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Congenital insensitivity to pain with anhidrosis: case report*

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Abstract

Congenital insensitivity to pain with anhidrosis is a rare disorder. A case of a male patient presenting with loss of pain and temperature sensation, lack of sweat, and mild mental retardation is described. Differential diagnosis with similar pathological conditions is presented. Although 15 similar cases have been reported in the medical literature, this is the first case in which the dental characteristics are described in detail and the dental treatment of patients is discussed.

Congenital insensitivity to pain or congenital indifference to pain is a rare pathological condition in which patients do not respond to painful stimuli. Dearborn (1931) was the first to describe the syndrome. Both the terms "insensitivity to pain" and "indifference to pain" are used in order to define the syndrome. However, we share Kunkle's view (1961) that the term congenital insensitivity to pain is more appropriate, because there is evidence that the afferent part of the neural system fails to transmit the stimuli to the somatesthetic cortex. Affected individuals are not an entirely homogeneous group because the lack of pain has been related to other pathological conditions (the lack of sweat is among them).

Congenital insensitivity to pain with anhidrosis (Gillespie and Perucca 1960), or congenital sensory neuropathy with anhidrosis (Pinsky and Di George 1966), or hereditary sensory neuropathy type IV (Dyck and Ohta 1975), is a well-defined entity among a group of sensory deficiency syndromes. To date, 15 cases have been reported since Gillespie and Perucca (1960) first described the disease. One case, identical or similar to congenital insensitivity to pain with anhidrosis (CIPA), was reported by the name of "generalized anhidrosis" by Nishida et al. (1951). Children with this genetic disease are insensitive to pain and temperature, suffer from anhidrosis, and are mentally retarded. The sensations of pain and temperature are absent over the entire body and there is no reaction even when tubes of boiling water are placed on the skin (Pinsky and Di George 1966), or when subjected to pin prick.

All other sensory modalities are intact. The children do not display any function of the sweat glands, suffer from recurrent episodes of unexplained fever, and even when febrile, do not sweat (Kriel 1982). They are mild to moderately mentally retarded.

At least 3 families with 2 or more affected siblings have been reported, suggesting an autosomal recessive mode of inheritance (Swanson et al. 1965; Pinsky and Di George 1966; Abruzzese et al. 1976).

Due to loss of the sensations of pain and temperature, the children are self-mutilated; they bite themselves and suffer burns and fractures. Fractures are often reduced with difficulty, leading to orthopedic problems and secondary osteomyelitis (Gorlin et al. 1976a).

Tendon reflexes vary from normal to depressed (Matsuo et al. 1981). Blood pressure is normal. A cold pressure test consisting of submersion of the forearm in ice water fails to produce any change in blood pressure or pulse rate (Kriel 1982). Fungiform papillae of the tongue are present (Vassela et al. 1968). Some children have displayed hypotrichosis of the scalp (Brown and Podosin 1966).

Skin biopsy reveals normal ectodermal organelles including sweat glands (Swanson et al. 1965). However, intradermal injection of pilocarpine and neostigmine have been uniformly unsuccessful in inducing local sweating (Pinsky and Di George 1966). Only simultaneous injection of acetylocholine with epinephrine results in some sweat secretion (Vassela et al. 1968). The Schirmer test to measure lacrimation results in a normal response (Swanson 1963). Intradermal injection of histamine phosphate produces the expected wheal but no axon flare (Pinsky and Di George 1966).

The ratio of homovanillic acid to vanillymandellic acid (HMA:VMA) in the urine is elevated similar to that

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in familial dysautonomia (Vassela et al. 1968). Histological examination shows normal peripheral neural networks. However, careful study by electron microscope reveals a marked loss of unmyelinated fibers of the median nerve (Itoh et al. 1986).

Case Report

A 5 1/2-year-old white male of healthy parents presented because he extracted his own primary molars. He was the first child of the family and his younger sister was unaffected. The mother reported no use of medicines or drugs during her normal pregnancy. Labor was delayed for 7 days and the fetus was delivered by aspiration. The child was kept in an oxygen incubator for 1 day due to hypotonia which ended the 20th day. He was admitted to the hospital at 3 months of age due to recurrent episodes of fever of 2 months' duration, each lasting 2 or 3 days. The fever, which varied between 37.5 and 39° C, was the only symptom and could not be attributed to infection. The fever would drop and the child would feel relieved after taking liquids, or having been exposed to the air without clothing. Physical examination revealed normal blood pressure, pulse, and temperature. The circulatory and respiratory systems were normal as was a chest radiograph. Serum electrolyte studies gave the following results: K = 5, 1 mEq/L, Na = 130 mEq/L, CL = 99 mEq/L, CO_2 = 23 mEq/L; Mantoux was negative. There was a lack of the enzyme G6PD. A blood test gave the following results: hemoglobulin = 8, 6 gr%, hematocrit = 27, and white blood count 9800. The differential count demonstrated 28% polymorphonuclear, 70% lymphocytes, and 2% mononuclear cells.

The urinanalysis showed no pathological results. From the very beginning the boy had shown hypoesthesia or complete insensitivity to pain, and he had not been seen sweating. A skin biopsy, which had been taken without local anesthesia, showed the existence of normal sweat glands and generally normal skin organelles.

His first visit to the dental office revealed scar tissue on the tongue and dental mucosa (Fig 1). The parents had observed self-mutilations. The fingers of his hands were short and stubby and the distal phalanges were foreshortened; the skin was dry and scarred (Fig 2).

The patient did not return to the dental office for three years. At this visit the greatest part of his tongue was missing and his buccal mucosa was covered by scar tissue, prohibiting the child from opening his mouth completely. A panoramic radiograph demonstrated an absence of the following teeth: permanent mandibular central incisor (26), mandibular premolars (20, 29, 30), and mandibular molar (19) (Fig 3). The mandibular left first premolar (21) had enamel hypoplasia. Orthodontic

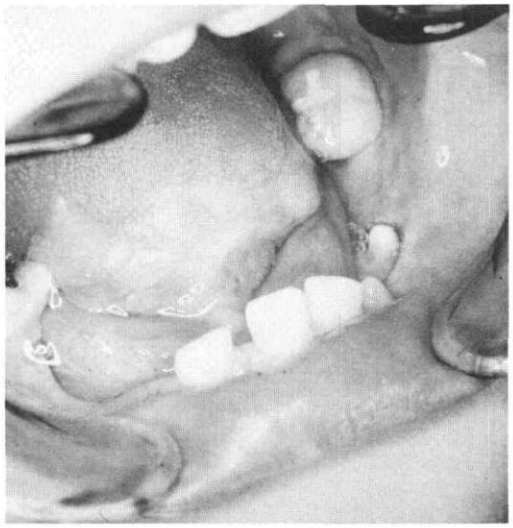

FIG 1. Self-mutilated tongue and the marked scar tissue of the buccal mucosa.

examination revealed that he had a Class II, division I malocclusion. All carious primary and permanent teeth were restored with silver amalgam or stainless steel crown restorations.

During the past 18 months the child suffered a fracture of the right leg which he keeps mutilating. He has been obliged to wear a special orthopedic shoe with metallic arms up to the middle of the calf. The orthopedist also recommended surgery of the left leg because of a previous fracture. Though the child is mentally retarded, he is sociable and his behavior has improved considerably during the last years. He has stopped oral self-mutilation. Even though he is hyperkinetic, he is friendly and cooperative.

Discussion

According to Dyck and Otha (1975) hereditary sensory neuropathy (HSN) is divided into 4 types. Congenital insensitivity to pain (CIP) is added to this group as a similar neuropathy. The clinicopathological characteristics of this case are compared to those of the sensory neuropathies and the CIP (Table).

HSN type I, which is also referred to as hereditary radicular sensory neuropathy (Hoscella and Wire 1962), differs from our case in the following characteristics.

- HSN type I is observed late in childhood, in contrast with our case which was present at birth.
- Children with HSN type I do not show mental retardation and also perspsire normally.
- Finally, the sensory loss is mostly distributed in the acral parts of the body (Table).

HSN type II, also referred to as congenital sensory neuropathy (Wilkenman et al. 1962), differs from our case in the following characteristics.

