Congenital Sensory Neuropathy with Anhidrosis

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We report an infant in whom congenital insensitivity to pain was associated with anhidrosis and delayed motor and mental development. This condition was described by Swanson (1963) and called 'congenital insensitivity to pain with anhidrosis'. Pinsky and DiGeorge (1966) proposed the term 'congenital familial sensory neuropathy with anhidrosis'.

Case Report

M.L. was born in December 1965, the third son of consanguineous parents. The father had married his niece, the daughter of his sister. There was no known Jewish ancestry. The parents and the two sibs were healthy, of average intelligence, and all reacted normally to painful stimuli. Gestation was uncomplicated, but labour was prolonged, and at birth there was an initial asphyxia (Apgar score 6) of a few minutes. He weighed 3850 g., had a length of 51 cm., and a head circumference of 35 cm. The postnatal period was uneventful, but at the age of 3 months fever of 40° C. was noted for the first time, though the general condition remained good. Unexplained episodes of high fever frequently occurred thereafter. At 4 months erosions of the gums were observed. At 4½ months, delayed motor development and slight microcephaly were noted: head circumference 41 cm. = 3rd centile; length 66 cm. = 90th centile. Pneumoencephalography demonstrated some enlargement of both occipital horns and of the third ventricle. CSF and EEG normal.

It was noted that the infant showed no signs of discomfort when a venepuncture was done. In hospital several periods of high fever occurred with peaks up to 41° C., but even with this fever the infant never sweated. A skin biopsy demonstrated the presence of histologically normal sweat glands. Therefore, a central disorder of temperature regulation was postulated.

As the picture remained obscure, when 6 months old he was referred to a second hospital, where previous findings were confirmed, and the following further facts recorded. Developmental quotient (Bühler-Hetzer) 71. Slight non-specific hyperaminoaciduria. Biopsy of sural nerve showed normal myelination, and no metachromatic substances.

After cutting his first tooth, an ulcer appeared on the

tip of the tongue, which became deeper, until the tip of the tongue was destroyed. Biopsy of the ulcerated border showed granulation tissue.

At 11 months he was admitted to this unit.

General examination. Rectal temperature 38·8° C. The skin was hot and dry with no evidence of sweating. An erythematous blotching of the face and forehead lasting for half to a few hours was often observed. Simian creases were present on both palms; no dysplasia of nails or teeth. Several areas of white hair on the scalp. Head circumference 44·5 cm. (3rd centile); fontanelles closed. The tip of the tongue was irregularly shaped, with a short longitudinal laceration in the midline, and ulcerations and scars (Fig. 1). Fungiform papillae were present. Blood pressure in the arms 115/60 mm. Hg; no postural hypotension elicited.

FIG. 1.—Irregular shape of the tongue with ulcerations and scars (self-mutilation).

Neurological examination. The infant mostly lay supine, showing little interest in his surroundings. He did not vocalize, but he could cry loudly, and tears rolled from the eyelids. Corneal reflexes and retching reflex were present. There was generalized muscular hypotonia. Head control was defective, the infant being unable to sit unsupported. His motor performances corresponded to a developmental age of 6 months. The

deep tendon reflexes were repressed or absent. There was no reaction to pinprick on the face, trunk, or extremities. Periosteal irritation with a sterile needle or pinching the Achilles tendon did not disturb him. A skin biopsy was performed without anaesthesia, and without the infant showing any discomfort. There was no reaction when a glass tube containing hot water was applied to the face or trunk. Reaction to tactile stimuli was present.

Laboratory examination: Hb 11.8 g./100 ml., reticulocytes 0.9%. White blood count and differential, normal. Sedimentation rate 24 mm./hr. Urinalysis normal. Plasma Na, K, Cl, Ca, and P, normal; urea-N 9.1 mg./100 ml. Serum protein 5.6 g./100 ml.; cholesterol 191 mg./100 ml.; uric acid 3.3 mg./100 ml. Serum enzymes (alkaline phosphatase, amylase, caeruloplasmin, cholinesterase, SGOT, SGPT, and LDH) normal. Paper- and immunoelectrophoresis: slight hypo- γ -globulinaemia (480 mg./100 ml.); IgG precipitation line weak, IgA precipitation line not detectable. Chest x-ray and EEG both normal.

