-injury often diminishes by 1.5 years of age, but may continue in late infancy.

The onset of walking is generally late. Once the child begins to walk, the most problematic issue is that the absence of sharp (fast pain, due to A-delta fibers) or dull, persistent pain (slow pain, due to C-fibers) results in frequent trauma in the form of fractures, sprains, and dislocations. There is a risk that symptoms may worsen and be noticed too late, and it is often difficult to identify when an injury occurred. In addition, risk avoidance and behavioral self-regulation due to feedback of the painful experiences is not possible, and individualized attention must be given by the family and the school or care facility staff until the child becomes aware of his or her own situation. It is important not to overlook unusual gait, hand usage, local swelling, and redness. Mechanical or inflammatory damage to the skeletal muscles or the gastrointestinal tract is often not perceived as pain and is not detected until later. Thus, pain is not perceived as a warning sign to the organism, and trauma and inflammation are often severe. The deformity and destruction of joints may lead to a long-term condition called Charcot joint.

Around the age of 3 years, fractures of the tarsal and metatarsal bones are common. Because of the impairment of the sensory input system, the child has an extremely strong grasping power but poor situational coordination[2]. Such unreasonable force is also applied to gait, which may lead to fractures of the tarsal region that do not normally occur[3]. Since there are fractures of unknown etiology in such cases, "abuse" may be suspected, and the syndrome should be included in the differentiation of "unknown fractures". Because of anhidrosis, the skin is often dry and keratinized as skin barrier function is impaired. It is more vulnerable to trauma such as bruises and other wounds, which can easily become infected and even result in osteomyelitis or cellulitis.

Intellectual disability and hyperactivity can also exacerbate these symptoms. The risk for burns is similar to that in infants.

There is also a risk of serious sequelae from convulsive status, heat stroke, and acute encephalopathy. In 2003–2004, a high incidence of deaths was reported, with two-thirds of the deaths occurring by the age of 3 years, one-sixth by the age of 8 years, and one-sixth in adults. Since then, the understanding of the syndrome has increased, but a few more deaths have been reported, mostly due to sudden high fevers and refractory convulsions; the majority of patients died within a few days, as management of high body temperature and convulsions in the intensive care unit is generally required[4,5].

3. School-age children

They are more mobile and more prone to further fractures, especially new fractures after treatment in a cast. Orthopedic problems such as joint deformity, joint laxity, and dislocation are common and can be difficult to deal with during this stressful time[3]. On the other hand, bites caused by permanent tooth eruption are less noticeable than those caused by deciduous teeth.

Facial features such as high and wide nasal roots (giving the impression of a well-defined nose), slightly flabby eyelids, and large auricles are characteristic of one-third to half of the cases. These characteristics are often more apparent at school age and later, irrespective of gender. On the contrary, there are cases of low nasal roots, small jaws, and close distance between the eyes. In addition, both head circumference and height are smaller than the age average in some cases[3].

4. Adolescents and adults

In general, from around the age of 10, hyperactivity decreases, habits of self-protection are established, and trauma and other injuries are reduced[3]. However, once damaged, continued overuse of a joint can lead to Charcot joints. Thermal dysregulation continues during this period without relief, and proper temperature control is necessary. The temperature difference between indoor and outdoor temperatures also affects homeostasis and causes great stress.

References

1. Awaya Y, Nihei K, Miyake J: Febrile seizures in congenital insensitivity to pain with anhidrosis. (In Japanese) Japanese Journal of Pediatrics 50: 2342-2344, 1997
2. Kawashima N: Grip control in congenital insensitivity to pain with anhidrosis. In: Report of the 15th Symposium in Kobe, Japan, by NPO CIPA Society of Japan " Tomorrow". pp 77-78, 2008
3. Awaya Y: Congenital insensitivity to pain with anhidrosis. (In Japanese) Japanese Journal of Pediatric Medicine 28: 184-190, 1996
4. Report of the International Symposium on Congenital insensitivity to pain with anhidrosis 2003. p 114 in Japanese; p 110 in English, published by NPO CIPA Society of Japan " Tomorrow", 2004
5. The 15th Congenital insensitivity to pain with anhidrosis Symposium in Sendai, Lecture handout. Published by NPO CIPA Society of Japan " Tomorrow" 2008

2-2 Convulsions, Epilepsy, Loss of consciousness

Congenital insensitivity to pain with anhidrosis (CIPA) is an autosomal recessively inherited disorder that is associated with a lack of temperature and pain related sensation, sweating disorders, and intellectual development disorders. The cause of the disease is a loss-of-function mutation in the gene encoding tyrosine kinase-type nerve growth factor receptor (TrkA). As a result, patients are deficient in nerve growth factor (NGF)-dependent neurons, namely NGF-dependent primary afferent neurons and postganglionic sympathetic neurons.

The lack of temperature and pain sensations and sweating disorders seen in CIPA patients are due to the specific loss of NGF-dependent neurons, and patients lack all pain, including visceral pain, as well as itching sensations.

Thermoregulation is an important function of the sympathetic nervous system, and postganglionic sympathetic neurons regulate the function of skin vessels, erector pili muscles, sweat glands, and all the various organs and tissues in the body. NGF-dependent primary afferent neurons and the sympathetic nervous system both need to function normally to maintain body temperature homeostasis, but these functions are impaired in CIPA patients, resulting in thermoregulatory failure leading to hyperthermia or hypothermia depending on the environmental temperature. In order to regulate body temperature when the ambient temperature is high, humans dissipate heat by dilating blood vessels in the skin and sweating, but in patients with CIPA, hyperthermia due to no sweating as well as no pain is one of the characteristic symptoms.

In infancy, premature infants who need to be placed in an incubator tend to have high body temperatures, because they cannot sweat, due to which there is a higher chance of their abnormalities being noticed. There are many cases of hospitalization for unknown fever in infancy, and CIPA should be included in the differential diagnosis.

1. Seizures during fever

In a survey conducted in our patient group, febrile seizures occurred in a high percentage (46%) of cases, and the onset of febrile seizures was earlier than usual, that is, before the age of 6 months. The fever at the time of onset was a high fever of 40 to

42 ° C, and 70% of the cases had convulsions, and up to 87% of the total had a short duration of 1 to 2 times and a good prognosis.

Overall, the threshold for seizures was not considered to be particularly low. About half of the patients were in early infancy and had not yet been diagnosed with CIPA or had been diagnosed but had not yet been adequately treated for fever. In addition, febrile seizures in infants younger than 6 months are generally suspected to be epileptic, and anticonvulsant medication is considered. However, in this case, medication was not administered immediately, and follow-up, including EEG examination, seemed to be sufficient.

In the 20 years since this study, there has been progress regarding early detection of this disease and early countermeasures against fever and other symptoms, and the frequency of seizures with fever seems to be decreasing now.

2. Breath holding spell

By the age of 1 to 2 years, 8 cases (12%) with breath holding spells with a good prognosis were reported. Some of these cases had a high frequency of tens or hundreds of spells.

3. Epilepsy

A high percentage (9%) of patients initially had afebrile seizures and were later considered to have epilepsy, and there was one case each of West syndrome and Lennox-Gastaut syndrome. Half of them developed epileptic syndrome in their 1s, and the rest by the age of 6. In addition, in two cases afebrile seizures were reported only in the neonatal period.

4. Convulsive status and acute encephalopathy

There were 8 cases (12%) of acute encephalopathy, presumed to be related to seizures or heat stroke, mainly before the age of 3 years. In most cases, the body temperature was as high as 41 °C, and convulsions occurred intermittently over several days in some cases. The prognosis was poor, with deaths and severe brain damage in some cases.

In one case, the onset of symptoms occurred one day after orthopedic surgery, suggesting the need for adequate management, including body temperature, during the

perioperative period and immediately afterwards.

In infants with this disease, there have been cases of sudden death or severe brain damage due to an encephalopathy-like state triggered by infection. It is important to detect this disease at an early stage and to provide early and adequate treatment at the time of fever or seizures, as well as regular follow-up by pediatricians and pediatric neurologists.

References

1) Indo Y: Nerve growth factor and pain physiology in the molecular pathogenesis of congenital anhidrosis: relationship between endosensory perception, sympathetic nervous system and emotion. (In Japanese) No To Hattatsu 47: S173-179, 2015

2) Awaya Y, et al: Congenital insensitivity to pain with anhidrosis and its associated febrile seizures. (In Japanese) Japanese Journal of Pediatrics 50: 2342-2344, 1997

3) Awaya Y: A study of fatal cases of congenital insensitivity to pain with anhidrosis. (In Japanese) No To Hattatsu 42: S294, 2010

4) Awaya Y: Congenital insensitivity to pain with anhidrosis in Japan: epidemiology and actual status of the convulsive disease. SSK CIPA International Symposium 2003 Report: 23-24

5) Awaya Y: Congenital insensitivity to pain with anhidrosis: from diagnosis to lifestyle guidance. (In Japanese) Advances in Pediatric Neurology 32: 28-37, 2003

2-3 Gastrointestinal symptoms and autonomic nervous system symptoms

In a questionnaire-based survey of patients with CIPA, 5 of the 23 patients included had a history of cyclic vomiting and 11 had a history of gastrointestinal symptoms such as diarrhea and constipation. The causes of these gastrointestinal symptoms are probably varied and it is not known if they are specific to CIPA, but repeated bowel inflammation due to the lack of pain and adhesions due to previous surgery could be the cause of the repeated gastrointestinal symptoms. Cyclic vomiting can occur even though there is no actual lesion in the digestive system. Cyclic vomiting is now included migraine, but there is no specific single reason for its occurrence. It is also thought that serotonergic nervous system abnormalities related to sleep rhythm problems may be involved. The hypothalamus-pituitary-adrenal system plays an important role in so-called stress tolerance. The serotonergic nervous system provides lateral support to this system in maintaining stress tolerance, but if this system is impaired, various stress-related physical symptoms may manifest. Treatment involves investigating the background of the cyclic vomiting, as it can also occur in the absence of stress, and possibly involve as yet unclarified and habituated neural pathways.

The antihistamine cyproheptadine may be helpful as a preventive oral medication, and is a good drug to try first. Antiepileptic drugs such as valproic acid, diazepam, and phenobarbital may also help. Cyproheptadine suppresses serotonin, while valproic acid increases serotonin activity. Thus, regulatory effects on the serotonin system are expected in either case[1)]. In severe cases, dehydration must be compensated for by administering intravenous fluids, but if the cycle is constant and the signs (auras) are known, the use of diazepam suppositories may be more helpful. Hypertension and depression are also common complications. In most cases with hypertension, follow-up without medication is sufficient. Antidepressants may help with periodic vomiting attacks as well as depression. In severe cases, the anti-migraine drugs sumatriptan (administered nasally or injected subcutaneously) and granisetron, used for nausea during chemotherapy, have also been found to be effective. However, data regarding the use of these drugs are empirical and their effectiveness varies from case to case. Although there is no established treatment for cyclic vomiting, it may be correlated with disturbances in sleep rhythm, and the establishment of an appropriate daytime and night-time sleep-wake

rhythm may indirectly lead to the symptoms becoming milder.

Measures against severe constipation and diarrhea are also important to ensure the quality of life of the patient's family. Although the frequency of defecation varies from person to person and failure to have daily bowel movements does not necessarily mean that the patient has a pathological issue, persistent constipation and diarrhea can lead to instability of blood levels in patients taking medications such as antiepileptic drugs. It also leads to mood instability. Therefore, medication should be administered after confirming that there is no organic disease in the digestive system, that is, functional constipation. Also, if it is not cured by lifestyle modifications related to diet, and exercise, it must be treated with medication. A high-residue diet rich in fiber, which includes foods such as seaweed, burdock and carrots, may also help. For constipation, picosulfate is easy to use, especially in infants. Generally, it is taken once before bedtime, although the dose varies greatly from person to person, and should be adjusted according to the properties of the stool, since even small doses can cause diarrhea in some instances while for older children they may not be effective. The standard dosage is 2-3 drops for 0–1 year olds, 6–7 drops for 1–6 year olds, and 10 drops for 7 years and older, depending on the effect. Glycerin enemas are also frequently used. If oral medications are ineffective, we believe that an enema should be given without much hesitation. The establishment of a bowel movement rhythm is as important for mood stability during the day and the establishment of a regular sleep rhythm.

If there is diarrhea due to food poisoning, infectious gastroenteritis, etc., the patient should be treated for the primary cause, or if these causes can be ruled out and the diarrhea is considered a physical symptom of low stress tolerance, the patient should be conservatively managed with fluid retention, switching to a softer diet, and antiflatulent agent use. As with cyclic vomiting and constipation, it is important to maintain the day/night rhythm.

Nocturia and diurnal enuresis are also known to occur frequently as autonomic symptoms. This is because anhidrosis causes increased urine output and because patients try to lower their body temperature by drinking more cold water (physiological polyuria), especially in hot environments. Appropriate treatment is necessary, because polydipsia and polyuria lead to disturbances in social life during the day and in sleep at night. Urinary retention may occur as a symptom of autonomic dysfunction (some of the mechanisms are the same as those of peripheral neuropathy—hypoactivity of the voiding

muscle and decreased bladder sensation—that causes urinary retention in diabetes mellitus[2]). It is also a common complication of taking multiple antiepileptic drugs. Urinary retention can lead to urinary tract infections and renal failure, cause discomfort, and induce mood disorders, so appropriate measures (intermittent urinary drainage) are necessary as in the case of constipation.

Experiments in cats have shown that the urge to urinate associated with bladder stretching is transmitted via A δ fibers, and that the normal voiding reflex is triggered by A δ fibers via the pelvic nerve[3]. On the other hand, C fibers do not respond to normal bladder extension, but only to strong nociceptive stimuli such as pain. In other words, under normal conditions, the C fibers originating from the bladder are inactive. The urinary storage reflex is mainly controlled by reflexes at the spinal cord level, and excitation of sympathetic (hypogastric nerve) and somatic (pubic nerve) nerves causes bladder relaxation and urethral contraction. The urinary voiding reflex is triggered by reflexes from the spinal cord to the brainstem, and excitation of parasympathetic nerves (pelvic nerves) causes bladder contraction and urethral relaxation.

These reflexes are caused via the A δ fibers, which are one of the two types of sensory nerve fibers—the myelinated A δ fibers and the unmyelinated C fibers—which pass through the pelvic nerve[3]. Urinary retention may occur due to insufficiency of the urinary voiding reflex in this disease, in which myelinated A δ fibers disappear. Details will require a urodynamics test by a urologist.

References.

1. Nomura Y, Yotani N, et al: Effects of medication and characteristics of motor and sleep development in periodic vomiting disorder. Brain & Development 48: 401-405, 2016

2. T. Sakakibara, M. Kishi, et al: Neurology and the bladder: neurological mechanisms of urination and how to view and treat dysuria. Clinical Neurology 53: 181-190, 2013

3. Yoshimura, N.: New ideas on the mechanism of the urinary reflex. Folia Pharmacol. Jpn. 121: 290-298, 2003

2-4 Sleep and Motor Development

1. Sleep and motor development in children

Due to its formulaic nature, infant development appears to follow a programmed timeline with little freedom and a narrow pathway. Nevertheless, interactions with the environment can significantly affect this process. In the second half of infancy, we can observe remarkable changes not only in motor development, but also in sleep-wake rhythms and joint attention, described as the "9-month miracle[1)].

Considering the sleep-wake rhythms in infancy, sleep in the first month of life is divided into 1–3 hour periods with few variations between day and night (known as polyphasic intermittent sleep), which is an ultradian rhythm. At 3 to 6 months, the proportion of nocturnal sleep increases and the basis for the circadian rhythm emerges. At 6 months, the longest sleep periods are at night, and the onset time of the longest sleep periods is almost constant, which can be interpreted as daytime sleep no longer having much influence on the time of falling asleep at night. The significance of daytime sleep is somewhat different in early and late infancy. From 6 months onward, night-time sleep becomes more continuous and its proportion increases, and between 9 to 12 months, night-time sleep is further enhanced and a two-part napping rhythm is established, with a cycle of about 24 hours. As shown in Figure 2-4-2, the 24-hour cycle is continuously reinforced. In the first 9–12 months of life, the infant learns the difference between day and night, especially in the context of more daytime wakefulness[2)]. The percentage of night-time sleep increases with age, but the total 24-hour sleep time tends to decrease because of the decrease in nap time (Figure 2-4-3). The establishment of this 24-hour circadian sleep-wake rhythm supports the entire development of the infant in the unconscious realm.

Figure 2-4-1 Changes in sleep-wake rhythms in the first year of life during canonical development (adapted from Reference 3).

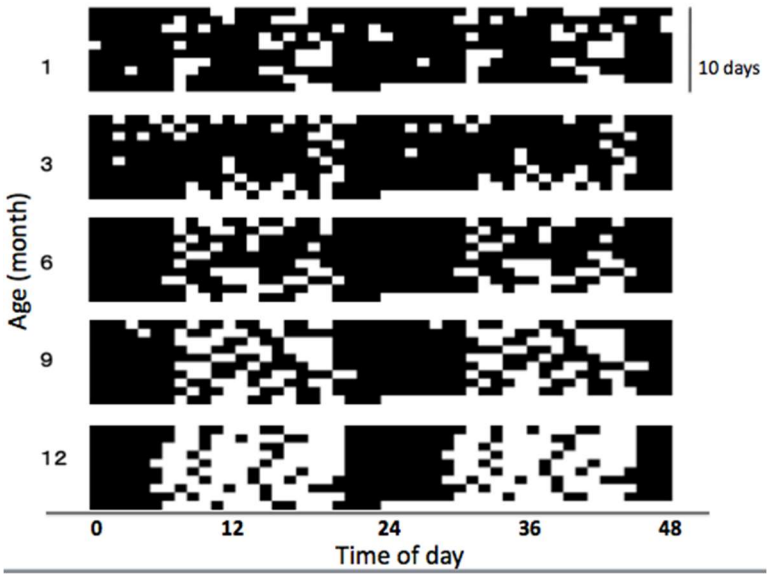


Figure 2-4-2 Changes in the cycle of sleep-wake rhythms during the first year of life during canonical development (Fast Fourier Transform (FFT) method).