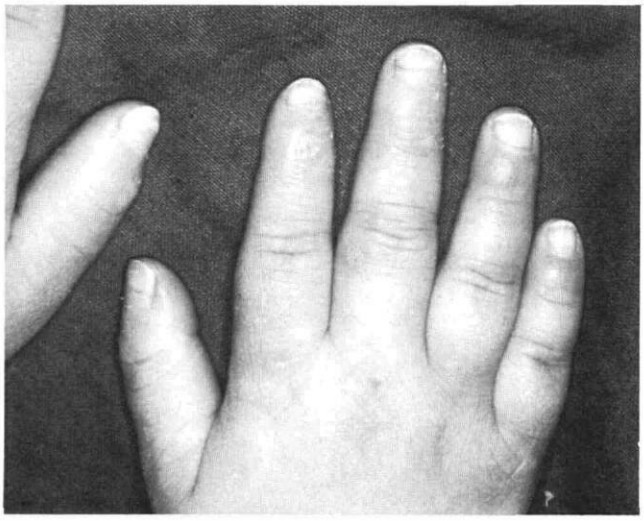

FIG 2. Note the foreshortening of the distal phalanges of the patient's hand.

- Children with HSN type II have normal IQ and do not display any problem with perspiration.
- The sensory loss is distributed distally.
- The peripheral nerves show a marked loss of the myelinated neural fibers and some reduction of unmyelinated fibers (Table).

CIP differs from our case as concerns perspiration, which is normal, and also in the fact that, except from the loss of pain, all other sensory modalities are normal (Thrush 1973). Deep tendon reflexes are intact (Gorlin et al. 1976a). Also, histological studies show the presence of abundant neural fibers (Thrush 1973; Table).

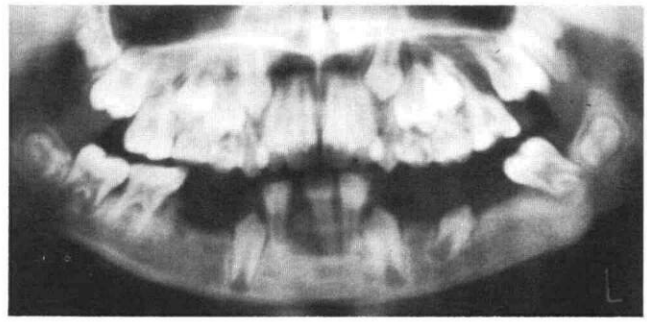

FIG 3. Orthopantomograph of the patient taken at 8 1/2 years of age. Note the missing teeth (20, 21, 25, 28, and 29), the enamel hypoplasia of 22, and the premature eruption of 19.

HSN type III or familial dysautonomia (FD) (Riley and Moore 1966) and HSN type IV or CIPA, share many common characteristics and clinical findings (Gorlin et al. 1976b). Both diseases are autosomal recessive and are present at birth. In both instances the children are mentally retarded. The sensory loss is distributed over the entire body and histological studies show normal sweat glands (Table).

In order to differentiate FD from CIPA, Riley and Moore (1966) proposed the following criteria: absence of the fungiform papillae of the tongue, absence of the corneal reflex and absence or very decreased manifestation of the deep tendon reflexes. Vardy et al. (1979) emphasized the increased perspiration in FD, in con-

TABLE . **Characteristics in This Case and Similar Sensory Neuropathies**

	Hereditary Sensory Neuropathy Type I	*Hereditary Sensory Neuropathy Type II*	*Congenital Insensitivity to Pain*	*Familial Dysautonomia or HSN III*	*Congenital Insensitivity With Anhidrosis*	*Present Case*
Onset	Childhood-Adulthood	Birth	Birth	Birth	Birth	Birth
Heredity	Dominant	Recessive	Recessive	Recessive (Jewish ancestry)	Recessive	
Intelligence	Normal	Normal	Dull → normal	Retarded	Retarded	Retarded
Sweating	Normal	Normal	Normal	Increased	Absent	Absent
Sweat glands	?	?	Normal	Normal	Normal	Normal
Unknown fever	?	?	?	Present	Present	Present
Distribution of sensory loss	Distal	Distal or Generalized	Generalized	Generalized	Generalized	Generalized
(Perception)						
Pain	−	−	−	−	−	−
Tough	−	−	+	+	+	+
Temperature	−	−	+	−/or Present	−	−
(Peripheral nerve)						
Myelinated fibre	Markedly reduced	Almost complete loss	Reduction in the large ones	Loss of the large ones	Reduced small fibre	not done
Unmyelinated fibre	Marked loss	Slightly reduced	Abundant normal	Loss (reduced or normal)	Markedly reduced	not done

trast to the absence of sweating in CIPA. Hyperhidrosis and impaired lacrimation also are mentioned by Pinsky and Di George (1966) and later by Vassela et al. (1968).

In the present case, the neurosurgical diagnostic procedure wasn't necessary due to the safe diagnosis of the disease from the clinicopathological characteristics of CIPA. We avoided surgery in order to protect the patient, since there wouldn't have been a curative benefit.

Since the congenital sensory neuropathies have overlapping clinical signs, it is important to decide whether they originate peripherally or centrally. A simple method is the control of the axon reflexes. It is generally accepted that afferent noxious stimuli cause reflex vasodilatation through the nerve fibers that reach the arterioles (Vassella et al. 1968). Given that the axon reflex to histamine was absent in at least 6 patients (Pinsky and Di George 1966; Vassella et al. 1968; Swanson 1963), there is strong evidence that the damage is localized to the peripheral nervous system.

The anhidrosis supports an involvement of the autonomic nervous system in this pathological condition. The presence of histologically normal sweat glands, in combination with the fact that local, chemical, and electrical stimuli could not induce sweating (whereas simultaneous injection of acetylcholine with epinephrine had some positive effect) could suggest a defeat of the neuro-effector mechanism (Vassela et al. 1968).

The peripheral neural networks seem to be normal. Biopsy of the sural nerve showed the presence of numerous myelinated nerve fibers, most of which were large. Electron microscopic study revealed only 1 or 2 unmyelinated nerve fibers (Matsuo et al. 1981).

Itoh et al. (1986) studied parts of the median nerve of a patient with CIPA, both histologically and with an electron microscope, and compared results with those of similar examination of a normal person. Histologically, the LFB-bodian stain showed many myelinated nerve fibers with normal axon. Electron microscopy showed a clear reduction of the small myelinated fibers, whereas the large ones were almost normal compared to the control group. There were fewer myelinated nerve fibers in the patient compared to the control group. The unmyelinated nerve fibers were drastically reduced (782/mm^2 in contrast to 17,717 mm^2 in the control group), and the median diameter was smaller.

Only one autopsy in a patient with CIPA has been reported by Swanson et al. (1965). There is absence of the Lissauer tract at all levels, absence of the small myelinated nerve fibers in the dorsal roots, and a similar absence of small neurons in the dorsal ganglia. Also, there were many adhesions between the arachnoid and the inner surface of the dura throughout the entire length of the cord. The meninges showed some thickening and a cavitation. Swanson (1965) believes that a defect in the migration and maturation of the neuron precursors is responsible for this pathological entity. There is speculation that CIPA may reflect some defect in the differentiation of the neural crest. Brown and Podosin (1966) summarized the normal differentiation of the neural crest and related the described congenital abnormalities of their case to a common defect in embryogenesis. Vardy et al. (1979) share the same view.

Treatment

The therapy of CIPA is symptomatic. If the disease is diagnosed early in infancy, the parents are aware of the hazards and try to avoid accidents as much as possible. Nevertheless, these children require special dental treatment. In the 1960s dentists used to extract the primary teeth of children with CIPA in order to avoid self-mutilations of the mouth, and suggested placement of full upper and lower dentures (Kriel 1982).

We suggest that the treatment depends on the attitude and the cooperation of the parents.

- If the parents are uncooperative we recommend extraction of the primary teeth with replacement by full upper and lower dentures. These dentures can be removed at night or when the parents are not home, helping the child to avoid further self-mutilation.
- Cooperative parents can teach a 3- to 3 1/2-year-old child with mild mental retardation not to bite himself, and a mouthguard can be placed to protect the child during sleep.

A rubber dam should be used during all dental work to avoid serious accidents or mutilations of the patients, since they are hyperkinetic and unable to feel pain.

Pulpotomies, root canal treatments, stainless steel crowns, and other ordinary dental work can proceed in children with CIPA without local anesthesia. In the case of extractions, we prefer to use local anesthesia due to the vasoconstrictor role of the epinephrine or norepinephrine.

Children with CIPA usually have orthodontic problems which must be considered and treated carefully, since the improvement of self-image that comes after orthodontic treatment is very important for all mildly mentally retarded children.

Children with CIPA are very rare. Nevertheless we must be aware of the painful consequences of the lack of pain.

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AIDS patient weight control

A new drug treatment that helps AIDS patients regain weight and could help them stave off deadly infections has been developed by researchers at Northwestern University.

Megestrol acetate, a horomonal medication that been given to breast cancer patients for more than 10 years, increased the appetite of AIDS patients, who then regained more than half the weight they had lost during their illness. No side effects were reported.

With the weight gain, patients would be healthier and could avoid infections they might otherwise develop, the researchers theorized.