Special investigations

Test of Schirmer. After local anaesthesia with 0.4% oxyprocain (Novesin) a sheet of litmus paper of 5 mm. width was inserted on one edge under the lower eyelid, and after 5 minutes the length of the moist part of the strip was 23 mm., indicating normal lacrimation. Intravenous injection of 0.4 mg. 3-hydroxyphenyldimethylethylammonium chloride (Tensilon) induced slight lacrimation (1 tear) and salivation, but no sweating. Pulse rate increased from 120 to 160 within one minute and fell again to 120 after 5 minutes. The axon reflex was checked by intradermal injections of 0.05 ml. 1:1000 histamine; no pain reaction was observed; wheal formation reached a diameter of 1 cm., as in controls, but while these controls had an erythematous zone of 3 to 4 cm. width, the patient had only a small zone of 1 to 2 mm. at the border of the wheal. An axon reflex could not be restored, either by intradermal injection of 30 μ g. adrenaline, or 25 μ g. carbanilcholine-hydrochloride (Doryl) into the spot where some seconds later histamine was injected.

Cold pressure test. The submersion of the forearm in ice-cold water produced no changes in blood pressure or pulse rate. During fluothane anaesthesia (on this occasion the teeth were filed off in order to prevent further injuries to the tongue), pulse rate decreased from 164 to 126 in the course of one hour and rose again to around 140/min. after 0.1 mg. atropine intravenously. This reaction is commonly observed during fluothane anaesthesia (Johnstone, 1956).

There were 4.8 μ g. homovanillic acid and 1.1 μ g. vanilmandelic acid per milligram creatinine in a 24-hour specimen of urine. The ratio of HVA:VMA was 4.4.

By pilocarpine iontophoresis (collection during 30 minutes) 7.8 mg. sweat were collected from the right arm, and 9.4 mg. from the left one. According to Shwachman and Mahmoodian (1966), the amount of

sweat obtained by this method in normal subjects is 252 mg., with a range of 44 to 613 mg. The overnight collection (14 hours), by means of a gauze pad, 2 sq. in., sealed to the back of the patient with a plastic sheet, amounted to 21.2 mg. sweat on the right side and 19.9 mg. on the left side. Normal values by this method range from 49 to 565 mg., with a mean of 205 mg./14 hours (Shwachman and Mahmoodian, 1966).

In order to study the function of single sweat glands, the sweat-sampling technique of Emrich and Ullrich (1966) was used: the hand of the subject is fixed in a moulded plastic plaster cast filled with mineral oil; using oblique illumination and a stereo-microscope single sweat droplets can readily be recognized. The droplets are aspirated with a siliconized glass capillary and pooled for analysis. Sweat rate per gland per hour is calculated from the volume of the sample. Sweat chloride concentration was determined by micro-electro-titration (Ramsay, Brown, and Croghan, 1955). Results are summarized in Table I. No sweat production was observed after pilocarpine-iontophoresis, nor after subcutaneous injection of pilocarpine, acetylcholine, or adrenaline. Only after simultaneous injection of acetylcholine with adrenaline, could local sweating be regularly induced, the sweat production corresponding to 5–12 nl. per gland per hour. In healthy children intracutaneous injection of comparable doses of acetylcholine induces a local sweat rate of about 200 nl. per gland per hour (Emrich, Stoll, Friolet, Colombo, Richterich, and Rossi, 1967). Chloride concentration in the sweat of the patient was 20–45 mEq/l., as in normal children (Di Sant'Agnese, Darling, Perera, and Shea, 1953; Emrich *et al.*, 1967).

Cutaneous histology demonstrated normal free nerve endings as well as normal nerve receptors (Fig. 2a and b).

Discussion

The main clinical features of this case are (1) a congenital analgia leading to self-mutilations, and (2) an inability to sweat on physiological stimuli leading to defective thermoregulation and periods of fever. A variety of conditions may present in infancy or childhood with failure to react to painful or noxious stimuli: congenital sensory neuropathy (Winkelmann, Lambert, and Hayles, 1962; Ervin and Sternbach, 1960), hereditary sensory radicular neuropathy (Denny-Brown, 1951), non-progressive sensory radicular neuropathy (Ogden, Robert, and Carmichael, 1959), syringomyelia or syringobulbia, acquired peripheral neuropathy of toxic or infectious origin (Farmer, 1964), congenital indifference to pain (Dearborn, 1932; Fanconi and Ferrazzini, 1957; Baxter and Olszewski, 1960; Beçak, Beçak, and Schmidt, 1963), familial dysautonomia (Riley, 1957), and severe oligophrenia (Couston, 1954). Differential diagnosis of some of the major sensory syndromes involving loss of pain is summarized in Table II. The conditions enumer-

FIG. 2.—Skin of cubital region (biopsy). (a) Note presence of all normal morphological components. (Low magnification. H. and E.) D, duct of sweat gland; P, pacinian corpuscle; E, eccrine sweat gland; S, sebaceous gland. (b) Meissner's corpuscle. (High magnification. H. and E.)

ated above invariably show normal sweating reactions, with the exception of familial dysautonomia which shows hyperhidrosis, and can therefore be excluded in the differential diagnosis of the present case. Conversely, conditions presenting with anhidrosis or hypohidrosis such as anhidrotic ectodermal dysplasia, angiokeratoma corporis diffusum, or incontinentia pigmenti, do not include sensory loss. The present case accords well with the syndrome of congenital sensory neuropathy with anhidrosis; six cases of which were found recently (Gillespie and Perucca, 1960; Swanson, 1963; Pinsky and DiGeorge, 1966). The main features common to these 7 cases (the present case being included) are collected in Table III.

Intelligence is defective with an IQ between 40 and 80. Cranial nerves are normal at neurological examination with the exception of analgia of the face and scalp. A specific mention of the presence of corneal reflexes is made in three cases; it is possible that corneal reflexes are less active than in healthy children. Muscular tone of the extremities, motility, strength, and coordination are normal. The superficial abdominal and the cremasteric reflexes are easily elicited; the deep tendon reflexes were reported to be normal in the 2 cases of Swanson and hypoactive in the remaining 5 patients. 6 of the 7 children show a generalized insensitivity to pinprick; only Case 2 of Pinsky and DiGeorge (1966) was reported to have some reaction to

TABLE I

Sweat Production and Chloride Concentration after Subcutaneous Injection of Various Drugs

Place of Local Stimulation	Method of Stimulation	Sweat Rate (nl./gland per hour)	Chloride Concentration (mEq/l.)
Back of left hand	Pilocarpine iontophoresis 2 mA 10 min.	—	—
Back of left hand, laterally	0.3 ml. 1% pilocarpine (3 mg.), subcutaneously	—	—
Back of left hand, medially	0.1 ml. 5% acetylcholine (5 mg.), subcutaneously	—	—
Back of left hand, midline	0.1 ml. 5% acetylcholine (5 mg.) combined with 1 mg./100 ml. adrenaline (1 µg.) subcutaneously	4.9	45
Back of left hand, laterally	0.1 ml. 5% acetylcholine (5 mg.) combined with 2 mg./100 ml. adrenaline (2 µg.) subcutaneously	7.5	20
Dorsum of proximal phalanx, ring finger	0.05 ml. 5% acetylcholine (2.5 µg.) subcutaneously, 5 min. arterial compression	—	—
Dorsum of proximal phalanx, middle finger	0.05 ml. 2 mg./100ml. adrenaline (1 µg.) subcutaneously, 5 min. arterial compression	—	—
Dorsum of proximal phalanx, forefinger	0.05 ml. 5% acetylcholine (2.5 mg.) combined with 2 mg./100 ml. adrenaline (1 µg.) subcutaneously, 5 min. arterial compression	Droplets after 20 min.	—
Back of left hand, medially	0.4 ml. 2 mg./100 ml. adrenaline (8 µg.) subcutaneously	—	—
Back of left hand, laterally	0.3 ml. 5% acetylcholine (15 mg.) combined with 10 mg./100 ml. adrenaline (30 µg.) subcutaneously	12.0	43

