Congenital sensory neuropathy

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Barry, J. E., Hopkins, I. J., and Neal, B. W. (1974). *Archives of Disease in Childhood*, 49, 128. **Congenital sensory neuropathy.** Two infants with sporadic congenital sensory neuropathy are described. The criteria of generalized lack of superficial sensory appreciation, hypotonia, areflexia, together with histological evidence of abnormalities of sensory neural structures in skin and peripheral nerves have been met. No abnormality of motor or autonomic nerves was shown.

Congenital sensory neuropathy is a nonprogressive condition in which there is absence of superficial sensory modalities, hypotonia, and absent tendon reflexes; delay in motor development is usual, but autonomic function is preserved. Histological examination shows abnormalities of neural structures in skin and sensory peripheral nerves.

Dearborn (1932) described a 54-year-old man who had once earned his living on the stage as a human pincushion and had never experienced pain other than headache. Neurological examination of this man apparently revealed only minor and insignificant signs apart from sensory loss. Since then many reports have appeared in which impairment of pain appreciation in early life has been a prominent feature. Ford and Wilkins (1938) described 3 cases of *congenital universal insensitivity to pain* in children. These children did not have neurological deficits, and 2 had intelligence ratings below normal but were not mental defectives. Histological studies were not undertaken. Denny-Brown (1951) coined the term *hereditary sensory radicular neuropathy* in the report of a female who was one of 11 affected members in a family of 36 over four generations and who were studied originally by Hicks (1922). These patients had absence of pain sensation distally with gross progressive trophic changes. Necropsy examination disclosed a primary degeneration of dorsal root ganglia.

Congenital sensory neuropathy was first adequately documented by Ortiz de Zarate (1955), and since then other accounts have been published (Sandell, 1958, Case 3; Ogden, Robert, and Carmichael, 1959, Case 3; Wadia and Dastur, 1960;

Winkelman, Lambert, and Hayles, 1962; Bourlond and Winkelman, 1966; Haddow, Shapiro, and Gall, 1970; Linarelli and Prichard, 1970). A similar condition, *congenital sensory neuropathy with anhidrosis*, has been reported by Swanson (1963), Pinsky and Di George (1966), and Vassella *et al.* (1968). However, congenital sensory neuropathy with anhidrosis has important clinical differences apart from the inability to sweat; affected patients are mentally retarded but touch sensation is preserved. A further type of sensory neuropathy has been described by Johnson and Spalding (1964) and Dyck (1966, Case 4) with electrophysiological and histological findings similar to congenital sensory neuropathy but in which the sensory loss starts distally and is progressive.

We report 2 infants with congenital sensory neuropathy, one of whom is the youngest documented case known to us, and in whom electron microscopical studies of skin and nervous tissue were undertaken, together with specific staining for autonomic nervous structures.

Case reports

Case 1. This patient was born on 26 April 1971 after a normal pregnancy and delivery. His parents were unrelated Australians, and all members of the family including an older sib were healthy. He weighed 2.58 kg at birth and gestational age was estimated to be 37 weeks. Progress in early infancy was normal until the age of 4 months when he began to chew his fingers and thumbs, often making them bleed. He vocalized normally, and sat unsupported at 7 months. He was admitted to the Royal Children's Hospital when aged 9 months. Examination revealed a male infant with deeply ulcerated and bleeding fingers and thumbs. The temperature, pulse, and respiratory rate were normal and

the blood pressure 120/80 mmHg. Head circumference was 46 cm (50th centile), weight 8.6 kg (25th centile), and height 70 cm (25th centile). Corneal reflexes, gag reflexes, and facial sensation were absent, but the cranial nerves were otherwise normal. There was generalized hypotonia with absence of deep tendon reflexes. However, motor activity and achievements were appropriate for his age. There was no appreciation of superficial touch stimuli over any area of the skin. He sweated normally. One year later the clinical picture had changed slightly. He could not walk and motor achievements were delayed; absence of pain sensation persisted, but some thermal appreciation was suspected when at the age of 22 months he was heard to say 'hot' on being put into a hot bath.

Injection of 0.1 ml intradermal histamine acid phosphate 1:1000 produced a weal 1 cm in diameter and a flare 1.2 cm in diameter. A control showed a weal and flare response of 1 cm and 6 cm, respectively.

Laboratory studies. Hb, white blood cells and differential count, acid-base status, blood urea and glucose, serum sodium, potassium, chloride, calcium, phosphorus, magnesium, uric acid, and creatine phosphokinase were all normal. There was a normal pattern of urinary amino acids. CSF contained 26,750 RBCs and 11 WBC/mm³ attributed to the procedure; protein 25 mg/100 ml; glucose 50 mg/100 ml; and VDRL was nonreactive.

X-ray of the chest normal. X-ray of the skull showed

a small area of translucency with a well-defined margin in the right frontal bone, thought to be due to a dermoid. No other abnormality was present.

Electrophysiological investigations. EEG showed an unusual amount of fast activity but was otherwise unremarkable. Electromyography was normal. Ulnar motor nerve conduction velocity (42 m/sec) was within the range of normal for the patient's age. No sensory potentials could be obtained with digital nerve stimulation.

Pathology. Specimens of sural nerve, skin from the thigh and dorsum of the hand, and quadriceps muscle were examined. Sural nerve was embedded in araldite/epon and stained with methylene blue; light microscopy showed small nerve fasciculi in dense connective tissue and only 1 to 3 myelinated fibres were noted in each fasciculus. Electron microscopy confirmed the presence of few myelinated fibres while most of the fibres were nonmyelinated (Fig.). There was no evidence of nerve degeneration.

Sections of skin from the dorsum of the hand examined with haematoxylin and eosin and silver stains (Naoumenko and Feigin, 1967) showed no neural structures. However, some cutaneous nerves of normal appearance were present in skin from the thigh. Electron microscopy of the skin confirmed these findings.

Adrenergic nerve endings in the skin were shown by

FIG.—Case 1. Electron microscopy of sural nerve showing only a single small myelinated fibre (thick arrow). All other nerve fibres (fine arrow) in the field are unmyelinated. Three Schwann's cell nuclei and one fibroblast nucleus are also shown ($\times 2880$).

fluorescent histochemical localization of catecholamines using the method of McLean and Burnstock (1966). Normal innervation of vessels and skin adnexae was shown histologically in both the subject and a normal control.

Muscle biopsy was normal with histochemistry showing a normal chequerboard pattern with 60% type 1 fibres. Muscle fibres were fairly uniform in diameter averaging 16.6 μm for type 1 and 18.7 μm for type 2, which was comparable with two controls of a similar age. A small nerve bundle in the muscle biopsy appeared normal.

Case 2. This infant, the only child of healthy, unrelated Australian parents, was born on 6 September 1970 after an uneventful pregnancy. Because of breech presentation with extended legs, caesarean section was performed and a healthy child weighing 2.6 kg was delivered.

At 4 months a scoliosis was noted and was treated conservatively. At 12 months she was admitted to the Royal Children's Hospital for investigation (see below) of possible neuromuscular disease as a cause of the scoliosis, but a diagnosis was not established. When 16 months old she was unaware of an injury to the right great toe and two months later was found to be unresponsive to pin prick stimulation of the skin when being fitted with an orthopaedic brace. She was readmitted to hospital in June 1972 at 21 months of age for further assessment. At this age she could not walk and was only just beginning to sit without support, indicating delay in locomotor development. She could speak in short sentences. