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Congenital Insensitivity to Pain with Anhidrosis : A Case Report

Congenital insensitivity to pain with anhidrosis (CIPA) is a very rare genetic disorder of the peripheral nervous system characterized by recurrent episodes of unexplained fever, generalized anhidrosis, insensitivity to pain and temperature, and accompanied by self-mutilating behavior and mental retardation. We report on a 16 month-old boy with CIPA who exhibited these characteristic clinical features. A sural nerve biopsy revealed markedly reduced numbers of unmyelinated and small myelinated fibers, consistent with the characteristic features of CIPA.

Key Words: *Pain insensitivity, congenital; Hypohidrosis; Sural nerve*

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INTRODUCTION

Congenital insensitivity to pain with anhidrosis (CIPA), or hereditary sensory and autonomic neuropathy type IV, is an exceedingly rare clinical disorder characterized by recurrent episodes of unexplained fever, absence of reaction to noxious stimuli with self-mutilation behavior, inability to sweat leading to defective thermoregulation, and mental retardation since infancy. The pathophysiology has not been clearly elucidated, but this syndrome seems to be transmitted through an autosomal recessive inheritance. Light microscopy does not reveal any consistent abnormality, but ultrastructural analyses of peripheral nerves have frequently demonstrated a characteristic loss of unmyelinated and small myelinated fibers (1-3).

Since Swanson's first report of CIPA in male siblings (4), only thirty or more cases have been reported in the literature (2, 3). We report on a case of a 16 month-old Korean boy with CIPA who exhibited the characteristic clinical features and was confirmed by neuropathologic findings.

CASE REPORT

A 16 month-old male child was referred to our hospital because of a recurrent high fever without sweating and failure to thrive. The patient was born after a normal pregnancy and had a normal delivery. Birth weight was 2.9 kg. He was the only child of healthy parents of a non-consanguineous marriage. There was no family history of neurologic or metabolic diseases.

From the first week of life, he experienced recurrent episodes of unexplained fever. He was always dry and hot. At three months of age, he was admitted to a local hospital for evaluation of high fever, but the cause of the fever was not found. At five months of age, he experienced high fever and generalized tonic-clonic seizure, and was treated with phenobarbital at another hospital. At that time, a full sepsis work-up showed no positive results. A computed tomography (CT) scan and magnetic resonance imaging (MRI) of the brain, electroencephalography (EEG), and 2D-echocardiography were normal for his age. Over the next 10 months, he had frequent bouts of fever, up to 41℃.

Absence of sweating with dry warm skin was consistently noted during the febrile period. During high fever, he was peevish and cried loudly with appropriate lacrimation. When he was cooled with a cold wet towel, the fever subsided rapidly and he calmed down. His body temperature was influenced by room temperature; when he was exposed to the sun or placed in a hot environment, he developed a high fever. After his teeth started to grow in, he began to chew his fingers and bit off the

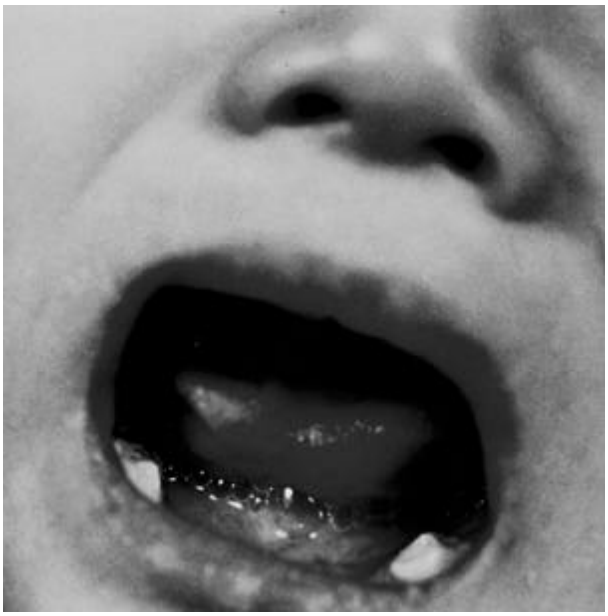

Fig. 1. Patient's oral cavity shows self-mutilated lateral tip of the tongue caused by his own teeth. Lower anterior teeth were extracted by himself.