TABLE II

*Comparison of Some Sensory Syndromes with Loss of Pain**

	Congenital Sensory Neuropathy with Anhidrosis	Congenital Sensory Neuropathy	Hereditary Sensory Radicular Neuropathy	Congenital Indifference to Pain (cong. analgesia)	Syringomyelia, Syringobulbia	Familial Dysautonomia
Intelligence	Defective	Dull to average	Normal	Normal	Normal	Dull to average
Heredity	Recessive	Sporadic and dominant	Dominant	None	None	Recessive
Time of onset	Birth	Birth	Late childhood	Birth	Exceptionally birth or infancy	Birth
Distribution of sensory loss	Universal	Incomplete	Radicular; distal extremities	Universal	Incomplete; dissociated anaesthesia	Universal
Pain perception	Absent	Absent	Absent	Absent	Absent	Reduced
Temperature perception	Reduced	Absent	Absent	Normal	Absent	Reduced
Touch perception	Present	Absent	Absent	Normal	Present	Present
Physiological pain reactions	None	None	None	Mostly absent	None	None
Axon reflex	None	None	None	Normal	Normal	None
Sweating	None†	Normal	Normal	Normal	Normal (local hyper-anhidrosis)	Increased
Sensory nervous system anatomy	Myelinated fibres and dermal nerve networks present; absence of Lissauer's tract and small dorsal root axon	No myelinated fibres, no dermal nerve endings	Loss of myeli- nated fibres	Normal	Normal skin and sensory nerve biopsy	Absence of fungi- form papillae and taste buds on tongue; normal dermal nerve endings
Tendon reflexes	Hypoactive	Hypoactive	Decreased or absent	Normal	Hypo- or hyper- active	Hypoactive

* Modified from Winkelmann *et al.* (1962) and from Pinsky and DiGeorge (1966).

† Restored by adrenaline and acetylcholine subcutaneously.

TABLE III

Frequency of Main Findings among 7 Cases of Congenital Sensory Neuropathy with Anhidrosis

Consanguinity	1/7
Familial cases	4/7
Males	5/7
Self-mutilations	7/7
Episodes of unexplained fever	7/7
Irregular blotching of face	5/5
Defective intelligence	7/7
Analgesia	7/7
Anhidrosis	7/7
Sweat glands present	6/6
Lacrimation present	5/5
Corneal reflexes present	3/3
Spinal fluid normal	4/4
PEG: mild ventricular dilatation	3/3
EEG normal	4/4
Chromosomes normal	3/3

pinprick on the face though not on the trunk and extremities, and the authors could not exclude a non-specific reaction of this mentally retarded girl. Bone pressure, pinching of the Achilles tendon, periosteal irritation with a sterile needle, prolonged ischaemia of the limbs, or testicular compression, provoke no response. This absence of protective pain reflexes explains the self-mutilations and frequent injuries these children acquire. During infancy all bit off the tip of the tongue; later bone fractures, dislocations, and wounds have been extremely frequent. There is no reaction to burning heat applied to the skin. Case 1 of Swanson (1963) sustained extensive burns of the hands when he reached into a hot oven, and his brother on one occasion purposely burnt a finger-tip with a cigar lighter.

Tactile sense is present in these children. Deficient intelligence or youth excluded the testing of functions requiring co-operation in all the cases with the exception of the two brothers reported by Swanson (1963). These showed a disturbed perception of differences between sharp and dull stimuli, with the tendency to interpret the stimulus applied with the greatest pressure as sharp. However, when test objects were dragged along the skin, accurate discrimination between sharp and dull was made. Temperature perception was impaired too: hot and cold moist sponges could not be distinguished accurately, but, on the other side, the difference between cool and tepid water was recognized when the hands were immersed. Position and vibration senses were intact. No visceral pain could be elicited by inflating a balloon in the lower oesophagus, normally a very painful procedure.

Pneumoencephalography detected a slight enlargement of the third ventricle in two cases (Swanson, 1963; present case), and a mild asym-

metrical lateral ventricular dilatation in a third patient (Swanson, 1963). EEG was normal in the 4 examined cases.