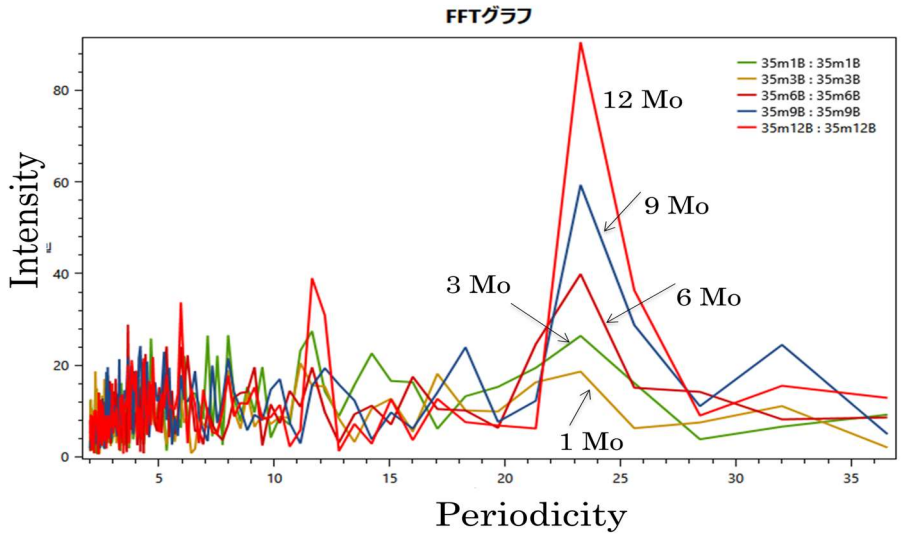
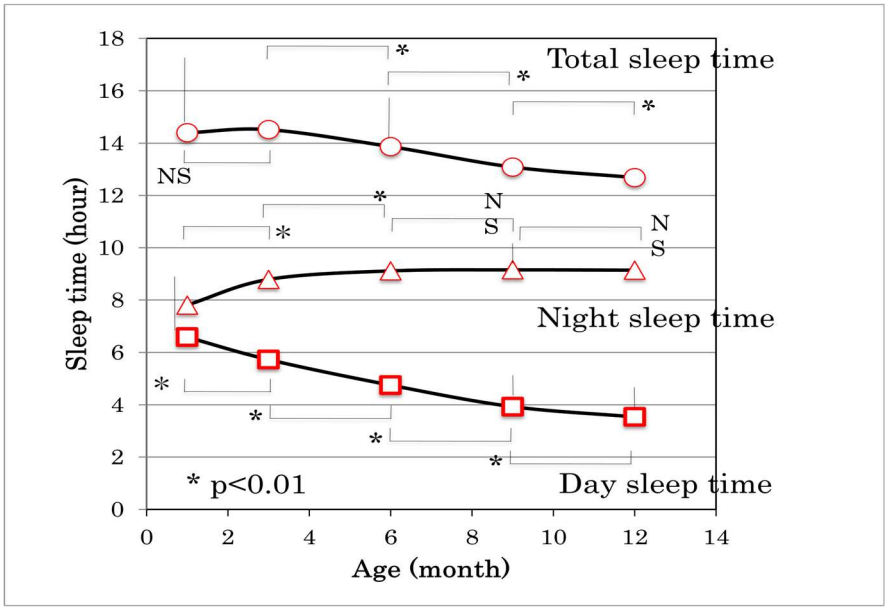


Figure 2-4-3 Changes in sleep-wake rhythms during the first year of life. 1 month of age: n=378, 3 months: n=252, 6 months: n=250, 9 months: n=252, 12 months: n=219.



In terms of motor development and sleep, it is noteworthy that the rapid eye movement (REM) stage of sleep is completed around 4 months of age, when head control has been attained. The loss of antigravity muscle tone is confined to the REM stage at this time[2]. The establishment of the REM phase requires cholinergic activation and serotonergic and noradrenergic inhibition, which also act as brainstem-derived muscle tone inhibitory and stimulatory systems, respectively. Here, motor development and sleep structure and rhythm are closely linked. These systems also function in conjunction with the reinforcement of sleep-wake rhythms (daytime arousal) and the maturation of crawling and walking (which are themselves arousal stimuli). Although the causes and relationships of these factors remain unclear, it is important to note that the REM stage of sleep is completed by the time the head is fully controlled.

The REM stage is characterized by rapid eye movement, low amplitude EEG, loss of antigravity muscle tone, and dreaming, etc. Among these, the loss of antigravity muscle tone is completed later than the other factors, at around 4 months. The brainstem cholinergic and serotonergic nervous systems are involved in this process. During REM, the cholinergic nervous system is active and the serotonergic nervous system is inactive. In addition, during locomotion, the cholinergic nervous system acts as an inhibitor of muscle tone, while the serotonergic nervous system acts as a facilitator of muscle tone. In this way, sleep and motor development mature through the coordination of multiple nervous systems.

In addition to the formation of attachment with close relatives after birth (dyadic relationships), from around 9 months of age, the degree of freedom of movement increases due to the development of the abilities of locomotion and posture maintenance. Moreover, the increase in daytime wakefulness leads to spatial expansion of the body and remote visual joint attention (triadic relationship).

2. Sleep and motor development in congenital insensitivity to pain with anhidrosis (CIPA)

A questionnaire-based survey of patients with CIPA revealed several problems related to sleep and motor development, as shown in Table 1. Thirteen of the 23 children had abnormalities related to being less likely to sleep well at night between the ages of 3–5 months, 16 of the 23 children between the ages of 6–12 months had a noticeable number of mid-night awakenings, and 10 of the 23 children had problems related to crying at night (Yonaki in Japanese). This was especially noticeable in infants who were of these ages in the summer, although this was not the only factor involved.

Delayed onset of crawling was observed in 14 out of 23 children, and 5 of them had incomplete crawling with impaired limb coordination. The start of walking tended to be slower, averaging at 18.5 months (range, 11–24 months) for the 17 patients included, and the families of all 23 patients felt that the body was hypotonic.

Analysis of changes in the TrkA-NGF system in the brain as a cause of CIPA in rats by Sobreviela et al. suggests that the cholinergic and serotonergic nervous systems may be developmentally impaired in CIPA, which may be related to the muscle hypotonia and immaturity of sleep architecture and locomotion development described above.

3. Countermeasures

Disturbed sleep-wake rhythms may be based on an inherent pathology of the nervous system, but there is no doubt that impaired body temperature regulation is a factor that impairs the establishment of circadian rhythms. Prevention of increase in body temperature in summer and avoiding low body temperature in winter using air conditioning is of utmost importance. Sleep rhythm problems may or may not resolve in early childhood. In order to ensure deep sleep, it is necessary to increase daytime activity, but this may be difficult if there is a history of bone fractures. If the child has trouble falling asleep, and frequently wakes up in the middle of the night or has

difficulty staying awake during the day, the administration of sleep-inducing drugs may be considered. Benzodiazepines such as nitrazepam and triclofos sodium can be used to help the child fall asleep, and if the child has a history of febrile convulsions and high body temperature, night-time diazepam suppositories can be used to help the child fall asleep. For abnormal night-time crying (Yonaki in Japanese), especially when the family is exhausted, L-dopa at a low dose, Chinese herbal medicine (such as 抑肝散 and 甘麦大棗湯), and drugs that act on the serotonin nervous system such as SSRIs for older children may also be used in addition to the above drugs, although their use is less common. Melatonin may also be helpful if the child has trouble falling asleep and tends to fall asleep later and later (9:00 PM one day, 10:00 PM the next day, 11:00 PM the day after that, etc.). Melatonin has been commercially available in Japan since 2020. Ramelteon is a drug with effects similar to those of melatonin and has been available since 2010. It is important to record a sleep chart for at least 2–3 weeks to determine what exactly the problems with the patient's sleep are.

With regard to motor development, catch-up is common, while for joint deformities associated with fractures, orthopedic treatment is the main countermeasure. Hyperactivity and difficulty with attention and concentration may also respond to improved sleep regulation.

Table 1 Sleep, muscle tone, and crawling in 23 CIPA infants

Case	**Age (years)**	**Sleep disturbance (at age 0–2 months)**	**Sleep disturbance (at age 3–5 months)**	**Sleep disturbance (at age 6–12 months)**			**Hypotonia**	**Start of crawling (month)**	**Crawling pattern**
				Frequent mid-night waking	Crying at night (Yonaki)	Tendency to sleep a lot			
1	3	-	＋	＋	-	-	＋	14	-
2	4	-	-	-	-	＋	＋	9	-
3	7	-	-	-	±	-	＋	9	-
4	12	-	＋	?	-	-	＋	12	＋
5	15	-	＋	＋	＋	-	＋	10	-

6	12	-	+	+	+	-	+	11	-
7	2	?	-	-	-	-	+	12	-
8	3	-	+	+	+	-	+	18	-
9	22	-	-	+	-	-	+	10	-
10	30	-	-	±	-	-	+	8	-
11	4	+	-	-	-	+	+	15	+
12	7	-	+	+	+	+	+	10	-
13	19	-	-	+	-	+	+	10	+
14	12	+	+	+	+	-	+	10	-
15	27	-	+	+	+	-	+	14	-
16	6	-	+	-	-	-	+	?	-
17	6	-	+	+	-	-	+	17	-
18	19	?	?	?	?	-	+	9	+
19	27	+	+	+	-	-	+	12	-
20	35	-	-	+	+	-	+	22	-
21	6	-	+	+	+	-	+	9	+
22	19	-	+	+	+	-	+	8	-
23	32	?	?	+	?	?	+	12	?

References

1) Tomasello M: On the interpersonal origins of self-concept. In: Neisser U (ed) The Perceived Self - Ecological and interpersonal sources of self knowledge, Cambridge University Press, pp 174-184, 1993

2) Segawa M: Mechanisms of sleep. (In Japanese) Japanese Journal of Pediatric Medicine 40: 14-17, 2008

3) Kubota M: Movement in infancy: Consciousness and unconsciousness in movement. (In Japanese) Hattatsu 148: 40-46, 2016

4) Sugiura Y, Kubota M, et al. Effectiveness of ramelteon in children and adolescents with neuropsychiatric disease-related sleep disorder. No To Hattatsu (In Press) 2020.

2-5 Disorders of the Skin

The skin is the outermost layer of the human body, separating the outside environment from the inside contents, and acts as a barrier to protect the body from various environmental changes, stimuli, and harmful substances. In addition to its barrier function, it also has sensory functions, such as temperature and pain perception, temperature regulation function through sweat secretion from sweat glands, and immune functions involving the recognition and elimination of foreign antigens. In CIPA, sweating is absent or extremely low, and the sensory nerves, including those responsible for the sense of pain, do not function properly, resulting in various serious disorders of the skin. In order to understand these, we will first briefly describe the anatomy and physiological functions of the skin, and then describe the characteristics of the skin in CIPA.

1. Structure of the skin

1) Epidermis (Figures 2-5-1 and 2-5-2)

The epidermis is the outermost layer of the skin and is composed of layers of epidermal keratinocytes arranged in a dense stone-wall-like structure. Cells in the lowermost basal layer divide and ascend toward the surface, reaching the uppermost layer in about 4 weeks[1)], losing their nuclei, becoming thin and flattened, and forming the stratum corneum, which is the outermost layer of the epidermis and resembles a tiled roof. The stratum corneum is only 10 μ thick, approximately the thickness of vinyl wrap, but even though it is thin, it acts as a strong barrier and protects the skin until just before it peels off in the form of flakes. In addition, the basal cells in the basal layer contain melanin, a pigment that protecting the skin by absorbing harmful ultraviolet (UV) rays and preventing them from reaching the deeper layers of the skin. Increased exposure to UV light increases melanin levels, resulting in skin tanning, which is simply a further strengthening of protection against UV light.

2) Dermis (Figures 2-5-1 and 2-5-2)

The dermis is the layer below the epidermis; it is rich in blood vessels, nerves, collagen fibers, elastin fibers. Hair follicles, sebaceous glands, and sweat glands also arise in the dermis. Sensory nerves control cutaneous sensations, can detect danger, and

protect the human body from invasive stimuli. Collagen fibers and elastin fibers maintain the flexibility and elasticity of the skin, making it resistant to damage to certain levels of force.

3) Subcutaneous adipose tissue (Figure 2-5-1)

It is located under the dermis and consists mainly of blood vessels and adipose cells, which store nutrients. It also cushions the skin and retains heat.

4) Skin appendages (hair follicles, sebaceous glands, and sweat glands; Figure 2-5-1)

In addition to the head and eyebrows, hair generally grows all over the skin, except on the palms and soles. Hair emerge from hair follicles in the dermis and extend outward through the epidermis. Blood vessels and nerves penetrate the hair follicles, supplying oxygen and nutrients to them; this supply is also regulated by the nerves.

In the middle of the hair shaft, running through the dermis, there is the erector pili muscle that erects the hair, and sebaceous glands that secrete sebum, which is secreted slowly through the pores, covering the surface of the skin with a waxy sebaceous film to protect it. The secretion of sebum is influenced by sex hormones, and increases rapidly during puberty.

There are two categories of sweat glands—apocrine sweat glands located in the axillae and pubic region and eccrine sweat glands distributed throughout the body—that secrete sweat to regulate body temperature and moisture. The part that secretes sweat is located deep in the dermis, and sweat ducts penetrate the epidermis to secrete sweat through sweat pores on the skin surface.

Figure 2-5-1 Cross-sectional view of the skin (taken from Reference 1).

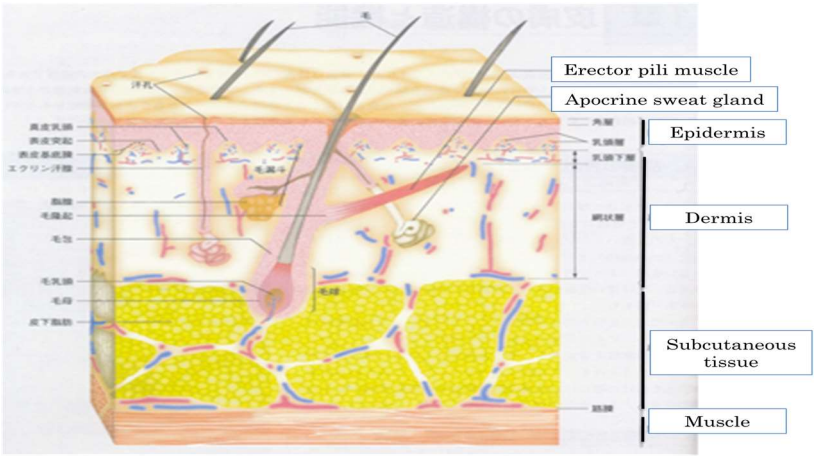
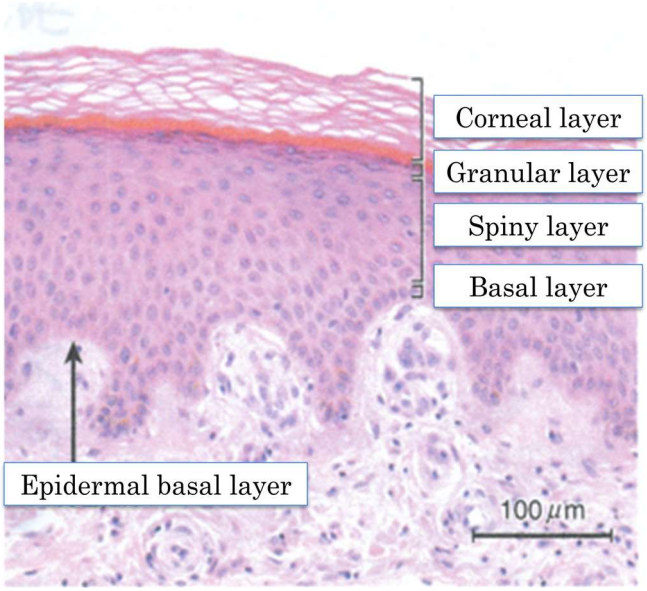


Figure 2-5-2: The four layers that make up the epidermis (Adapted from Ref. 1).



2. Functions of the skin

1) Protective and barrier functions

The skin acts as a barrier to keep out various harmful substances in the outside environment—such as bacteria, viruses, molds, dust, UV rays, chemicals—and also provides a certain level of protection against mechanical forces and stimuli. It also works to prevent water and other fluids from leaking out of the body. The stratum corneum and epidermal cells are mainly responsible for this function, while the sebaceous layer on the surface layer also assists in this.

2) Sensory perception

The skin has a variety of sensory nerve receptors to protect the human body from danger, including pain sensory nerves, heat sensory nerves, pressure sensory nerves, and vibration sensory nerves. Recently, it has become clear that there are separate nerves for the itching sensation.

Autonomic nerves are also distributed in the skin, and unmyelinated C fibers of postganglionic nerves surround the eccrine sweat glands, erector pili muscles, and blood vessels to regulate them. For example, when it is hot, they induce sweat secretion and blood vessel dilation to promote the release of heat, and when it is cold, they suppress sweat secretion and induce the contraction of erector pili muscles to reduce heat loss.

3) Sweating and secretion

(1) Eccrine sweat glands

Eccrine sweat glands are distributed throughout the body, with their number being highest on the palms and soles of the feet, followed by in the axillae and on the forehead. Perspiration has two important functions: body temperature regulation and skin moisturization. Adults can perspire significantly, up to 2 to 3 liters of sweat per hour, in high temperatures. However, sweating can be in response to not only high temperatures, but also mental tension (cold sweat, etc.), taste (gustatory sweating when consuming extremely spicy or sour food, etc.), and insensible sweating (which one may not be aware of).

Eccrine sweat glands are located in the dermis and are surrounded by many capillaries that supply the components of sweat. Sympathetic postganglionic fibers (C fibers) are distributed in the dermal blood vessels and sweat gland secretion areas to control sweat production and secretion.

The amount of water that evaporates through the skin (transdermal water transpiration) is about 500 ml per day in adults. It is higher in children than in adults, especially in winter when the air is dry.

(2) Apocrine sweat glands

Apocrine sweat glands are located in the axillae, peri-areolar areas, and vulva, and develop during puberty. They secrete not only water but also lipids, which can be a source of body odor.

(3) Sebaceous glands

Most are distributed on the face and head, and after puberty, sebum is secreted from

them under the control of sex hormones. Sebum covers the surface of the skin like wax—it prevents the evaporation of water, has an antibacterial effect, and functions as a barrier that protects the skin from various external stimuli.

The secretion of sebum is not nerve-controlled, but is stimulated by sex hormones. High sebum secretion levels cause seborrheic dermatitis and acne, while low levels cause dry skin (xerosis) and pruritus.

4) Immune function

The skin is a major site where immune and allergic reactions occur. Langerhans cells, keratinocytes, and dermal dendritic cells are the main skin-specific immune cells.

(1) Langerhans cell

Langerhans cells are dendritic cells that have Birbeck granules in their cytoplasm. These skin-specific antigen-presenting cells function in combination with epidermal keratinocytes as lookouts for foreign antigens. When antigen is presented to T cells, they leave the epidermis and travel through lymphatic vessels to the lymph nodes. When stimulated by antigens, keratinocytes express CD-68 and CD-86, which are secreted and act as potent T cell activators, through the action of GM-CSF and TNF-α.

(2) Keratinocytes

Keratinocytes are involved not only in keratinization but also in skin immunity. The main role of keratinocytes is to produce and secrete various cytokines and to stimulate the activation of immune cells.

(3) Dermal dendritic cells

Dendritic cells are bone marrow-derived cells that reside in the upper dermis. They possess factor XIIIa on their cell surface, have antigen-presenting abilities, and play an auxiliary role in cutaneous immunity.

3. Skin characteristics of congenital insensitivity to pain with anhidrosis (CIPA) and congenital insensitivity to pain without anhidrosis (CIP)

1) Disorders of temperature and pain perception (CIPA and CIP)

Patients are unable to feel pain in response to mechanical or chemical stimuli, as well as heat and cold due to dysplasia affecting the terminal C fibers of the sensory nerves[2)]. As a result, bruises, cuts, bites, burns, and frostbites are more likely to occur; moreover, the inability to maintain rest after an injury can lead to serious illness.

Teething can also lead to biting off of the tongue, lips, and fingertips, and it is not uncommon for part of the tongue or lips to be chewed off (Figure 2-5-3) or for the fingertips to be shortened (Figure 2-5-4)[3]. Because patients do not complain of pain, people around them are often slow to notice and start treatment, which is thought to be one of the reasons why they tend to often become severely ill. It is not uncommon for skin wounds to spread to deeper parts of the body, leading to osteomyelitis, septicemia, meningitis, and encephalitis.

2) Sweating disorder (CIPA only)

Normally, when it is hot, the autonomic nervous system controls the body temperature by producing sweat from eccrine sweat glands to lower body temperature. However, in CIPA, although the number of sweat glands is normal and there is no abnormality in their morphology, sweating is not possible due to the lack of C fibers, which are postganglionic fibers that stimulate sweat secretion[4]. As a result, the body is unable to regulate body temperature, which rises considerably, leading to heat retention and even heat stroke. In addition, the lack of moisture-retaining sweat causes the skin to dry out easily and the stratum corneum to become thick (Figs. 2-5-4, 2-5-5); its lack of flexibility also makes it prone to cracking, resulting in poor barrier function[5]. This makes patients more vulnerable to bruises and abrasions due to trauma, and because of this in combination with sensory disturbances, wounds tend to reach deeper into the skin, causing bacterial infections and slower wound healing[5]. In CIP, there is no sweating disorder, so the above symptoms may not be present.

3) Sebaceous secretion is normal

The sebaceous glands are not controlled by nerves and are stimulated to secrete by sex hormones. Generally, pre-pubertal children have little sebum production on their face, head, and other parts of the body, and do not have sufficient moisturizing or protective properties. Acne can be aggravated by picking or plucking until the affected area bleeds, causing it to become infected.

4) Delayed mental development and self-injurious tendencies on the skin

Patients do not have any actual experience of pain, heat, and cold, and even if explained, it is difficult for them to understand, which makes safety education difficult

and also makes it difficult for them to perceive danger and avoid it on their own. In addition, because they are hyperactive and have a tendency to self-injure, they move a lot and can do so violently, repeatedly bumping their heads, falling, hitting their knees hard on the floor without restraint, and jumping from high places, all of which results in constant trauma[5]. They often repeatedly bite and pluck their fingertips, nails, tongue, and lips. They may also intentionally hit their head or forehead against objects[5]. The inability to relieve stress may further increase hyperactivity and self-injurious behavior. It has been reported that neurodevelopmental disorders are less common in patients with CIP[2], and the effects of self-injury on the skin are also thought to be minimal.

Fig. 2-5-3 Parts of the tongue and lips are often bitten off and missing.

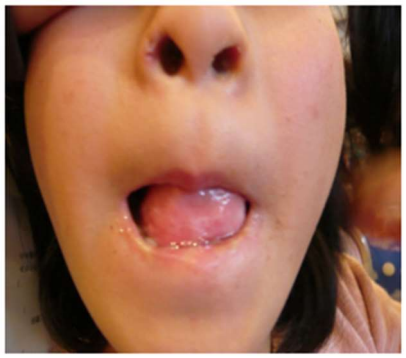


Fig. 2-5-4 Bitten off fingertips, shortened and deformed terminal segments, shortened and missing nails, and thickening and fissuring of the stratum corneum is observed.

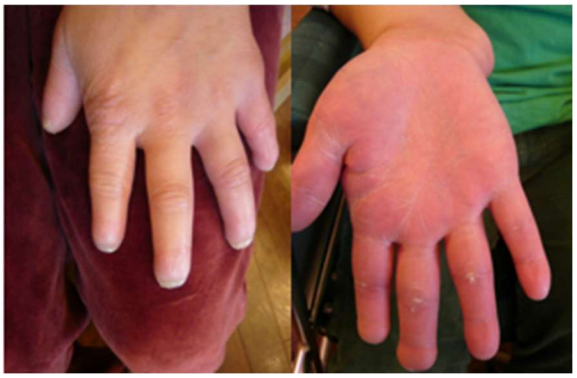
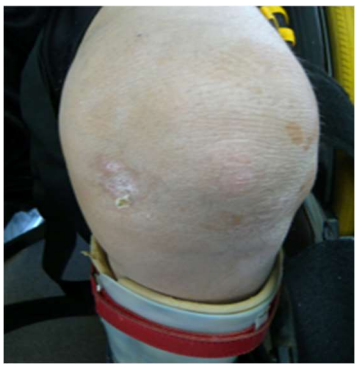


Figure 2-5-5 Swelling and club-shaped deformity of the knee joint (Charcot joint) due to hitting the knee hard against the floor. Dry skin and thickened stratum corneum due to constant trauma to the knee.



4. Measures to protect the skin

1) Maintain cleanliness

Take care to keep the surface of the skin clean and wash it once a day in the bath or shower. Check the skin all over the body, even for small bruises and scratches. As soon as you find them, apply topical medication to prevent them from becoming infected, and protect them with gauze or wound dressing.

2) Moisturize and protect

Since the skin is prone to dryness, it is important to apply moisturizers from early infancy[3]. It is especially effective to apply it all over the body within 20 minutes after bathing, when the stratum corneum is still moist. The area around the mouth, hands, and the diaper area, which are easily soiled, should be moisturized and protected by applying moisturizer every time they are washed or cleaned. Apply moisturizer to the soles of feet, toes, palms of hands, and fingertips, where the stratum corneum is thicker and more prone to cracking, to make it as thin and flexible as possible.

3) UV protection

On a normal sunny day, unprotected exposure to UV rays for more than 20 minutes will cause sunburn and injury to the skin. In the short term, sunburn causes redness, blistering, and darkening of the skin, but in the long term, it can damage the connective tissue of the dermis, accelerate aging, and even cause skin cancer. Before going out, use sunscreen and hats or parasols and dress the patient in long-sleeved clothes and long pants to avoid direct exposure to UV rays.

4) Nutrition

Various nutrients, including trace elements, are necessary to prevent skin problems and to repair damage to the skin. It is important to eat a well-balanced diet with many different types of foods.

5) Safety measures

(1) Prevention of burns

Avoid placing high-heat sources such as stoves, rice cookers, and hot water kettles, as well as items that produce steam, within easy reach. Pay attention to the temperature of showers and hot water and set the temperature low. When eating, cool all hot food before placing it nearby, and be careful of foods that are can be hotter inside, such as croquettes, gyoza, and hamburgers.

(2) Prevention of frostbite

During the cold season, dress the patient in gloves, thick socks, and hats when going out to prevent their hands and feet from getting too cold, and make sure the temperature indoors does not fall below 20℃.

(3) Prevention of falls and trauma

Do not expose the skin and cover it with clothing as much as possible. It is advisable for patients to wear padded supporters to soften impact, especially on the knees, shins, elbows and forearms. Make sure the patient's shoes fit the feet properly to prevent falling. Use furniture with rounded corners and cushioning to lessen the impact of bumps. Take care to put away items that are at a height where patient might hit the head or shins. It is better to use a non-slip, shock-absorbing carpet instead of a hard, slippery floor.

5. Treatment methods and approaches when skin symptoms appear

As mentioned in the previous section, the frequency of skin symptoms in CIPA and CIP is extremely high, and it is known that they sometimes become severe, but there are no systematic reports of the symptoms or coping strategies. At present, the attending physician is treating symptoms in their own way. Therefore, the level of evidence in this section is at the level of advice from experts, and further accumulation of case data is necessary before a theory can be established. In addition, this section does not explain the use of moisturizers used for prevention in the pre-treatment stage. Regarding the method of using moisturizers, the explanation about atopic dermatitis can be applied.

This is because it is pathophysiologically common to atopic dermatitis.

1) How to understand skin symptoms

The most difficult aspect in CIPA and CIP skin diseases is to check subjective symptoms, because subjective symptoms such as pain, itching, and heat, which are most important for differentiating between eczema and infection, are much fewer than in healthy people. Treatment begins with differentiating between eczema and other forms of non-infectious inflammation (for which immune modulation such as steroids is the key to treatment) and infectious inflammation (for which antibiotics and other anti-pathogenic microbial agents must be used), but diagnosis is often difficult. Of course, inflammation can be differentiated not only based on pain and heat, but also by the presence of infiltration (slight hardening and elevation of tissue due to increased cell density), edema, and lichenification (thickening and stiffening of the skin due to chronic inflammation) on the skin surface. However, the most important factor is the interview with the patient and family members. The opinions of skilled observers should also be used to the maximum extent to identify the symptoms.

This should be done under the supervision of a dermatologist with some degree of experience, and a system should be established to allow consultation with a dermatological primary care physician.

2) General guidelines for treatment methods

As indicated in the previous section, the initial goal is to differentiate whether the inflammation is non-infectious or infectious.

If non-infectious inflammation is diagnosed, immunosuppressive and modulating agents, mainly topical steroids, should be used. For severe cases or symptoms that are difficult to differentiate, oral medication may be considered, but it should be used for a minimum period of time in consideration of drug interactions and systemic side effects, and it should be discontinued immediately if there is no improvement in symptoms. This should be done under strict observation.

If a diagnosis of infectious inflammation is made, the next step is to identify the pathogenic microorganism. Bacterial infections, viral infections, and fungal infections, in that order, are expected to occur more frequently, and the first therapeutic agent to be administered in each case is oral medication. It is better to presume that topical drugs

will not reach the infected site sufficiently. In general, the course of treatment for infectious inflammation in patients with CIPA and CIP tends to be longer than in healthy individuals. In addition, the development of deep infection is also expected to be more common than in normal patients, because they are often unable to maintain rest during treatment. Therefore, oral medication is necessary to ensure high local blood concentrations. The dosage should take into account drug interactions, but if possible, a high dosage may improve the outcome of treatment.

3) Use of topical dermatological agents

As mentioned in the previous section, topical dermatological agents often include immunosuppressive and modulating agents such as steroids. In this section, we would like to discuss their usage and indications in particular.

Regarding immunosuppressive and modulating agents, we do not recommend the use of non-steroidal anti-inflammatory and analgesic drugs. This is because they are less effective, and the incidence of contact dermatitis increases with the length of treatment. The remaining agents are topical steroids and tacrolimus ointment. The use of tacrolimus ointment is the most beneficial in terms of side effects and efficacy. In general, tacrolimus ointment is used for atopic dermatitis (and is only covered by insurance for atopic dermatitis), but it is also effective for other eczema and dermatitis types. The most significant advantage of tacrolimus ointment is that it has fewer side effects such as skin atrophy, lipoatrophy, telangiectasia, and hypertrichosis than topical steroids during long-term use. On the other hand, the side effects associated with the use of tacrolimus ointment, such as skin irritation and heat sensation in the early stages of topical application, are not a problem in CIPA and CIP, both theoretically and in actual prescriptions. The skin irritation associated with the use of tacrolimus ointment is caused by a temporary increase in the level of neurotransmitters in the skin's peripheral nerves, but in CIPA and CIP, the peripheral nerves that feel this irritation are congenitally lost, so this side effect does not occur. For this reason, it is recommended that tacrolimus ointment be used from the beginning (especially if prolonged treatment is expected). Of course, topical steroids can be used from the beginning, but if prolonged use is expected, it may be better to consider switching to tacrolimus.

6. Skin and wound healing

Physical defects due to trauma to the skin are common in CIPA and CIP. In this section, we will discuss the concept of wounds down to the subcutaneous level.

In clinical observations, the wound healing process for skin injuries is the same as in normal subjects, but the time required for wound healing in CIPA and CIP is longer than in the general population. This is thought to be due to the inability to maintain local rest. Therefore, the treatment of the local skin areas, i.e., whether it should be treated with topical medication or a dressing, should be the same as for healthy people.

What is more important is how to maintain the local rest of the skin. This issue should be discussed with plastic surgeons and orthopedic surgeons, and also how the patient should be protected, taking into account the patient's lifestyle.

Reference

1) Baba N: Anatomy and physiology of the skin. (In Japanese) The Japanese Journal of Child Nursing 34: 1505-1514, 2011

2) Awaya Y: Congenital insensitivity to pain with anhidrosis. (In Japanese) Japanese Journal of Pediatric Medicine 41: 762-768, 2009

3) Sasaki R, Matsunaka H, et al: Physiological findings in congenital insensitivity to pain with anhidrosis. (In Japanese) Journal of the Japanese Society of Pediatric Dermatology 28: 27-32, 2009

4) Nolano M, Crisci C, et al: Absent innervations of skin and sweat glands in congenital insensitivity to pain with anhidrosis. Clin Neurophysiol 111: 1596-1601, 2000

5) Yoshimi K, Tanaka C, et al: Actual conditions of daily life in congenital insensitivity to pain with anhidrosis. (In Japanese) Occupational Therapy 21: 45-54, 2002

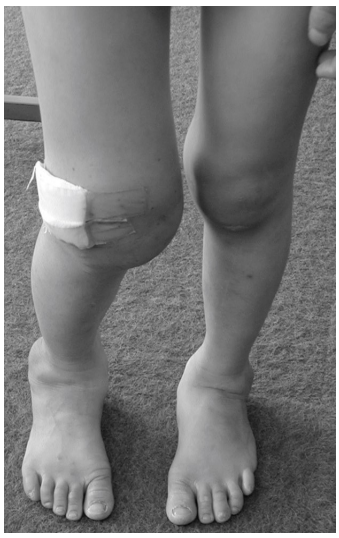
2-6 Bone and Joint Disorders

1. Characteristics of bone and joint disorders

In congenital insensitivity to pain with anhidrosis (CIPA), there is no sense of temperature and pain, so the child feels no pain even when burns, bruises, fractures, or dislocations occur. As affected children cannot learn to experience and avoid physical harm through pain, they are unable to recognize danger and suffer repeated trauma. In addition, the risk of trauma may be increased in CIPA due to delayed intellectual development, hyperactivity, and autistic tendencies. Osteoarticular deterioration is also a major problem that can severely impair physical functions and interfere with daily life.

This can manifest in a variety of ways as the child grows. During infancy, motor development is delayed due to weak muscle tone throughout the body. Insensitivity to pain causes discomfort and obsession with teeth, biting of one's own fingers, deformity and loss of fingernails and finger ends, and infection. Standing and proper gait development is delayed, but the child begins to walk by the age of 2 years. As the child becomes more mobile, trauma from falls and jumping becomes more common. There is also a tendency for hyperactivity in CIPA. When fractures or sprains occur, they can worsen, as the affected child does not complain of or feel pain. In addition, the vicious cycle repeats itself as the child continues to move without protecting the injured area, causing other injuries and injuries to adjacent areas. From infancy onward, the child may suffer repeated fractures and dislocations of the lower limbs, and from school age onward, bone growth disturbances and joint deformities may lead to joint destruction (Charcot joint) (Fig. 2-6-1). In a Charcot joint, there is chronic joint effusion and loss of support due to deformity and instability, but walking for short distances, such as indoors, is generally possible. Fractures of the upper extremities are less common than those of the lower extremities. After adolescence, trauma decreases, but wheelchair use and time spent in a sedentary position increases. Occasionally, spinal ligament injuries or vertebral fractures may occur, resulting in spinal cord compression, paralysis of the lower limbs, and bladder/bowel dysfunctions.