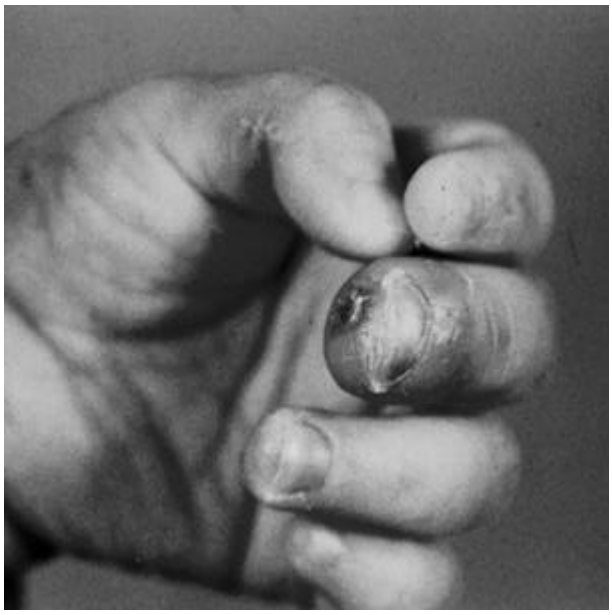

Fig. 2. Scars from burns on the tip of the left middle finger, and self-mutilated interphalangeal joints of the left thumb and the index finger caused by patient's teeth.

tip of his tongue. At that time, his parents noticed that he was insensitive to painful stimuli, moreover, he exhibited a failure to thrive for his age.

On admission, he was poorly developed and thin, his anterior teeth were missing, and the right lateral tip of his tongue had been bitten off (Fig. 1). There were scars from a burn on the tip of his left middle finger, and he had self-mutilated interphalangeal joints on the left thumb and index finger (Fig. 2). His body temperature was 38.7℃, but his skin was dry and warm. His weight was 7.7 kg, height, 71 cm, and head circumference, 42.4 cm below the third percentile. Neurologic examination revealed mild hypotonia, depressed deep tendon reflexes, and a lack of reaction to painful stimuli such as pinpricks. Temperature sensation was also absent. However he showed normal tactile sensation, lacrimation, salivation, and corneal reflex. He could stand with support, and communicated by babbling.

The peripheral white blood cell count was 12.5×10^9/L, with a normal differential cell count, and hemoglobin was 7.7 g/dL. Serum iron was 21 μg/dL, total iron binding capacity, 445 μg/dL, and serum ferritin, 10.9 ng/mL. His failure to thrive and iron deficiency anemia were thought to be related to decreased oral intake. Other laboratory examinations, including serum electrolytes, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, renal function values, creatine kinase, uric acid, and urinalysis, were normal. Routine examination of cerebrospinal fluid (CSF) was normal. Electromyography and motor and sensory nerve conduction velocities were within normal range. Chromosome analysis, EEG, chest X-ray, and brain MRI were normal. Intradermal injection of 0.05 mL 1:1,000 histamine solution gave rise to the expected wheal without axon flare. Pilocarpine iontophoresis did not produce sweat. Histologic features of sweat glands in a skin biopsy from the left palm were normal. Electron microscopic examination of the sural

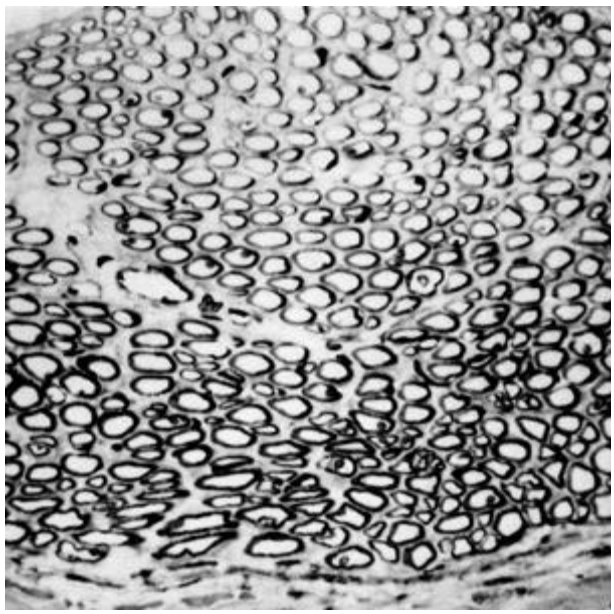

Fig. 3. Cross section of the sural nerve is mainly composed of large myelinated fibers and only a few small myelinated fibers (Toluidine blue stain, ×400).

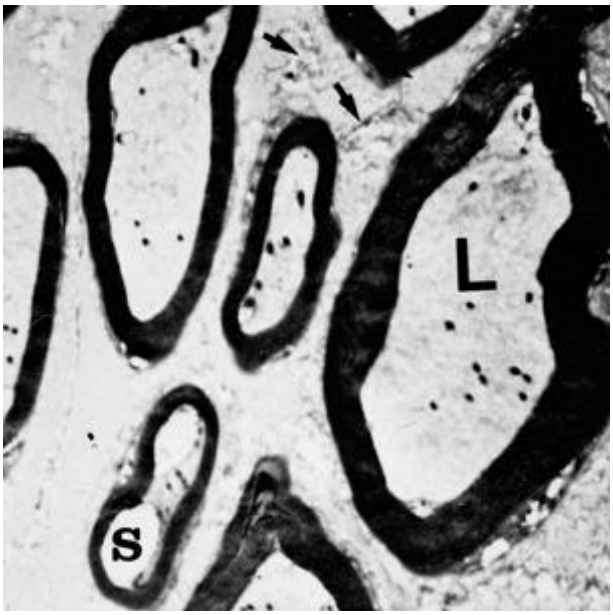

Fig. 4. Electron microscopy demonstrates extremely atrophic unmyelinated fibers (arrows) surrounded by large (L) and small (S) myelinated fibers (Lead citrate-uranyl acetate, ×2,000).

nerve revealed a marked reduction in both the number of unmyelinated and small myelinated fibers. Still the density of the large myelinated fibers was normal (Fig. 3, 4). These results were diagnostic of CIPA. His general condition improved with supportive treatment. Before his discharge, his parents were instructed on how to take precautions against accidental injuries to the child and how to prevent self-mutilation.

DISCUSSION

CIPA is a very rare hereditary disorder caused by a lack of maturation of small myelinated and unmyelinated fibers of the peripheral nerves, which convey senses of pain and temperature. Dyck (1) recognized five types of hereditary sensory and autonomic neuropathies (HSAN) according to the type of hereditary transmission, natural history, clinical manifestations, and neuropathological findings. CIPA corresponds to the fourth of the five types. Swanson first identified this peculiar disorder in 1963 based on his observation of two brothers with congenital anesthesia to deep pain and anhidrosis (4). Only thirty-three cases have been reported in the literature (2, 3). The available data suggest an autosomal recessive mode of transmission (1-3, 5, 6), but there is a possibility of sporadic occurrence without family history like our patient.

CIPA shows a stereotyped clinical picture. Generally, the patients have repeated episodes of unexplained fever, anhidrosis, self-mutilation, impaired pain and temperature sense, and mental retardation since early infancy (1-3). Insensitivity to pain and temperature explains their self-mutilating behavior or scars from getting burned. In most cases, these children begin to bite their tongue or finger after their teeth come out. As they grow older, accidental injuries such as burns or falls may lead to multiple scars, bone or joint fractures, osteomyelitis, and Charcot joints (2, 7-9). Anhidrosis may be attributed to recurrent high fever or defective thermoregulation. Life span is variable. All reported cases concern infants, children, and adolescents, the youngest being two months old (10) and the oldest being 17 years old (11). Almost 20% of the patients die from hyperpyrexia within the first three years of life. Most patients are mentally retarded with IQs varying from 41 to 78, the majority being in the 60s (2), but the cause has not been defined. On the other hand, their sense of touch, lacrimation, and salivation are normal. Neurologic laboratory studies such as EEG and CSF, which were performed in most of the patients, were normal, as were the imaging studies of brain and results of sweat glands histology. Motor and sensory nerve conduction velocities did not reveal abnormalities.