A simple method of deciding whether analgesia is due either to a lesion of the peripheral sensory neurones, or at levels central to the dorsal root ganglion, is to test the axon reflex. Cutaneous pain fibres have branches reaching the arterioles, and it is generally accepted that afferent (orthodromic) pain impulses pass antidromatically to the arterioles causing reflex vasodilatation (Lewis, 1928). As the axon reflex to intradermal histamine was absent in all 6 cases tested (Swanson, 1963; Pinsky and DiGeorge, 1966; present case), a defect at the peripheral level must be present. Biopsies from our patient demonstrated the presence of normal dermal nerve networks and myelination of fibres in the sural nerve. The same findings were reported by Pinsky and DiGeorge in their Case 2. The pain end-organs of skin are distributed in a punctate fashion and correspond to free nerve endings. Not all free nerve terminals are pain receptors, and at present it is impossible to differentiate pain receptors morphologically from nerve terminals having other receptor functions (Fleischhauer, 1966). Despite 'normal' free nerve endings in skin biopsy, absence of pain receptors and of the corresponding (mainly non-myelinated) fibres cannot be excluded. A post-mortem study (Swanson, Buchan, and Alvord, 1963) of the nervous system of Case 1 of Swanson (1963) revealed the absence of the small thinly myelinated sensory fibres of the dorsal roots C1 to S1. In these segments Lissauer's tract (dorsolateral fasciculus) could not be identified. Many adhesions were present between the arachnoid and the inner surface of the dura throughout the entire length of the cord and cauda equina, but without any distortion or compression of the spinal cord. Unfortunately no mention is made of dermal nerve networks.

All these patients show unpredictable rises of temperature, which can at least partially be explained by their inability to sweat normally. The presence of histologically normal sweat glands (Swanson, 1963; Pinsky and DiGeorge, 1966; present case) could suggest a defect in the neuro-effector mechanism. Local sweating could not be induced either by electrical stimulation (Swanson, 1963) or by intradermal injection of pilocarpine (Swanson, 1963; Pinsky and DiGeorge, 1966; present case), mecholyl (Pinsky and DiGeorge, 1966), or by 0.1 ml. 1 : 10,000 levarterenol (Swanson, 1963). In our patient, local sweating could be induced only by simultaneous application of acetylcholine and adrenaline. Kuno (1965) observed that in normal

subjects local sweating, which had been elicited by pilocarpine or acetylcholine, could be increased by small amounts of adrenaline subcutaneously, and he concluded that this was a humoral effect of adrenaline on the gland. Present knowledge of the innervation of sweat glands is still imperfect.

The eccrine sweat glands are supplied with nerves which, though belonging anatomically to the sympathetic nervous system, are cholinergic (Dale and Feldberg, 1934). On the other hand, intradermal application of adrenaline or noradrenaline in man causes local sweat production which cannot be inhibited by atropine, but can be by sympatholytics (Sonnenschein, 1949; Sonnenschein, Kobrin, and Grossman, 1949; Chalmers and Keele, 1951). A cholinergic and adrenergic double innervation of sweat glands has been proposed by Haimovici (1948, 1950). The discovery, however, that thermal sweating is suppressed by atropine but not by sympatholytics leads to the conclusion that sweat glands are innervated only cholinergically (Chalmers and Keele, 1951, 1952).

Since the effect of adrenaline upon the sweat gland is not yet clear, it is no use to speculate at which level of the neuroeffector mechanism a block should be postulated which would lead to anhidrosis. We can only say that this block is not absolute, for it can be partially eliminated by simultaneous injection of acetylcholine and adrenaline.

Further observations will be needed to decide if other signs of autonomic dysfunction are constantly present. Pinsky and DiGeorge (1966) observed only a weak response of lacrimation to injection of cholinergic agents, despite good lacrimation when the patients were frustrated. Intravenous infusion of dilute noradrenaline resulted in an exaggerated hypertensive response in their Case 1, while fluothane anaesthesia in their Case 2 failed to produce bradycardia, as was usually observed by Johnstone (1956). Furthermore, the ratio of HVA to VMA in the urine was higher than 2.5 in 2 of their 3 patients, as has been described in familial dysautonomia (Smith, Taylor, and Wortis, 1963). Apart from a high HVA : VMA ratio and repeated erythematous blotching of the face, no other signs of autonomic dysfunction were detected in our patient.

Summary

A case of congenital sensory neuropathy with anhidrosis is described in a boy of 11 months of consanguine parents. He showed the typical picture of self-mutilations (biting off of the tip of the tongue), recurrent episodes of unexplained fever, and delayed motor and mental development. There was generalized analgia and failure to sweat on

thermal, emotional, noxious, or the usual chemical stimuli. Local sweating at a low rate, but with normal sweat chloride concentration could be induced only by the simultaneous injection of acetylcholine and of adrenaline. The case is compared with six other published cases.

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