Figure 2-6-1 Charcot joint of the right knee.



2. Characteristics and treatment of disorders by site

1) Upper limbs

Phalanges: The ends of the fingers are damaged due to self-mutilation, such as biting one's own fingers during infancy and early childhood. Infection often leads to cellulitis and osteomyelitis.

Elbow joint: Fracture of the distal humerus can occur due to a fall. Delayed detection or inadequate cast immobilization may lead to delayed union.

Shoulder joint: Joint laxity is usually marked and dislocation may occur, but joint morphology is relatively preserved and functional impairment is minimal.

(2) Lower limbs

Foot: Fractures of the calcaneus, talus, and metatarsal bones occur frequently from the age of 3 years onwards, when walking becomes more active. They are rarely detected in the acute phase because there is no complaint of pain, and healed and/or malunited fractures may be detected later on radiographs. The calcaneus often has a peculiar deformity in which the posterior part protrudes in a beak-like shape; compression deformities of the cuboid and scaphoid are also common (Fig. 2-6-2).

Lower leg: Injuries may be caused by jumping from a height or falling, or other unknown causes. In the ankle joint, many fractures are associated with physeal separation, and if proper treatment and rest is not maintained, osteoarthritis and even a Charcot joint may develop. Cast immobilization is the basic treatment for diaphyseal fractures of the lower leg, but surgical internal fixation may be used if rest and load reduction cannot be maintained. Reduction should be as precise as possible. If the

deformity persists, the burden on the adjacent joint will increase and it will also be damaged. Careful attention should be paid to avoid pressure ulcers when applying casts.

Knee joint: In adolescents, swelling and effusion of the joint often lead to the discovery of osteonecrosis and depression of the lateral femoral condyle. As the ligaments gradually become looser, the joint becomes deformed. The use of knee braces or knee-ankle-foot orthoses may be helpful during with standing and gait and may reduce swelling and joint effusion of the joint.

Femur: Fractures occur due to jumping or falling. Diaphyseal fractures are an indication for traction therapy in children, but aggressive surgery is often used because of the inability of patients with CIPA to maintain rest. If the fracture is minimally displaced, it may be treated using a hip spica cast.

Hip: Dislocations are thought to be caused by unnatural positioning or falls and based on muscle weakness, decreased muscle tone, and joint laxity. In the case of traumatic dislocation, rest and load prohibition of loading for 2–3 weeks is the general rule, but if the patient begins walkings too soon immediately after dislocation, the ligaments and muscles around the joint do not repair sufficiently, leading to repeated dislocation. Dislocations are easily reduced, and it is possible for the parents to pull the leg to reduce the dislocation once they are used to it. Hip abduction braces are also used to prevent dislocation, but even so, it is difficult to completely prevent re-dislocation. Dislocations associated with fractures of the proximal femur or the femoral head are difficult to treat. Most of them are treated surgically, but it is difficult to maintain the correct position, which may lead to re-dislocation, head absorption, or acetabular fracture, resulting in permanent dislocation (Fig. 2-6-3).

Spine: Abnormal mobility of the spine and scoliosis/kyphosis are common. Spinal paralysis due to kyphotic deformity may occur after adolescence.

Figure 2-6-2 Calcaneal fracture and subsequent compression of the navicular bone.

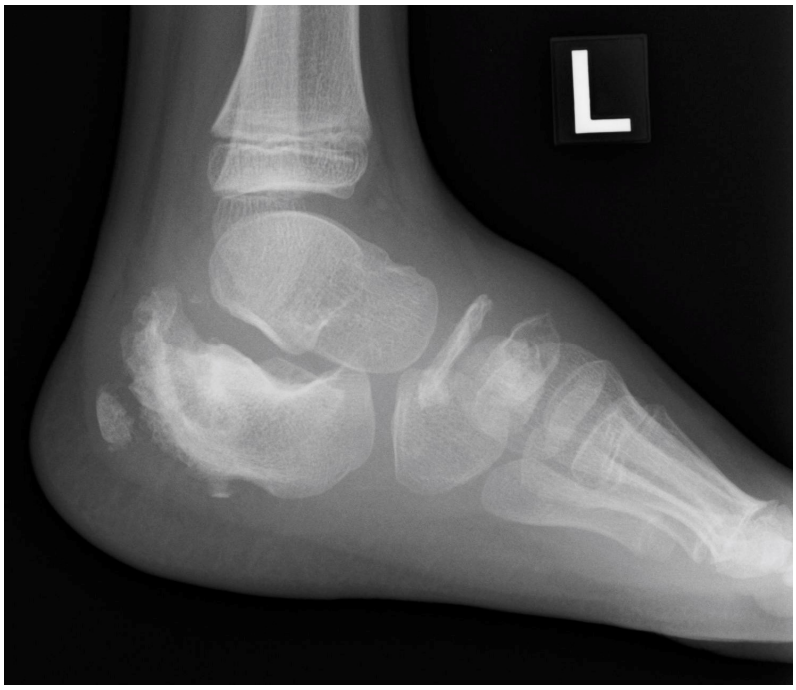
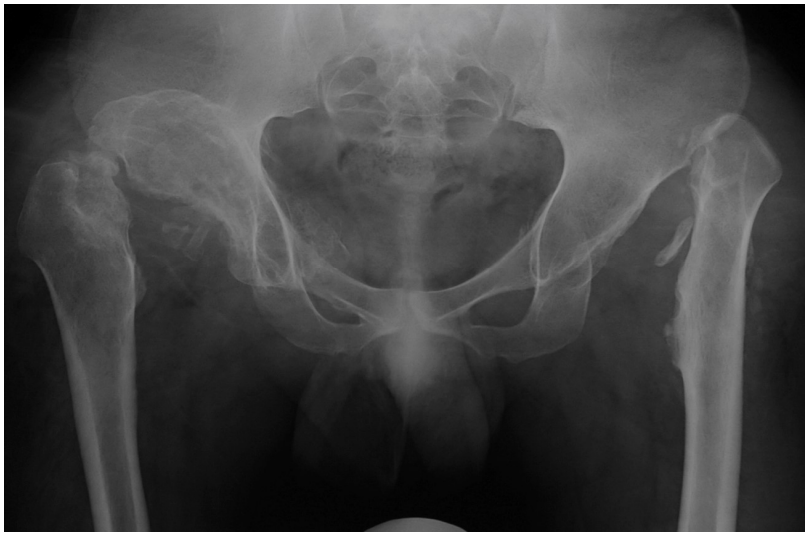


Figure 2-6-3 Charcot joints in both hips with femoral head loss and dislocation.



3. Casting treatment

Fractures and dislocations are often treated with casting. Although anesthesia is not required for manual reduction because of the absence of pain, it is better to use anesthesia if judged necessary because of the possibility of difficulties in obtaining patient cooperation due to intellectual disability in CIPA. Great care should be taken when applying the cast. The skin is dry and prone to dermatitis in CIPA, the lack of pain makes it difficult to maintain rest, due to which the fracture site is also not maintained at rest because the patient continues to stand or walk even with the cast on. When applying

a cast, pads should be applied to the protruding parts of the bone in advance to prevent pressure ulcers, and the cast should be checked every one to two weeks and re-applied frequently if it becomes loose. After removal of the cast, care should be taken in post-treatment to prevent re-fracture due to early full-weight bearing.

In addition to casting, traction therapy is often used for pediatric fractures, but it is often not appropriate because the patient cannot tolerate bed rest and can easily move.

4. Fracture healing mechanism

In CIPA, bone healing after fracture is relatively good, but is delayed if the fracture site is not maintained at rest. Excessive calluses may form, and the associated swelling and local heat sometimes resemble osteomyelitis. It is difficult to accurately differentiate between the two, as patients may actually be prone to osteomyelitis. If in doubt, perform bacteriological tests or administer prophylactic antibiotics.

5. Orthotics

1) Types of orthotics

In early childhood, insoles and high-cut shoes that fully cover the ankles may be used to protect the feet (Fig. 2-6-4). Knee braces and knee-ankle-foot orthoses are often used to protect the knees. Wearing a hip abduction brace to prevent hip dislocation may also be effective.

School-aged children and adolescents can wear plastic ankle-foot orthoses or orthopedic shoes to protect and stabilize the feet. Some patients begin using wheelchairs at an early age for long-distance travel, and in adulthood, electric wheelchairs may be fitted depending on the condition of the patient.

2) Precautions to be taken while fabrication of braces

Since the patient does not feel pain, cuts and pressure sores easily occur due to the contact and pressure of orthoses. Moreover, in CIPA, the skin is prone to dryness and cracking. Materials that are comfortable, scratch-resistant, breathable, and warm should be used. Since immobilizing one joint burdens the adjacent joints, avoid strong immobilization by considering the balance of the entire lower limb.

Braces are used in various situations, but it is important to clarify the purpose, as wearing braces can also be stressful for patients. It should be determined whether the

purpose is rest or unloading after surgery, preventing exacerbation of joint deformity, or limiting joint laxity.

Figure 2-6-4 Reinforced side of a high-cut shoe.

6. Early detection of trauma

Instruct family members to inspect the entire body every day when taking a bath, etc., and if there is any swelling at all, to consult a doctor early. Abrasions and open wounds should be treated appropriately until they are completely healed.

7. Physical condition and lifestyle

In order to prevent trauma, it is important to manage the physical and mental condition of the affected child. Stress should be relieved through moderate exercise, and the parents should be instructed on how to improve the housing by covering the floor with soft mats and eliminating corners and steps.

If a child with CIPA is left in a chair or wheelchair for too long to avoid trauma, stress may build up, leading to increased self-mutilation and unexpected behavior such as running around. They often attend special needs schools or special needs classes at regular schools, so it is important to have teachers understand the characteristics of the disease and create a safe and stress-free environment at school.

References

1. Zhang Y, Haga N: Skeletal complications in congenital insensitivity to pain with anhidrosis: a case series of 14 patients and review of articles Published in Japanese. J Orthop Sci 19: 827-831, 2014
2. Haga N, Kubota M, Miwa Z: Hereditary sensory and autonomic neuropathy types IV and V in Japan. Pediatr Int 57: 30-36, 2015
3. Haga N, Tanaka N, Tanaka H: Therapeutic strategies for congenital insensitivity to pain with anhydrosis. (In Japanese) Journal of the Japanese Orthopaedic Association 87: 57-60, 2013
4. Tian K, Tanaka H, et al: Current status of patients with congenital painless anhidrosis and conservative treatment approaches. (In Japanese) Journal of the Japanese Society of Pediatric Orthopedics 25: 55-57, 2016
5) Haga N: Pathogenesis and management of congenital anhidrosis. (In Japanese) Journal of New Remedies & Clinics 65: 77-80, 2016

2-7 Dental and Oral Disorders

Dental problems associated with CIPA include bite wounds on the tongue, lips, buccal mucosa, and finger tips, osteomyelitis of the upper and lower jaws caused by dental caries and/or periodontal infection, and lacerations and fractures of the jaw caused by trauma. Concurrently with deciduous teeth eruption beginning around 6 months after birth, bite wounds on the tongue, lips, and buccal mucosa first occur; patients may be first diagnosed with the disease at this time. Such bite wounds are seen in almost all patients with CIPA, and many patients are forced to have their teeth extracted due to continued bleeding from the tongue and/or lips. It can be easily inferred that such early tooth loss will adversely affect the growth of not only the alveolar and jaw bones but of the body overall because of deteriorated masticatory function and associated nutritional deficiencies. If the teeth are conserved in spite of repeated bite wounds, the tongue will almost always be scarred (in a keloid state), and the lingual papillae and taste buds will disappear, resulting in abnormal taste sensation. The clinical manifestations of this disease in the oral cavity and possible preventive measures against them are discussed below.

1. Dental problems according to age

1) Infancy

The most primary teeth, the mandibular central incisors, start to erupt around 6 months after birth. An ulcer can develop on the inferior surface on the tongue due to a congenital tooth in neonatal period even in normal infants (teeth that erupt at birth or within the first month of life). This condition is called Riga-Fede’s disease and is characterized by a sort of abrasion resulting from to-and-fro movements of the tongue during breastfeeding. In the past, if the tooth damaged the mother's nipple, it was extracted. However, nowadays, conservative measures, such as drilling the sharp edges of the teeth and rounding them, are mostly adopted.

In children with CIPA, ulcers on the inferior surface of the tongue occur with the eruption of the deciduous mandibular anterior teeth. Naturally, bleeding occurs, and the ulceration can be so deep that it reaches the muscular stratum of the sublingual surface. When the deciduous maxillary central incisors also erupt at around 10 months of age,

the tongue can be bitten off by the upper and lower teeth, and sometimes the tongue tip is completely severed (Fig. 2-7-1). In addition to tongue biting, patients may have loosened teeth or teeth loss resulting from severe bruxism or strong biting of toys, cords, etc., as infants are commonly very eager to put anything in their mouth. In most cases, however, they may manipulate the teeth by themselves causing self-extraction, probably because of the uncomfortable sensations that accompany tooth eruption (Figure 2-7-2). Bite injuries may occur not only with the eruption of deciduous anterior teeth but also with the eruption of deciduous posterior teeth on the lateral edge and/or the dorsum of the tongue or the buccal mucosa.

Figure 2-7-1 Tongue bite during eruption of deciduous teeth.

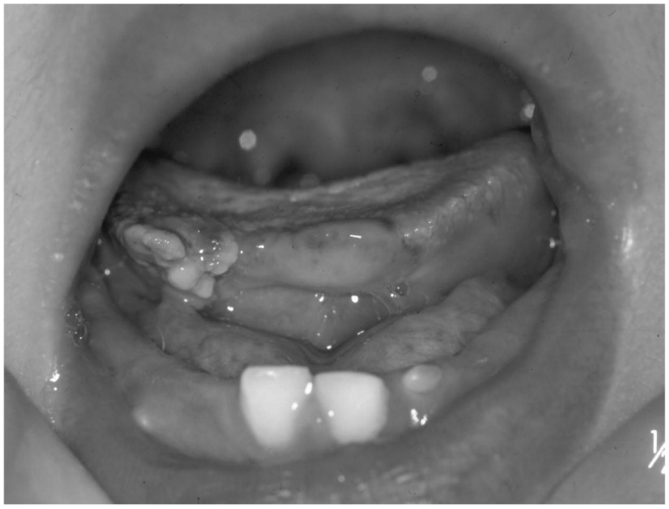
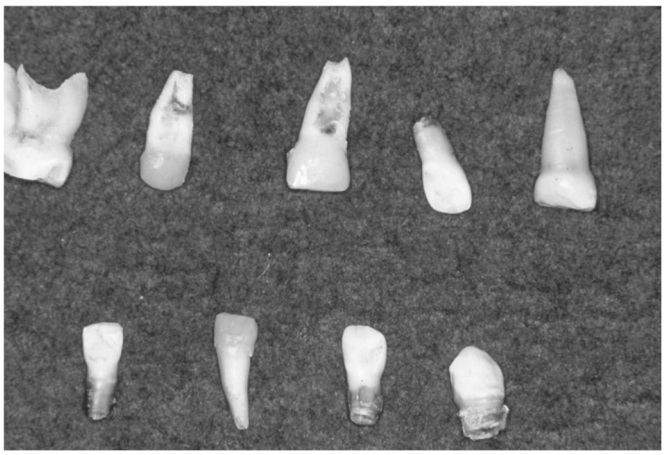


Figure 2-7-2 Teeth self-extracted one after another in one patient.



2) Early childhood

The primary dentition of 20 teeth is complete around 2 and a half years of age. Until this time, tongue bites are often observed as teeth erupt. In addition to those on the tongue, bites on the buccal mucosa, lips, fingernails, and fingertips are also common. Many patients already lose several teeth, and tongue bite injuries are more severe when the tongue thrusts into the empty space.

Dental caries may progress undetected because the patient does not feel pain, which can lead to further progression of the disease. Even if pulpitis or periodontitis develops, there are no subjective symptoms, and they may only be noticed when the gums, cheeks, or jaw become swollen. Abscesses or cellulitis can also develop. There have also been cases where infection from carious teeth has caused osteomyelitis in the jawbone, resulting in jawbone fractures. Therefore, patients must visit a dentist regularly for the examination of the oral condition, treatment, and prophylaxis.

3) School-age period

The eruption of permanent teeth starts at around 6 years of age. The incidence of self-injury by biting is lower than that during primary dentition, although it is not clear whether this is an effect of learning on the part of the individual. It is also possible that the tongue edge has been so severely scarred and shortened that the patient can no longer bite the tongue as readily. However, bite wounds, self-extraction, and severe tooth attrition due to bruxism can occur and may be attributable to the discomfort of deciduous tooth loss and permanent tooth eruption. The patient should have regular dental surveillance, because he/she may not complain of pain even when suffering from pulp inflammation or infection. In addition, apprehension, fear, and conflict may result in behavior that increases self-biting and bruxism, so daily psychological support is also important.

4) Adolescence

During the adolescent period, prosthodontic treatment may be necessary both for the rehabilitation of masticatory function and for preventing bite injuries to the tongue and buccal mucosa, as many patients have lost teeth by this time. The denture should be frequently examined and may need to be repaired or even remade as the jaw grows (as the denture will not grow as the jaw grows). Wisdom teeth generally erupt after 17 to 18

years of age. In particular, the lower third molar is susceptible to purulent pericoronitis due to the lack of space for eruption. The symptoms of pericoronitis include fever, swelling, bad breath (halitosis), and difficulty in opening the mouth (trismus) and swallowing (dysphagia). Since not all individuals have four wisdom teeth on the upper and lower sides, it is advisable that a panoramic radiograph is obtained to detect the presence of third molar(s) and to measure the space available for eruption.

5) Adulthood

Dental problems in adults with CIPA seem to be less severe than in infants and children. Denture wearing is commonly recommended for teeth missing as a result of caries, periodontitis, trauma, or self-extraction. A fixed, non-removable denture (a bridge) can be set safely if the number of missing teeth is low the patient does not significantly grind the teeth.

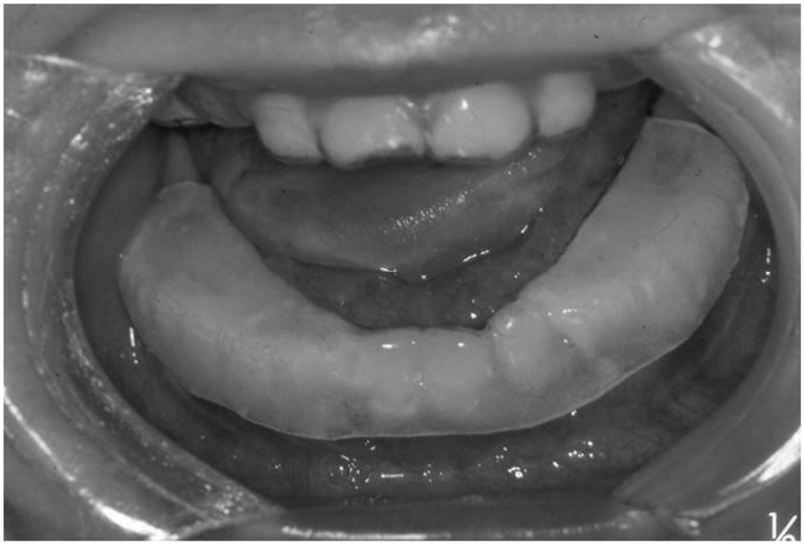
Removable dentures are indicated for patients with many missing teeth. Close attention should be paid to the oral condition of the patient, as he/she does not feel pain and can tolerate an ill-fitting denture even though it can result in ulcers, loose teeth, and even bone exposure.

2. Special Dental Considerations for patients with CIPA

1) Prevention and treatment of bite wounds

A protective plate should be used by the patient when the teeth are erupting and especially if a bite wound appears. Thermoplastic resin is a useful material for fabricating these plates. When the patient frequently has bite wounds in the region of missing teeth or in the space for eruption, it can be effective to fill the space with soft resin. These devices must be remade according to tooth eruption and jaw growth (Figure 2-7-3).

Fig. 2-7-3 Upper and lower jaw protective plates. The lower jaw is reinforced with soft resin for better retention.



2) Prevention and treatment of dental caries

To prevent dental caries, it is important to brush teeth properly (for adequate plaque removal) and to reduce the intake of sugary foods and drinks.

Fluoride application and the use of fluoride toothpaste are the most effective ways to prevent dental caries. When wearing a protective plate, it is effective to apply fluoride (in the form of formulations such as Check-up Gel®) to the inner surface of the plate to prevent dental caries. It is necessary to have regular dental examinations and to have dental treatment as soon as possible if a caries develops.

3) Prevention and treatment of periodontal diseases

Gingivitis and periodontitis (alveolar pyorrhea) are infectious diseases caused by obligate anaerobic and other types of bacteria in the oral cavity. In order to prevent periodontal diseases, it is necessary to remove plaque and tartar through daily brushing and regular dental examinations, and to undergo periodontal treatment. Periodontal disease can also be affected by systemic conditions such as fever and malnutrition.

4) Dental complications associated with epilepsy

It is estimated that 17% of children with CIPA have epileptic seizures. Dental complications associated with epilepsy include tooth injuries such as tooth or jaw fractures and tooth luxation. Symptoms may not be apparent shortly after injury and may manifest after a few weeks or even months. The patient should undergo dental

examination when the history suggests orofacial injury.

Some antiepileptic drugs may cause hyperplasia of the gum (gingival enlargement). Gum hyperplasia manifests in approximately 50% patients taking phenytoin (Aleviatin ®), which attains maximum size in adolescence in many cases. Gingivitis can increase hyperplasia, but this complication can be prevented by cleaning the mouth and tooth surfaces by brushing. Sometimes aggressive dental management, such as a gingivectomy (surgical removal of the enlarged gingival margin), may be necessary in light of considerable cosmetic and/or functional disturbances.

3. Findings of recent studies

1) Tooth pulp sensation and innervation

We used electric pulp testing (EPT) pulpal innervation of extracted teeth donated by patients with CIPA and CIP to examine tooth pulp sensation. Patients with CIPA (HSAN-4; lacking Aδ and C fibers but with Aβ fibers), had no pain sensation or pre-pain sensation, while patients with CIP (HSAN-5; lacking Aδ fibers but with C and Aβ fibers), had pre-pain sensation with thresholds similar to those in normal subjects. This suggests that the mechanism of pre-pain sensation in the dental pulp may involve C fibers, although it was previously thought to depend on Aβ fibers.

2) Sense of taste and smell

The sensitivity of patients with CIPA to pungent substances (such as capsaicin) that stimulate TRPV1, a receptor for taste and pain sensations transmitted by Aδ fibers, was tested. The results showed that most patients were able to recognize the five basic tastes, but their cognitive thresholds tended to be significantly higher for umami, and higher for sour and bitter tastes, when compared to those of normal subjects. Most subjects were able to perceive irritation due to capsaicin as well, although the threshold was higher than that of normal subjects, suggesting that the systems involved in pain perception due to physical stimuli and chemical substances may be different. We also measured the sense of smell and found that most subjects were able to recognize the odors they had previously encountered.

References

1. Ikeda M, Nihei K.: Dental Guideline of Hereditary Sensory and Autonomic Neuropathy With Anhidrosis. Ministry of Health and Welfare in Japan; Study on System of Good Rearing of Children with High Risk; Study on Care of Children with Motor Disorders. Aikawa Shobo, Tokyo, 1999. 3.
2. Miwa Z, Kakino S, et al.: Mandibular osteomyelitis in the presence of congenital insensitivity to pain with anhidrosis ― A case in which transmitted-light plethysmography (TLP) was used for pulp diagnosis. (In Japanese). Journal of Pediatric Dentistry 49: 41-46, 2011.
3. Miwa Z, Kubodera T, et al.: A study on the mechanism of pulp sensation in patients with congenital painless anhidrosis. (In Japanese) Journal of Japanese Society of Disability and Oral Health; 29: 341, 2008.
4. Miwa Z, Kubodera T, et al.: Pulp sensation and nerve distribution in patients with congenital painless anhidrosis. (In Japanese) Journal of Japanese Society of Disability and Oral Health. 30: 510, 2009.
5. Ikeda M, Akiyama M, et al.: Dental support for congenital anhidrosis at different life stages: Toward understanding the actual situation and developing guidelines. (In Japanese) Journal of Japanese Society of Disability and Oral Health. 32: 184-186, 2011.
6. Miwa Z, Inoue K, et al.: Evaluation of pulpal vitality in patients with hereditary sensory and autonomic neuropathy Type IV or V. J Dent Oral Health. 1: 022, 2015.
7. Tsuchihashi N, Miwa Z, et al.: Perception of pungent, gustatory and olfactory stimuli in patients with congenital insensitivity to pain with anhidrosis. J Oral Science, 63: 104-106, 2021.

2-8 Eye Disorders

Since 2004, we have participated in the annual symposium and annual medical examination sessions organized by the "Society for Congenital Insensitivity to Pain with Anhidrosis-Tomorrow" Until 2017, we conducted ophthalmological examinations of 63 patients with CIPA (age at first examination ranging from 3 months to 59 years) and one patient with congenital insensitivity to pain (CIP, age at first examination: 17 years). In this section, we will mainly discuss the ophthalmological problems in CIPA.

As a result of the ophthalmological examinations, we found that the eyes of the patients with CIPA had

1) reduced corneal sensation due to the loss of corneal nerve fibers[1)]

2) various types of tear film abnormalities as a result of difficulty in maintaining homeostasis between tear film fluid and lipid[2)]

3) superficial punctate keratopathy (scattered, fine, punctate corneal epithelial loss or damage), which was observed more frequently in patients over 6 years of age[3)]

4) severe visual impairment due to corneal opacity after corneal ulcers in some patients[3)]

5) normal development of visual function in most patients without corneal opacities[3)]

Therefore, we believe that the most important thing for achieving normal development of visual function in patients with CIPA is to prevent corneal ulcers and, if corneal ulcers do occur, to detect and treat them as soon as possible.

1. Abnormalities in the Cornea and Tear Film

Superficial punctate keratopathy was observed more frequently in older patients with CIPA[3)] (Fig. 2-8-1). Patients had fewer corneal nerves and weaker corneal sensations than those in healthy subjects.[1)] Due to the reduced sensitivity to pain, superficial punctate keratopathy may trigger serious corneal disorders such as persistent corneal epithelial defects, corneal ulcers, and corneal infections. Even if these problems are cured, visual impairment due to scarring and corneal opacity may remain as sequelae. Studies conducted in other countries have reported keratitis, corneal ulcers, and corneal leukoma in patients with CIPA.[4-7)] Studies in Japanese subjects have reported that refractory corneal ulcers seemed to be related to neurotrophic

keratopathy[8] and keratoconus in both eyes.[3]

1) Decreased Corneal Sensation

Peripheral nerves arising from the first branch of the trigeminal nerve, sympathetic nerves, and parasympathetic nerves are distributed in the cornea. It is well known that disorders of the trigeminal nerve contribute to persistent corneal epithelial defects and neuroparalytic keratitis. In patients with CIPA and CIP, corneal nerves are reduced and corneal sensation is impaired.[1] Congenital sensory nerve fiber defects of the trigeminal nerve may also interfere with normal wound healing in the corneal epithelium.

Figure 2-8-1 Superficial punctate keratopathy in a patient with CIPA.
22-year-old male, right eye. Superficial punctate keratopathy was observed in the lower part of the cornea. There was scattered, fine, punctate epithelial loss on the surface of the cornea, which was stained as punctate yellow dots using fluorescein dye.

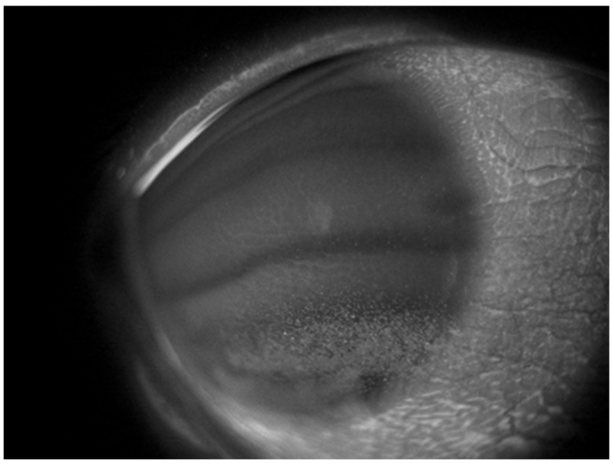
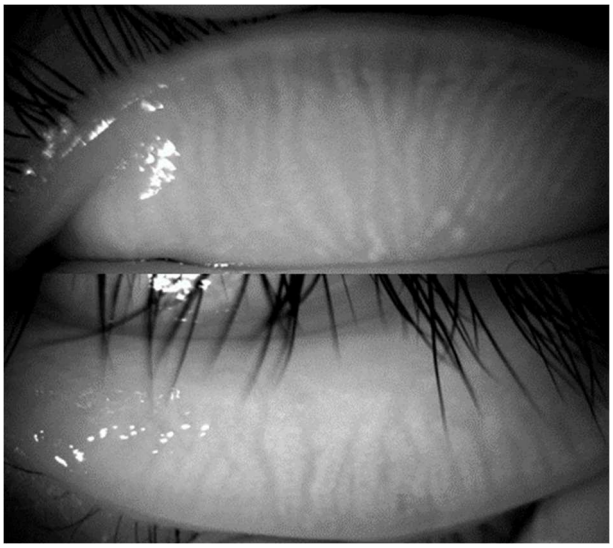


Figure 2-8-2 Non-invasive meibography in a patient with CIPA.
22-year-old male, left eye (same case as in Figure 2-8-1). Narrowing and shortening of the upper eyelid meibomian glands and shortening of the lower eyelid was observed. The morphological changes of the meibomian glands were mild. The thickness of the tear film lipid layer was 35 nm, which is thin (normal thickness is >75 nm). The thinning of the tear film lipid layer was thought to be caused by loss of meibomian gland function rather than by morphological changes in the meibomian glands.



2) Abnormalities in tear film

The surface of the eye is composed of three layers: the lipid layer, the aqueous layer (water and secretory mucin), and the keratoconjunctival epithelium (membrane mucin and epithelial cells). The tear film lipid layer is secreted by the meibomian glands in the eyelids and prevents excessive evaporation of the tear film. Tear fluid is produced by the lacrimal gland. In our initial examinations of patients with CIPA, the results of Schirmer's test 1 showed normal tear fluid secretion, but tear film breakup time (BUT) was reduced. Therefore, we had thought that evaporative dry eye was typically associated with CIPA.[3)] Meibomian gland dysfunction (MGD) is generally thought to be the leading cause of evaporative dry eye. The quantity and/or quality of lipid secreted from meibomian glands deteriorates in MGD patients. In most cases of CIPA, the morphological changes in the meibomian glands as assessed using non-invasive meibography[9,10)] were mild (Figure 2-8-2), which may be due to dysfunction rather than morphological abnormalities of the meibomian glands.[2)]

According to the Japanese dry eye diagnostic criteria, revised in 2016[11)], dry eye is diagnosed when the patient exhibits both the tear abnormality and dry eye symptoms (ocular discomfort and/or deterioration of visual function). Patients with CIPA often do not meet the criteria for the diagnosis of dry eye, because they do not feel pain in their eyes and have few subjective ocular symptoms, even if they have tear abnormalities and keratoconjunctival epithelial damage. Even without subjective symptoms, by starting treatment when corneal damage is minimal, it is possible to prevent progression to severe corneal damage and visual impairment. If the patient has superficial punctate

keratopathy, we recommend that regular ophthalmological examinations are conducted every few months. It is recommended to use eye drops such as diquafosol sodium ophthalmic solution (Diquas®), rebamipide (Mucosta®) ophthalmic suspension, and hyaluronic acid eye drops. We do not recommend prophylactic administration of antimicrobial eye drops due to the possibility of developing bacterial resistance.

3) Corneal ulcers

A corneal ulcer is an erosion and opacity not only in the corneal epithelium but also extending deep into the corneal stroma (Figs. 2-8-3 and 2-8-4). Superficial punctate keratopathy is observed more frequently in older patients with CIPA (Fig. 2-8-1), and the corneal surface is often vulnerable to bacterial and fungal invasion. To prevent corneal ulcers, it is recommended that they avoid rubbing their eyes as much as possible and avoid contacting the eye with dirty hands or water.

A corneal ulcer usually causes severe eye pain along with findings such as redness, tearing, cloudy white spots on the cornea, and discharge. However, patients with CIPA do not complain of any pain, which may lead to delayed detection.

Once a corneal ulcer develops, it does not heal spontaneously nor become transparent without treatment. The first step in the examination of a corneal ulcer is to identify the causative microbial pathogen. Depending on the pathogen, one to three antibacterial or antifungal eye drops are administered frequently, every 1–3 hours. Severe cases may require hospitalization. Usually, the infection can be controlled within 2 to 4 weeks of starting treatment. Delayed detection of a corneal ulcer can lead to scarring corneal opacities as sequelae[2,3] (Fig. 2-8-5). In particular, if the opacity is in the central part of the cornea and covers the pupillary region, it can lead to severe visual impairment. It is recommended that family members or others around patients with CIPA should always pay attention to signs of eye infection and self-injury, and take them to an ophthalmologist as soon as possible if they notice any abnormalities.

Figure 2-8-3 Corneal ulcer. Newly developed small ulcer.

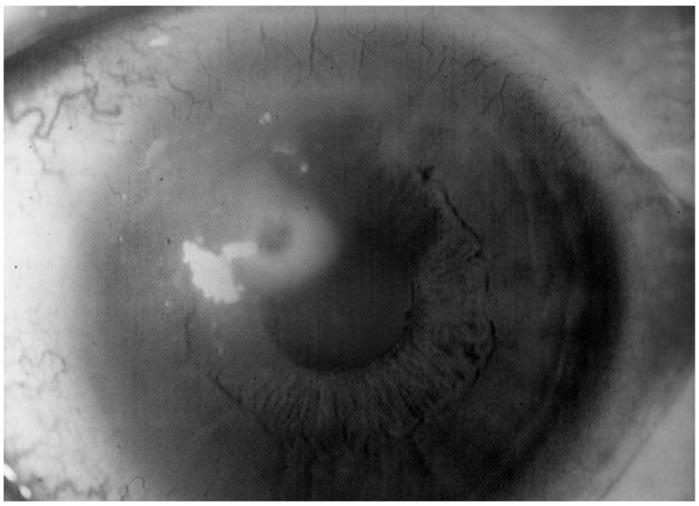


Fig. 2-8-4 Corneal ulcer.
Serious ulcer spreading over a large area of the cornea.