The pathophysiology of this disease has not been clearly elucidated. Almost complete absence of the first-order afferent system, generally considered responsible for pain and temperature sensation, was found at autopsy (6). A genetically determined defect in differentiation and migration of neural crest elements early in embryogenesis has been postulated to be the cause of this disease (6, 12). Rafel et al. studied the cutaneous branch of the radial nerve by electron microscopy and found complete absence of small myelinated fibers (A delta fibers) and unmyelinated fibers (C fibers), these are afferent fibers for the pathway of sensation of pain and temperature (13). Other studies also found these ultrastructural findings (2, 9-11, 14), and results were confirmed by morphometric analysis whenever performed (2, 9-11, 13, 14). Another characteristic feature in CIPA is anhidrosis. Sweating is important to maintain body temperature under hot environmental conditions, especially in humans. Eccrine sweat glands are innervated by sympathetic cholinergic fibers originating from the paravertebral ganglia, although the great majority of the postganglionic sympathetic fibers are adrenergic (15). Sweat glands on skin biopsy in CIPA appeared to be normal, but an ultrasturctural studies of skin biopsies revealed noninnervation of eccrine sweat glands (16). This noninnervation of eccrine sweat glands seems to be the main cause of anhidrosis observed in CIPA.

According to an animal study, nerve growth factor (NGF) induces neurite outgrowth and promotes survival

of embryonic sensory and sympathetic neurons in culture (17). Mice lacking the gene for p75 neurotrophin receptor (18) or TrkA (19), a receptor tyrosine kinase for NGF, shared dramatic phenotypic features of CIPA, including loss of response to painful stimuli. Anatomic changes in the dorsal root ganglion (DRG) neurons and spinal cord in TrkA-deficient animals are similar to those noted in CIPA, including the absence of the small neurons in the DRG, absence of Lissauer's tract, and lack of small myelinated fibers in the dorsal roots and in the spinal tract of the trigeminal nerve (6). Indo et al. considered the human TRKA homologue as a candidate for the CIPA gene. They detected a deletion-, splice- and missence-mutation in the tyrosine kinase domain of TRKA. These findings strongly suggested that defects in TRKA cause CIPA and that the NGF-TRKA system has a crucial role in the development and function of the nociceptive reception as well as establishment of thermal regulation via sweating in humans (20).

Characteristic clinical features and neuropathologic findings of our patient allowed the diagnosis of CIPA. Impaired senses to pain and temperature, absence of sweating, recurrent episodes of unexplained fever, presence of self-mutilated lesions and scars from burns, and delayed development in motor and language were the most prominent findings. Ultrastructural analysis of the sural nerve demonstrated marked reductions in unmyelinated and small myelinated fibers.

When faced with a child presenting with insensitivity to pain, anhidrosis, and self-mutilation, it is necessary to consider three groups of disorders according to the dominant clinical feature in the differential diagnosis. CIPA can be differentiated easily from other types of HSAN as it is the only syndrome accompanied by anhidrosis. Included in the second group are hereditary anhidrotic ectodermal dysplasia and Fabry disease, both X-linked hereditary disorders having complete clinical expression only in males. Hereditary anhidrotic ectodermal dysplasia is characterized by typical faces, with scalp and eyebrow hypotrichosis, and major dental abnormalities, and in contrast to CIPA, it is not accompanied by peripheral neurologic manifestations. Fabry disease is distinguished from CIPA by the presence of paroxysmal pain and paresthesia, fever, transient proteinuria, and cutaneous angiokeratomas. The third group is represented by Lesch-Nyhan syndrome, a X-linked recessive disorder clinically characterized by self-mutilated lesions. Hyperuricemia, which constitutes a major diagnostic criterion for Lesch-Nyhan syndrome, is not found in CIPA.

CIPA, although rare, is a serious illness that may be fatal in the first years of life if hyperpyrexia is not properly corrected (2). Later, osteomyelitis and bone and/or joint deformities demand surgical treatments including amputations (2, 7-9). Severe osteoarticular alterations are one of the most feared complications of CIPA due to the need for early recognition and treatment in patients not experiencing pain. This disease is important to clinicians, since the degree of anhidrosis and self-mutilation influence the prognosis of patients with CIPA (8).

There is no specific treatment for this disease, however, the most important thing of all is accurate diagnosis and special training programs to prevent self-mutilation or accidental injuries. Further investigations are needed to establish the actual etiology and pathophysiology based on the detection of mutations in the TRKA/NGF receptor gene, and to highlight the antenatal diagnosis and proper treatment.

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