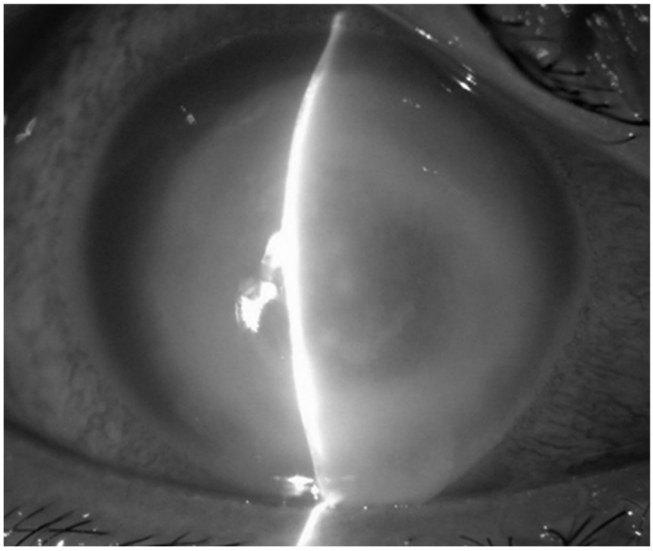
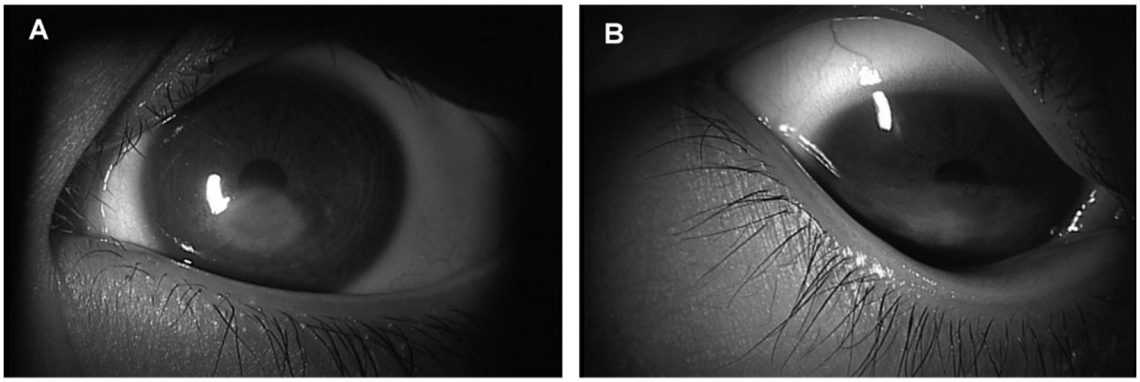


Figure 2-8-5 Corneal opacity and visual impairment in a patient with CIPA.
A: 7-year-old male, corneal opacity after infectious corneal ulcer in left eye. Uncorrected visual acuity of the right and left eyes was 1.0 (uncorrectable) and 0.7 (uncorrectable).
B: 10-year-old female, right eye. Corneal opacity after corneal ulceration due to self-injury in both eyes. Uncorrected visual acuity of the right eye was 0.2 (uncorrectable), and that of the left eye was not measurable.



2. Abnormalities related to Visual Function

Most patients with CIPA have normal visual development[3]. In some patients, severe visual impairment occurs because of corneal opacity due to corneal ulcers[3] (Figure 2-8-5).

Strabismus, or crossed eyes, is a condition in which both eyes do not align when looking at an object and are directed in different directions. This can lead to problems such as double vision, eye fatigue, as well as decreased binocular stereopsis and perspective (depth perception). Amblyopia is a developmental disorder usually diagnosed based on a reduction in visual acuity which cannot be improved by refractive correction. Anything that interferes with clear vision in either eye of a child during the critical period of vision development can cause amblyopia. Conditions that may lead to amblyopia include strabismus, a large refractive error (myopia, hyperopia, or astigmatism), a large difference in refractive error between the eyes, or structural problems such as corneal opacity. Some patients with CIPA have strabismus and amblyopia even in the absence of corneal opacity. The critical period for visual development is from 1 month to about 8 years of age, at which time the child may respond to treatment, such as the use of glasses and eyepatches or strabismus surgery, and gain visual development. Patients with CIPA can be associated with various degrees of mental retardation, which may make it difficult to examine them for visual acuity and ocular alignment. If the child has difficulty seeing even with glasses or has strabismus, it is recommended that an ophthalmologist is consulted as soon as possible, as the child may need treatment by a specialist in strabismus and amblyopia.

3. Other Ocular Abnormalities

There has been a case report of retinal detachment in both eyes of a Japanese patient with CIPA.[12] Self-injurious behaviors such as rubbing or tapping the eyes hard or contusion of the globe may require not only examination of the cornea but also the fundus.

Iris dilator muscles are controlled by the sympathetic nerve. Patients with CIPA lack sympathetic postganglionic neurons, and their pupils are therefore contracted because their dilator muscles do not work.

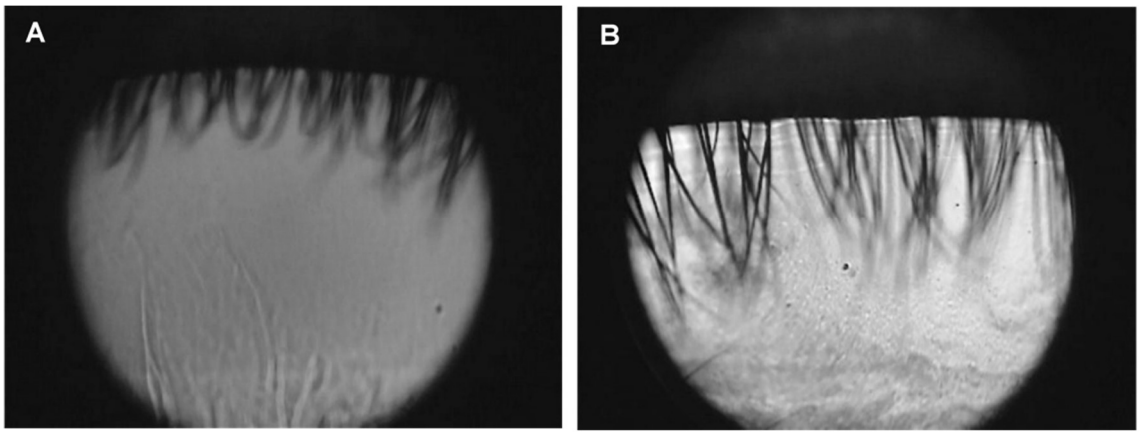
4. Recent Research - Abnormal Balance between Tear Film Fluid and Lipid

We non-invasively examined tear film parameters such as tear film lipid layer thickness, tear meniscus height (the amount of tear fluid on the lower eyelid margin), and non-invasive tear breakup time (NIBUT, an index of tear film stability) in patients with CIPA using recently developed medical devices. We found that the values of these parameters varied considerably from case to case.[2] Tear film interferometric measurements revealed both evaporative dry eye patterns without interference fringe and aqueous deficient dry eye patterns with multicolor interference fringes[2] (Fig. 2-8-6). These results indicated that patients with CIPA could have various types of tear film abnormalities in addition to evaporative dry eye (Fig. 2-8-6).

Normally, the stability of the tear film is maintained by a balance between tear fluid and lipid. An increase in tear fluid production compensates for loss of tear film lipid, and increased lipid secretion compensates for loss of tear fluid (compensation theory).[13] However, tear fluid secretion did not increase even when the thickness of the tear film lipid layer decreased in some of the patients with CIPA, and no shortage of tear fluid was observed even when the tear film lipid layer thickness increased (Figure 2-8-6). Patients with CIPA lack nerve growth factor (NGF)-dependent neurons, which have been found to contribute to the formation of neural networks that maintain homeostasis in the body.[14] Thus, in patients with CIPA, corneal sensation is decreased and homeostasis is difficult to maintain, which may lead to deterioration of the fluid and lipid balance of the tear film, resulting in tear film instability and various types of tear film abnormalities.

Figure 2-8-6 Interferometric image of the tear film in a patient with CIPA.
Various types of tear film abnormalities were observed in patients with CIPA.

A: Evaporative dry eye type without interference fringe.
26-year-old female, right eye. Tear film lipid layer thickness was 40 nm, tear meniscus height was 0.12 mm, and NIBUT was 1 second.
B: Aqueous deficient dry eye type with multicolor interference fringes.
16-year-old male, left eye. Tear film lipid layer thickness was 133 nm, tear meniscus height was 0.19 mm, and NIBUT was 1 second.
The tear film of healthy humans maintains a balance between fluid and lipid. Typically, in evaporative dry eye, the lipid layer is thin, but there is sufficient tear fluid. In aqueous deficient dry eye, there is insufficient tear fluid, but the lipid layer is sufficient. Both tear fluid and lipid were insufficient in case A. The lipid layer was thick and tear meniscus height was almost normal in case B. The maintenance of tear film homeostasis may be impaired in patients with CIPA.



References

1. Mimura T, Amano S, et al: In vivo confocal microscopy of hereditary sensory and autonomic neuropathy. Curr Eye Res 33: 940-945, 2008
2. Fukuoka S: Dry eye in congenital insensitivity to pain with anhidrosis (Dry eye and related diseases). (In Japanese) Frontiers in Dry Eye 13: 48-51, 2018
3. Amano S, Fukuoka S, et al: Ocular manifestations of congenital insensitivity to pain with anhidrosis. Am J Ophthalmol 141: 472-477, 2006
4. Jarade EF, El-Sheikh HF, Tabbara KF: Indolent corneal ulcers in a patient with congenital insensitivity to pain with anhidrosis: a case report and Eur J Ophthalmol 12: 60-65, 2002
5. John D, Thomas M, Jacob P: Neurotrophic keratitis and congenital insensitivity to

pain with anhidrosis--a case report with 10-year follow-up. Cornea 30: 100-102, 2011
6. Biedner B, Dagan M, et al: Congenital insensitivity to pain with neuroparalytic keratitis. Ann Ophthalmol 22: 312-313, 1990
7. Yagev R, Levy J, et al: Congenital insensitivity to pain with anhidrosis: ocular and systemic manifestations. Am J Ophthalmol 127: 322-326, 1999
8. Ueda M, Arichi M, Okami T: Corneal ulcer in a patient with congenital insensitivity to pain with anhidrosis. (In Japanese) Ganka Rinshou Iho. 95: 37-40, 2001
9. Arita R, Itoh K, et al: Noncontact infrared meibography to document age-related changes of the meibomian glands in a normal population. Ophthalmology 115: 911-915, 2008
10. Arita R, Itoh K, et al: A newly developed noninvasive and mobile pen-shaped meibography system. Cornea 32: 242-247, 2013
11. Japan Dry Eye Society, Committee on Definition and Diagnostic Criteria of Dry Eye. Revised definition and diagnostic criteria for dry eye in Japan (2016 version). http://www.nichigan.or.jp/member/guideline/dryeye.pdf (accessed 6/23/2018)
12. Nomoto H, Matsumoto K, Shimomura Y: A case of congenital insensitivity to pain with anhidrosis and retinal detachment with ruptures of the serrated edges in both eyes. (in Japanese) Ganka Rinsho Kiyo 1: 755-758, 2008
13. Arita R, Morishige N, et al. Tear interferometric patterns reflect clinical tear dynamics in dry eye patients. Invest Ophthalmol Vis Sci 57: 3928- 3934, 2016
14. Indo Y: Nerve growth factor and the physiology of pain: the relationships among interoception, sympathetic neurons and the emotional response indicated by the molecular pathophysiology of congenital insensitivity to pain with anhidrosis. (In Japanese) No To Hattatsu 47: 173-180, 2015

2-9 Notes on anesthesia

Congenital insensitivity to pain with anhidrosis (CIPA) is a disease that occurs from birth and is characterized by unexpected fever, generalized anhidrosis, and neurodevelopmental disorders. However, since CIPA is rare, it has been difficult to accumulate experience regarding anesthesia management and to reach a consensus on anesthesia methods for surgery. Until some time ago, the only comprehensive research paper on anesthesia management for patients with CIPA was published in Japan by our group[1)], but recently, a comprehensive research paper by an Israeli group[2)] was published. We will discuss the current anesthetic and perioperative management for patients with CIPA here, including the findings of other papers.

In general, anesthesia is necessary when a patient with CIPA undergoes surgery. There is a misconception among patients and medical professionals alike that anesthesia is for pain relief, and there are also some opinions that anesthesia is not necessary for patients with CIPA because of their lack of pain perception. However, the management of anesthesia during surgery is not only to obtain analgesia, but also to support the maintenance of homeostasis in the body by inducing sedation, preventing body movement, and controlling body temperature. In patients with CIPA, body temperature management during the perioperative period (preoperative, intraoperative, and postoperative) is extremely important, and anesthesia management, including not only anesthesia during surgery but also body temperature management throughout the perioperative period, is required[1)]. Since CIPA is characterized by lack of pain perception, it is often thought that there would not be any response to invasive stimuli such as pain in medical procedures, but it is known that there is a reaction to hemodynamics during tracheal intubation to secure the airway in patients with CIPA. This is one of the grounds for the need to respond to invasive stimuli for patients with CIPA[2)].

Anesthesia methods should be similar to those used in the general population. For minor surgeries, such as dental extractions, local anesthesia may be sufficient as long as the patient cooperates with the procedure and remains calm. On the other hand, general anesthesia is recommended for moderately invasive surgeries, such as orthopedic surgery for large bone fractures. There have been few opportunities regarding major

surgery, such as surgery for malignant tumors in the abdomen, because the long-term prognosis of patients with CIPA is generally not very good, and there have been few reports worldwide. Nevertheless, life-expectancy is increasing, and anesthesia methods for major surgery will be an issue that needs to be considered in the future.

There are no contraindications for specific local anesthetics. Regarding general anesthetics, there have been no reports of serious side effects with either inhalational or intravenous anesthetics. However, some patients with CIPA have a strong aversion to the use of a dental drill during tooth extraction[1)], which may be due to tactile hypersensitivity[1)]. Considering that inhalation anesthetics have stronger effects on tactile sensation than intravenous anesthetics, it may be preferable to use inhalation anesthetics in such cases. Malignant hyperthermia may occur in patients with neuromuscular diseases when inhalational anesthetics or depolarizing muscle relaxants (e.g., succinylcholine) are used, but there have been no reports of fulminant or subacute type malignant hyperthermia in CIPA[1,2)]. In recent years, general anesthesia is often combined with regional anesthesia (spinal anesthesia, epidural anesthesia, etc.) in surgeries of moderate or greater invasiveness. However, since there is little significance in attempting to actively use regional anesthesia for analgesic purposes for patients with CIPA, general anesthesia mainly using inhalation anesthetics is the preferred method of inducing anesthesia during surgery.

During general anesthesia, it is advisable to evaluate the degree of sedation using a device such as an electroencephalogram monitor[3)]. It has been reported that regional anesthesia (spinal anesthesia) was possible for patients with CIPA[4)]. However, the safety of general anesthesia has improved dramatically, and there is little reason to actively use regional anesthesia for patients with CIPA. Fortunately, there have been no reports of serious complications related to anesthesia for patients with CIPA in Japan, but according to a report from Israel, the incidence of cardiovascular complications is high in anesthesia for patients with CIPA[5)].

Next, we will discuss individual points to keep in mind when managing anesthesia for patients with CIPA. In general, nausea and vomiting after surgery, especially general anesthesia, is a common symptom, and their causes include the effects of nitrous oxide (N_2O) as an inhaled anesthetic, excessive use of narcotics, and certain surgical techniques. Nausea and vomiting are conditions that should be avoided as much as possible because they interfere with prompt postoperative recovery. In addition, there

was a report of a case of unexpected vomiting during anesthesia for a patient with CIPA, which was suspected to be due to stagnation of gastric contents[6]. Autonomic dysfunction in CIPA may also be involved[2].

Since aspiration of gastric contents is dangerous, the following three points should be kept in mind: avoid nausea and vomiting as much as possible, make sure that the patient is fully awake after general anesthesia and that the pharyngeal reflex is reliable, and make sure that the stomach is empty as far as possible. Specifically, during general anesthesia, it is wise not to use a supraglottic airway securing device (e.g., laryngeal mask airway), but to intubate the trachea to shield the airway, and then place a gastric tube to empty the gastric contents.

As for perioperative temperature control, patients with CIPA are more susceptible to external temperature changes, and active temperature control is desirable even in the perioperative period. In other words, it is advisable to control the patient's body temperature through active temperature control. In the case of postoperative shivering, active warming is all that is needed. It has also been reported that patients with CIPA tend to have bradycardia in the perioperative period[2], which may be due to the autonomic dysfunction in CIPA.

The patient's usual institution should be sufficient for minor surgery such as dental extractions. If a surgery requires general anesthesia, it is better to go to a hospital with inpatient facilities, preferably one that is certified in anesthesiology. Hospitals accredited by the Japanese Society of Anesthesiologists can be found by searching for accredited hospitals on the Japanese Society of Anesthesiologists website (Japanese Society of Anesthesiologists Accredited Hospital Search: http://www.anesth.or.jp/ accessed June 25, 2018).The risk of anesthesia for patients with CIPA is the same as that for normal patients, but considering the possibility of developing fever after surgery, it is preferable to perform surgery in a facility that has inpatient facilities and can provide good post-operative care. There are some pediatric patients who require sedation for MRI examinations, but there is still no established method of sedation for patients with CIPA. If it is not possible to perform the examination with the same sedation as used for general pediatric patients, it may be advisable to avoid excessive administration of sedative drugs and consider requesting a local children's hospital that provides general anesthesia for the examination.

Finally, we are sometimes asked by patients' families about the risks associated with

anesthesia, but we do not have a concrete answer at this time. According to a survey of general patients, until the 1990s, it was approximated that there was one death in every 10,000 cases due to anesthesia. However, the safety of anesthesia has improved dramatically in recent years due to the improvement of monitoring methods and pharmaceuticals. According to a recent report, the number of unexpected deaths during surgery in Japan is 4.91 in every 10,000 individuals, of which 0.07 (less than 1 in 100,000) is thought to be caused by anesthesia. This figure is about 1/1000 of the number of people who die in a traffic accident in one year in Japan. Thus, current anesthesia is extremely safe, even though the risk of anesthesia for patients with CIPA may be slightly higher.

References

1. Tomioka T, Awaya Y, et al: Anesthesia for patients with congenital insensitivity to pain and anhidrosis: a questionnaire study in Japan. Anesth Analg 94: 271-274, 2002

2. Zlotnik A, Natanel D, et al: Anesthetic management of patients with congenital insensitivity to pain with anhidrosis: a retrospective analysis of 358 procedures performed under general anesthesia. Anesth Analg 121: 1316-1320, 2015

3. Brandes IF, Stuth EA: Use of BIS monitor in a child with congenital insensitivity to pain with anhidrosis. Paediatr Anaesth 16: 466-470, 2006

4. Oliveira CR, dos Santos FA, et al: Spinal anesthesia in a patient with congenital insensitivity to pain with anhidrosis. Anesth Analg 104: 1561-1562, 2007

5. Rozentsveig V, Katz A, et al: The anaesthetic management of patients with congenital insensitivity to pain with anhidrosis. Paediatr Anaesth 14: 344-348, 2004

6. Zlotnik A, Gruenbaum SE, et al: Risk of aspiration during anesthesia in patients with congenital insensitivity to pain with anhidrosis: case reports and review of the literature. J Anesth 24: 778-782, 2010

2-10 Mental development and behavioral characteristics

1. Psychomotor development

1) Infancy and early childhood

The development of congenital insensitivity to pain with anhidrosis (CIPA) in infancy varies among individuals, from normal development to children who show certain delays. Some patients develop normally with regard to motor development, such as head control, sitting, and walking, but moderate delay is observed in about 60–70% of all patients.

Early childhood is characterized by uneven development, and various problems arise, such as little interest in objects, clumsiness while playing with toys, impairments in social interaction, speech delays, and difficulties in feeding and defecating independently. This is often due to delays in overall development, such as movement, exploratory activity, social skills, language, and lifestyle. Particularly with regard to language development, it takes time to acquire words, and there is a noticeable delay in comprehension, expression, and conversation.

The characteristics of early childhood include finger and tongue biting, hyperactivity, impulsivity, obsessions/repetitive nature, and hypersensitivity. If there are concerns about developmental delays or biases, it is important to assess the degree of development by using developmental and intelligence tests (e.g., the Tsumori-style infant mental development test, the Kyoto Scale of Psychological Development, and the Tanaka-Binet V Intelligence Test). In the case of infants, it is advisable to use developmental support centers and day-care services for children to initiate the necessary interventions at an early stage.

2) School-age children

As in early childhood, intellectual development in school-age children varies from normal to moderately delayed. When we examine the characteristics of cognitive development based on the commonly used Tanaka-Binet V Intelligence Test, we find that they are poor in memorization, categorization, and graphic copying, and have difficulty learning numerical concepts in particular. With regard to Wechsler Intelligence Scale of Children Third Edition (WISC-III) score, the working memory index score tends to be higher than those for the other indexes (verbal comprehension

index, perceptual reasoning index, processing speed index), and patients are also good at mechanical short-term memory for numbers. There are individual differences in intelligence quotient based on the WISC-IV, but there is a common weakness in verbal explanation. In terms of school subjects, many patients have difficulty with arithmetic, which is thought to be due to delayed comprehension and poor numerical processing skills.

Characteristics such as attention deficit, obsessions/repetitive nature, hyperactivity, and impulsivity are also observed in school-age children. Patients may be enrolled in a variety of schools, including regular classes, special-needs classes, and special-needs schools, but even when they are enrolled in regular classes, they often have learning difficulties. It is important to choose a school where they can learn with confidence, fun, and less burden, taking into consideration their level of intellectual development, group adaptability, and behavioral characteristics.

3) Adolescence and adulthood

In adolescence and later, there is a slight stagnation in terms of intelligence test scores, and mild to severe delays are observed. It is thought that learning disability and inexperience due to various restrictions reflect in these test results. As in the school-age, patients are good at mechanical short-term memory for numbers based on the WISC-III. In school life, clumsiness with hand use and in adjusting of strength and balance of the body become more noticeable. However, in an environment that is suitable for them, they may find more enjoyment in friendships, or find things in which they can exert their strong points, and growth that cannot be measured by intelligence tests can be seen. Even if they do not understand pain, they try to protect themselves from danger as their own growth progresses.

One of the characteristics of puberty is sexual awakening. This period of sexual maturity is not very different from that of typically developed children. There is no need for those around them to be too nervous, though they may act out of curiosity, because they do not have a proper understanding of sexuality and have difficulty in controlling and moderating it.

When the Wechsler Adult Intelligence Scale Third Edition (WAIS-III) is administered to late adolescents and adults, some patients are observed to have mild retardation, but most have moderate to severe levels. Among the various cognitive

abilities, short-term memory for numbers is one of the abilities that patients excel in regardless of their level of intelligence or age between school-age to adulthood.

In late adolescence, there are more and more difficulties for the individual in daily life, such as in terms of hygiene and money management. However, it is necessary for them to have opportunities to participate in social life as much as possible to become independent. They generally have various problems related to employment, and there are many cases where patients are unable to get the job that they want due to interpersonal problems, complexity of the work, inability to keep up with the speed of work, or unstable physical condition. In addition to the individual's willingness to work, it is important to have a clear understanding of their social skills and aptitude, and to find what they can do to create a rhythm in their lives.

Understanding the development and intelligence of children from infancy to adolescence is an important aid in dealing with and guiding them. Intelligence tests are not just about making judgments based on the intelligence quotient, but also about how the child's difficulties affect learning and behavior, which can be useful in considering various ways to help. It is advisable to take the tests in a medical institution or developmental support center.

2. Concerning worrisome behavior

Patients with CIPA show various worrisome behaviors from infancy. Figure 2-10-1 shows the average frequency of fever, tongue biting, finger biting, hyperactivity, bone fractures, and burns according to age.

1) Fever, tongue biting, finger biting

Fever, biting of the tongue, and biting of the fingers appear from infancy, but decrease rapidly between the ages of 4 to 5 years. Self-injurious behaviors such as tongue biting, finger biting, and hitting the head on the wall or floor generally occur when there is a developmental delay. Patients may indulge in self-injury when they do not get their way, when they feel uncomfortable, when they are unable to communicate verbally, or even as a self-stimulating behavior for no reason at all. Even if you warn them to stop the self-injurious behavior, they may repeat it without any effect. If we can observe the child's behavior and understand under what circumstances the child is prone to self-injury and the reasons for it, we can devise countermeasures. It is important to

reduce anxiety and stress in their daily lives; the frequency of these behaviors decreases as the child acquires more understanding, has more interests, and develops language skills.

2) Leg fractures

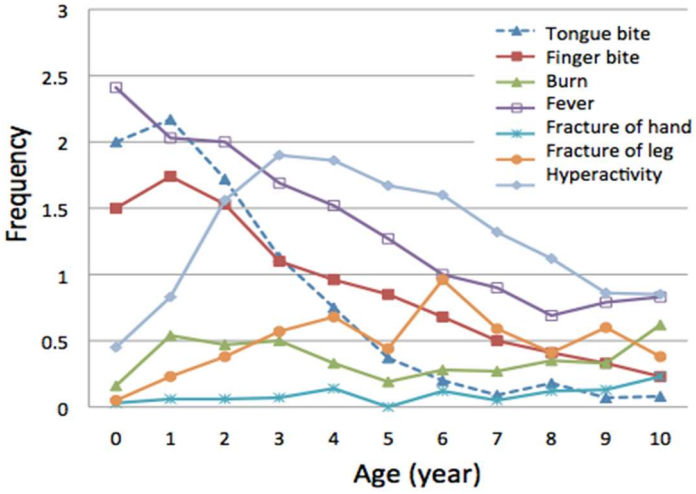
Fractures of the leg begin to appear when the child is able to walk, peaking at 3 to 4 years of age. Fractures also tend to increase when children are adjusting to new environment, such as at the time of elementary school admission. In essence, intellectual development is achieved through daily life and experiences, so living a restricted life for fear of fracture can inhibit intellectual activity. It is difficult but important to prevent bone fractures and still allow children to have rich experiences.

3) Hyperactivity

Hyperactivity can also be seen from the time a child becomes stable in walking. In infancy, they are unable to sit still and move around a lot, which causes a lot of stress for parents because they cannot take their eyes off their children even for a moment. After school, they are unable to maintain attention and may panic when behavior is restricted, which causes problems in educational guidance and support. However, we find that hyperactivity calms down with age.

All of the behaviors of concern are concentrated between the ages of 1 and 4 years, but they do not last forever and gradually decrease as interests and behavioral range expand and comprehension develops.

Figure 2-10-1 Main symptoms of patients with CIPA according to age



3. Characteristics of developmental disorders

Patients with CIPA can also have developmental characteristics that cannot be explained by simple delays in intelligence. The characteristics of autism spectrum disorder, such as obsessive behavior, hypersensitivity, social communication problems, hyperactivity, and impulsivity, are observed from early childhood. There is a wide range of symptoms, with patients with a high autism score to those with a low autism score but with other communication problems.

Particularly in early childhood, there are many patients who are hypersensitive to sounds, textures, smells, tastes, etc. Furthermore, when they have obsessive behaviors, they often feel uncomfortable in their daily lives, and their frustration at not being able to communicate verbally can lead to problematic behaviors such as self-injury, harming others, and panic. In adulthood, hypersensitivity is also increased when one is not able to do what one wants to do or is under stress. It is necessary to devise countermeasures in daily life and reduce stress.

In addition, hyperactivity and impulsivity can lead to dangerous situations. Problems arising from developmental characteristics become apparent when children enter a group, even if they are not so obvious in the home. If it is not understood that there are various developmental characteristics behind their behavior, everything the child does tends to be seen as problematic behavior, which can cause group maladjustment.

It is necessary to understand that the problems these patients have can easily lead to learning difficulties and interpersonal problems. In order to deal with this, it is

necessary to adjust the environment to reduce stimulation, and to devise ways to improve learning and daily life, with medication also being an option.

As the patients get older, hyperactivity reduces, but hypersensitivity and obsessiveness remain, and communication problems are particularly noticeable. They have some weakness of interpersonal relationships with regard to keeping an appropriate distance from others and reading between the lines. They often cannot build good relationships and lose confidence. If they seem to be having interpersonal problems, they may need to seek counseling and communication skill training. In addition to environmental adjustments and considerations for pain and body temperature, support and responses that support the characteristics of developmental disabilities are required when providing medical and educational guidance.

4) Psychological care

Patients with CIPA are forced to live with a variety of restrictions from infancy. In order to prevent problems such as bone fractures and burns, physical and lifestyle restrictions are naturally necessary, but this causes a great deal of stress for the child. If they are not able to do what they want to do, or if they are not understood, as mentioned above, they become more irritable, which often manifests itself in panic and anger. Even in such cases, it is advisable to understand their feelings and respond in a way that does not dampen their motivation.

In adolescence as well as later, they often become frustrated because they cannot do what they want to do, even if they have their own goals. The balance between the mind and the body is not well maintained, in what is known as the "rebellious phase," and they begin to resist interference from their parents. In addition, if they have communication difficulties due to their developmental disabilities, they will not be able to express their feelings and thoughts in words to others. It is necessary to make them realize what they can do and what they cannot do, and that just getting frustrated and hitting out at those around them will not solve anything. In order to do this, they need an environment where they can express their feelings and talk to people, such as in schools, day services, medical institutions, and counseling organizations. It is important for them to gain the experience that others will understand them if they express their feelings, not only through their parents, but also through relationships with other supporters, which will lead to self-understanding.

Many patients with CIPA have a cheerful and friendly personality, but on the other hand, they are sensitive and delicate. They are sensitive to their parents' reactions and attitudes, as one patient put it, "My parents are worried about my disease, not me." Some patients suppress their feelings because they do not want to bother their parents or others around them. For this reason, it is important to provide adequate psychological care.

We would like to recommend that both patients and parents make good use of counseling and medical institutions to avoid stress. Problems that patients and parents have change with age, but there is no end to them. In the future, it is hoped that a system will be established to provide mental health care for both patients and parents.

5) Characteristics of congenital insensitivity to pain without anhidrosis (CIP)

The characteristics of CIP should also be briefly described. When examining the intellectual development in CIP, WAIS-III test results indicate a lack of balance in cognitive development, especially low work speed, but they have no intellectual delay; that is, intelligence is at the normal to average level. Thus, in terms of intelligence, there is a clear difference from CIPA, but although there are no intellectual problems, CIP patients sometimes have the same characteristics of autism spectrum disorder as those with CIPA. They are characterized by obsessions, a peculiar way of perceiving things, roundabout expression, difficulty to keep an appropriate distance and to read between the lines, and to often change their mind.

Chapter 3: Social Participation and Welfare

3-1. Social participation before and after school

1. Preliminary considerations

1) Choosing group childcare

Families of infants with congenital anhidrosis worry about whether or not to enroll their children in group childcare. There are many concerns, such as "My child could get seriously injured or break a bone," "Will my child be able to regulate his or her body temperature during the care?", and "Will my child be able to play well with his or her friends?"

It is well known that children with disabilities have the same rights as everyone else and are guaranteed equal opportunities to participate in society. The concept of integrated childcare and education, in which children with disabilities receive care and education together with normal children, is becoming more and more popular, but there are many aspects that are difficult to accept in the real-world setting.

It goes without saying that engaging with others in a group enhances a child's social skills and allows them to learn about human relationships and various rules through their interactions with other children. In addition, play is not only fun, but also stimulates sensory-motor functions and promotes development. Thus, group childcare is an opportunity to promote a child's overall development. Although there are concerns and worries, it is important for medical professionals to support children in making appropriate choices, believing in their potential for growth and development.

2) Choosing a preschool and considering the facilities

(1) Nursery schools and kindergartens

If the family visits a preschool and likes its policies and the attitude of the staff, they should first ask about enrollment. There may be cases where a child is refused admission due to illness, or where it is difficult to find a preschool that will accept the child immediately. The school may also be cautious initially, so the family will need to persevere in trying to get them to understand. Recently, more and more nurseries are accepting children with disabilities and assigning medical care and nurses accordingly.

The standards vary from municipality to municipality and from school to school, but nursery schools sometimes assign additional nurses who have a medical care certificate to take care of children with disabilities.

Before admitting a child into a nursery school, the first step is to have the staff of the school understand the child better. To do this, it is easy to understand the disease and disability by using the books, DVDs, and websites published by the Association for CIPA. Next, it is necessary to tell them exactly what assistance is required for the child. It is also effective to have a senior member of the CIPA group sit in on the meeting and explain, based on actual experience, the precautions and benefits received in group childcare.

In some cases, it may be necessary to consider the facilities provided in order to ensure safe group childcare. Air conditioners are necessary to regulate body temperature in both summer and winter, showers to cool the body in case body temperature rises, refrigerators to store cold drinks, and barrier-free buildings and pathways for wheelchair access. In order to have the required facilities in place by the time the child begins attending the school, it is necessary to take action as soon as possible.

(2) Day-care support services for children with disabilities

In addition to kindergartens and nursery schools, there are also daycare facilities for children with disabilities. For children under 6 years of age, there are so-called welfare-type child development support centers (which provide support such as instruction in basic daily activities, imparting knowledge and skills, and training for adapting to group life) and medical-type child development support centers (which are intended for children with functional disabilities of the upper limbs, lower limbs, or trunk, and the support includes treatment in addition to those included in welfare-type support).

In the case of day-care support services for children with disabilities, it is desirable for the child to receive treatment and education as early as possible, since treatment and education can be expected to be tailored to the child's disability and development more easily.

(3) Preparing for pre-school counseling

When a child starts elementary school, pre-school counseling (school guidance) in the community is provided. The purpose of pre-school counseling is to ensure equal educational opportunities by providing the most appropriate educational opportunities

for each child. Depending on the level of disability and development of the child, a school will be chosen based on the pattern of regular classes, special needs classes, and special needs schools.

Families need to think carefully about what kind of education they want their children to receive, and communicate their ideas at the preschool consultation. If it is difficult to make a decision, it is also a good idea to ask the opinions of your doctor, a clinical psychologist who provides developmental counseling, or a physical or occupational therapist who understands your child's disability. Once the family has decided on the school they would like to enroll their child in, they should visit the school and assess the school's educational policy and facilities (see above for details on nursery schools and kindergartens).

Although it is called integrated education, it may unfortunately be difficult to meet all the family's wishes regarding the acceptance of children with CIPA in regular classes. Teachers will also feel a little confused when encountering a child with the disease for the first time. It will be necessary to set up discussions with the school board and patiently explain the situation to them so that they can prepare the educational environment. If there is no understanding of the disease and only a standard response is given, it may be necessary to have a medical professional present at the discussion. Families of children with CIPA who have experience with nursery schools and school teachers should be invited to participate in the discussion, so that the anxiety of school teachers can be alleviated.

2. Coordination for an enjoyable group life

1) Dealing with the staff of the day-care facility and the teachers at the school and adjusting the environment

It would be good to have regular discussions with the staff and teachers once the child is admitted to the school. As children actually attend preschool or school, they will grow and develop, and there may be situations where they would like the staff or teachers to change their attitude. It is important to maintain close communication with the staff at the preschool or school, and to build a relationship with them in which you can express your opinions and wishes. If necessary, it is also possible to have a specialist give an explanation and help the child understand the disease and what to do in different situations in daily life.

In schools, there may be teachers with the role of "special needs education coordinators" who serve as key persons in promoting special needs education, act as consultants to home-room teachers, and coordinate the creation of support systems. For children with special needs, the coordinator will draw up an individual support plan that meets the needs of the child, so that they can discuss any concerns with the home-room teacher.

The first thing that needs to be done at the preschool or school is to have the living environment prepared. Air conditioning is a necessity to regulate body temperature. Staff and teachers should learn how to immediately cool the body externally by using frozen or refrigerated food and how to cool the body from the inside by administering water when the body temperature becomes high due to heat retention caused by play or exercise. It is also necessary to ensure that children have free access to water at all times. It would be helpful to have the same cooling products that are used at home available at preschools and schools.

It is important to understand that these children are not only prone to fractures and trauma, but also lack pain sensation, making it difficult for staff to detect them. Make sure that they are carefully observed so that they do not jump from heights or hold unnatural postures. It would be helpful to let the staff and teachers know how much exercise is possible so that they can have a rough idea.

We also need to be careful about burns. Although it is unlikely that children will be handling fire on their way to preschool or school, it is possible for them to get oral burns from hot, freshly fried foods such as croquettes, so we need to be careful when they eat. By the time their teeth erupt, they often touch their teeth and self-extract, or bite their tongues, so care needs to be taken in this regard as well.

It is necessary for the safety and comfort of the children to inform the staff and teachers about these things that they are aware of them and can prepare the environment accordingly. It will be easier to cope with the situation if the staff/teachers are given specific information about the measures and methods that are actually taken at home. Schools often also employ nurses to manage physical conditions and wound care. It is necessary to maintain good communication with the school nurse in order to manage the health of the child.

Children with CIPA do not understand pain, so it is difficult for them to protect themselves. It is the role of the adults around them to help them avoid danger, but if we

forbid them to do everything, not only will the meaning of group childcare be lost, but the children may feel angry and stressed. It is a good idea to explain to the staff/teacher to tell the child that "it is dangerous" and to ask them to stop their behavior when it is really dangerous. In the beginning, children may be required to be accompanied by their mothers when they go to preschool or school. Once both the child and the staff have become accustomed to each other, the number of times the mother accompanies the child to school should be gradually reduced, so that the mother can have respite and the child can be independent.

2) Dealing with preschoolers and classmates

It is important to inform them beforehand that the child has an illness and that we would like their cooperation in order to create an environment where the child can easily build a relationship with them.

After play or exercise, in case of heat retension or fever due to anhidrosis, tell them to cool down and to drink cold drinks outside of the allotted time. It is important to explain in a simple and understandable way that this is not a special treatment, but a necessity to maintain good health. It should also be explained that painlessness makes them prone to sustaining fractures and wounds, so they cannot jump, which everyone else is fine with, and that even if they are able to walk, they may use a wheelchair to prevent disability, and that this means more quiet play. A picture storyboard made by the "Society for Congenital Insensitivity to Pain with Anhidrosis-Tomorrow" can be used to help them understand.

Since they do not understand pain, they may not be able to control the amount of force they use when playing with friends. It is very important to teach preschoolers and classmates that if someone does something painful to them, they should say it hurts and ask them to stop their behavior, etc. to maintain good relationships among children. Even if they do not feel pain, they can understand that they should not do anything that others do not like or are sad about. It is important for the adults around them (staff and teachers) to guide them so that they can learn well what not to do to other preschoolers and classmates so that friendships are not broken in play situations. Play can be a place where children with CIPA can learn to understand the pain of their friends. It is also an opportunity for preschoolers and classmates to understand children with the disease and learn about relationships.

3) Responding to the parents of preschoolers and classmates

It is necessary to inform the parents of preschoolers and classmates in advance about the nature of CIPA and what they need to do to help, so that they can also stop them when they are about to engage in dangerous behavior. It is also important to have the parents inform their children about the disease and encourage them to build friendships with their children, so that they will be aware of the importance of watching over and nurturing their children together with the staff.

3) Consideration for advancement to higher education

From elementary school to junior high school to high school, it is necessary to review and reconsider several aspects at the time of advancement to the next level or higher education, taking into consideration the child's health, growth, and development, as well as the child's relationship with friends and teachers.

References

1. Yoshimi K, Tanaka C, et al: Actual conditions of daily life in congenital insensitivity to pain with anhidrosis. (In Japanese) Occupational Therapy 21: 45-54, 2002

2. Iino J.: Education. Okada Y. (supervisor): New edition of the manual for treatment and education of severe mental and physical disabilities: pp 294-302, Medical and Dental Publishers, Tokyo, 2015

3. Tamai M and Teramoto A: Integrated childcare and education. Oikawa I (supervisor): Nursing Care of Children with Developmental Disabilities: pp 351-353, Medical Friend, Tokyo, 2005

4. Ministry of Health, Labour and Welfare: System of Support for Children with Disabilities: Integration of Facilities and Services for Children with Disabilities under the 2012 Amendment to the Child Welfare Law: http://www.mhlw.go.jp/file/06-Seisakujouhou-12200000- Shakaiengok yokushougaihokenfukushibu/0000117930.pdf (accessed 2018.6.30)

5. Ministry of Education, Culture, Sports, Science and Technology, Promotion of Special Needs Education (Notice): http://www.mext.go.jp/ b_menu/hakusho/nc/07050101.htm (accessed 2018.6.30)

3-2 Social Participation after Graduation and Family Support

1. Support for flexible social participation

1) Employment

After graduating from school, one of the major goals is to find a job. In order to continue working for a long time, it is good to be able to make choices based on one's interests. Employment is not only for earning wages, but also for adjusting the rhythm of life. It also leads to independence, making friends and expanding human relationships, and establishing one's own existence in the family and society.

There are various forms of employment, such as general employment with general companies and civil servants, self-employment, protective employment where protective measures are taken, and welfare employment (employment transition support under the Services and Supports for Persons with Disabilities Act: employment-type support for continuous employment, non-employment-type support for continuous employment). In addition, it would be good to be able to obtain and provide information on welfare systems such as consultation, guidance, training, employment assistance, and loans for funds necessary for the livelihood of people with disabilities in order to promote their employment.

Nevertheless, the current situation is that protective employment and welfare employment, which are easy for people with disabilities to work in, do not completely meet their needs in terms of quality and quantity. Small-scale workplaces and other facilities have been increasing recently, but it is very difficult to find a place that can fully respond to individual physical conditions, interests, and needs.

Since the symptoms and mental development of CIPA vary greatly from person to person, it is necessary to be flexible and visit several companies and offices, taking into consideration the condition and interests of the individual, and to patiently talk with employers to gain their understanding and support.

For employment, it is necessary for room temperature to be controlled, to avoid working in the same posture for a long time so as to avoid exerting force on one part of the body, to work in a wheelchair, secure a room where one can take a break to regulate body temperature, and adjust human relationships. Since it would be unreasonable to use the same room temperature as everyone else, it is necessary to consider the location

of air-conditioning and heating systems, as well as the use of cooling agents and fans. In particular, it is necessary to take extra precautions against the heat when commuting or working in the summer. In some cases, it may be necessary to take a long summer vacation or leave of absence. The same posture or movement for a long time increases the burden on the joints, so consideration is needed. It is also necessary to create an environment in which people around them understand and take care of the fact that they do not feel pain and are therefore unaware of it. Specifically, it is important to obtain information from the individual, their family, or the school from which they graduated, and to respond to this information.

It is necessary to coordinate with the workplace, as it may be necessary to take leave due to medical examinations or changes in physical condition. It is necessary to create an environment where the patient can express in words what he or she cannot do and what is necessary to protect the body, so that the people around him or her can understand, and so that these considerations will not be misunderstood as special treatment.

Since the number of patients with CIPA is small, it is probably the first disease that the recipient encounters when entering a new group. It is necessary to create an image of support by using books and DVDs about CIPA.

2) Use of day services

Even in cases where employment is not suitable, it is important to secure a place for daytime activities by using a day service such as a community activity home or a workplace for the support of independence for persons with disabilities. It is also necessary to support them to increase their number of friends and understanding people in the community by using social activities such as those in local clubs, sports centers, and NPOs. When using a combination of several facilities and activities on a weekly or monthly basis, consideration should be given to ensure that it is not too much for the body and mind.

However, there are times when a person may not be able to continue working as they wish due to reasons such as unsuitable work, problems in interpersonal relationships, or unstable physical condition. The people around them need to watch over them and support them to continue their participation in society without undue strain, without rushing, and while choosing a place that suits them.

2. Independence

People tend to think that "independent living" means living alone and making a living independently. However, there are various options such as living with family, living together, or living in an institution. Furthermore, if we think of independence as being able to live independently with the cooperation of many people, it is important to consider how many people they are connected to in society and how they can expand their circle of support.

It is important to provide support to expand the number of people who understand the disease and cooperate with them in the community and society so that they can actively use social services and live their own lives while also participating in society.

3. Family members are also targets of support

Since CIPA is a rare and intractable disease and the number of patients is extremely small, it is difficult to obtain information on the disease, treatment, rehabilitation, education, and welfare, and there are few professionals with experience in dealing with the disease. In addition, CIPA shows a wide variety of symptoms, which requires repeated visits to many departments related to various disciplines such as orthopedics, rehabilitation, dentistry, infectious diseases, dermatology, and anesthesiology, as well as pediatrics.

From a parent's point of view, they have to face their child being diagnosed with an intractable disease that they have never heard of, continuous tests and treatments, and the burden of the anxiety of not knowing what will happen to their child and of accompanying them. Wherever parents go—to hospitals, rehabilitation centers, kindergartens, schools, neighborhoods—they are always having it pointed out their child is different from the "norm". As a result, parents inevitably focus only on the disability, and feel resentful, pitying, or burdened by the child who is not "normal". It is common for parents of children with any kind of disability or illness to find the start of child-rearing, which was supposed to be fun, to be very painful.

Family members should be instructed to do their best by medical personnel and school teachers, encouraged by relatives to do their best, and respected by friends for their efforts. In this way, family members are naturally expected to be hardworking people who support and care for the patient (the family resource model). However, "do

your best" as if it is someone else's responsibility can push the family into a corner, saying, "I'm working hard 24 hours a day, 365 days a year, how can I work any harder ?" Sometimes professionals are actually pushing them into blaming themselves for not doing their best.

Sometimes families need to be considered as a target for support. The message, "Mom, you don't have to work so hard, just take a break," will help the family and encourage them to try again. It is necessary to support a partnership of "let's work together" rather than "good luck".

4. Support for CIPA groups and social connections.

It is important to support families to connect to the outside world so that they are not alone. Access to the "Society for Congenital Insensitivity to Pain with Anhidrosis-Tomorrow," should be the first step. The "Society for Congenital Insensitivity to Pain with Anhidrosis-Tomorrow," is an association of families of children with CIPA, as well as professionals, and it disseminates a variety of information, including information on medical care, education, and welfare services. It also uses its network to use the experiences of patients' families to their daily lives and prevention. In a different way from professional support, the family network plays a major role as peer support for families to support and nurture each other.

It is also important to help families change their perception of holding on to the idea that "no one understands me," and to "go out into the streets and get people to understand me" to increase the number of people who understand and support them. While supporting the socialization of families, professionals and supporters should also go to kindergartens, nursery schools, schools, and society to increase the number of people in the community who understand these diseases.

5. Respite to take a breather.

Respite refers to assistance that allows families caring for children (or persons) with disabilities to be temporarily released from caring for them and to take a breather.

As mentioned earlier, families caring for children with disabilities are often occupied with caring for them 24 hours a day, 365 days a year, and the continuous tension and anxiety often leads to chronic fatigue and health problems. It is important for family members to be healthy, maintain a normal rhythm of life, and have a normal quality of

life. Sometimes, it is necessary to take a breather by entrusting them to a day care service or short stay.

However, the reality is that respite services are extremely inadequate to meet the needs and are difficult to use. I hope that each and every supporter who understands this and accepts children on a daily basis at nursery schools, kindergartens, schools, workplaces, etc. will demonstrate the spirit of "mom, take a breather".

Entrusting the child to others will increase the number of understanding people in the community and promote the child's independence. It is important to create such a supportive environment.

References

1. Yoshimi K, Tanaka C, et al: Actual conditions of daily life in congenital insensitivity to pain with anhidrosis. (In Japanese) Occupational Therapy 21: 45-54, 2002.
2. Tanaka, C., Hamabe, F., et al: Medical and educational consultation by family members and professionals using a website for a rare intractable disease (congenital insensitivity to pain with anhidrosis). Journal of Child Health 69: 496-502, 2010
3. Tanaka C, Oda S, et al: Congenital insensitivity to pain with anhidrosis: Our care guide. Tachikawa Printing, 2010

3-3 Welfare Services and Information Resources

1. Welfare services

The following is a list of typical welfare services for congenital insensitivity to pain with anhidrosis (CIPA) that may be available in Japan.

1) Specific pediatric chronic diseases

With the revision of the Child Welfare Law in 2015, the previous system for pediatric chronic specific diseases became the Pediatric Chronic Specific Disease Countermeasures, and nearly 800 diseases are now recognized as eligible. CIPA is covered as one of the congenital neuropathies in the group of neuromuscular diseases, corresponding to hereditary sensory and autonomic neuropathies types 4 and 5. In addition to subsidizing a portion of out-of-pocket medical expenses, children with specific chronic diseases are eligible to receive benefits for daily use equipment (including wheelchairs and cool vests). New applications are accepted until the age of 18 years, and continuing applications are accepted until the age of 20. Patients and their family members must apply to the municipal office along with a medical opinion, which must be renewed every year. This system also has a research aspect, and the registered information is used for disease research.

2) Designated intractable diseases

In 2015, the "Law Concerning Medical Care for Patients with Intractable Diseases" (Intractable Disease Law) was enacted, and in July of the same year, CIPA was designated as an intractable disease. Hereditary sensory and autonomic neuropathy types 4 and 5 correspond to this disease. For some designated intractable diseases, only those who meet certain severity criteria are eligible for medical subsidies, but in the case of CIPA, the subsidies are available regardless of the severity of the disease. New diagnoses can only be made by "designated physicians for intractable diseases," but annual renewals can also be made by "designated physicians for co-operative intractable

diseases". Twenty percent of the medical expenses are borne by the patient, but the maximum amount of co-payment depends on the income. This system also has a research aspect, and the registered information is used for disease research.

3) Disability certificates

If you have a physical disability such as a Charcot joint, you may be eligible for the Physical Disability Certificate. If you have an intellectual disability, you may be eligible for the Rehabilitation (Ryoiku) Certificate, and if you have a developmental disorder, you may be eligible for the Mental Disability Certificate. To obtain a certificate, you can apply to the city office with a written opinion from a designated doctor, or go to a designated health and welfare center in your area for a decision. Using the disability certificate, you can receive various tax exemptions, medical fee exemptions, discounts on various types of transportation, and exemptions on the use of public facilities. If you hold a physical disability certificate, you can receive benefits for orthotic devices based on the Comprehensive Support Law for Persons with Disabilities.

4) Medical care for independence support

This is a generic term for Inclusion Medical Care, Rehabilitation Medical Care, and Outpatient Mental Health Care. Of these, Inclusion Medical Care is for individuals with physical disabilities who are below the age of 18 and undergo surgery, etc., and whose disability is expected to improve as a result. As a general rule, 10% of the cost of the treatment is borne by the patient, but the maximum amount per month depends on the income. Rehabilitation Medical Care is for patients 18 years of age or older who hold the Physical Disability Certificate and who receive medical treatment that is expected to have a definite effect on their disability.

5) Special child support allowance

This allowance is provided by the government to caregivers (guardians) for the

purpose of promoting the welfare of mentally- or physically-handicapped children under the age of 20 years. There are two allowance levels according to the degree of disability: Level 1 (severe) and Level 2 (moderate). Level 1 allowance is generally equivalent to Level 1 or 2 of the Physical Disability Certificate or Grade A of the Rehabilitation Certificate, and Level 2 allowance is generally equivalent to Level 3 or 4 of the Physical Disability Certificate or Grade B of the Rehabilitation Certificate.

6) Welfare Allowance for Disabled Children and Allowance for Specially Handicapped Persons

The welfare allowance for handicapped children is paid to handicapped children under 20 years of age who "have severe mental or physical disabilities," and the special handicapped allowance is paid to adults who "have extremely severe mental or physical disabilities". While the special child support allowance is paid to the caregiver, these benefits are paid to the person with disabilities themselves.

2. Information resources

With the advancement of the Internet, it has become easier to gather information related to diseases. Here are some sites related to CIPA.

1) NPO Association for CIPA "Tomorrow": www.tomorrow.or.jp

This is an association mainly for families of patients with CIPA. Information for patients with congenital insensitivity to pain (CIP) is also available.

2) GeneReviews Japan: grj.umin.jp

This is the Japanese version of GeneReviews, an U.S. genetic disease information site for medical staff. CIPA is registered as hereditary sensory autonomic neuropathy type 4.

3) Intractable Disease Information Center: www.nanbyou.or.jp

This is the website of the Ministry of Health, Labour and Welfare (MHLW) regarding measures against intractable diseases, and provides information related to the research on CIPA conducted from FY2009 to FY2011 in the research promotion field of the Research Project for Overcoming Intractable Diseases.

(4) Revised version of CIPA - For the understanding of intractable diseases and life support:
http://www.mhlw.go.jp/bunya/shougaihoken/cyousajigyou/dl/seikabutsu1-2-02.pdf

The booklet prepared by the Ministry of Health, Labour and Welfare's Project for the Promotion of Comprehensive Welfare for Persons with Disabilities is available for viewing.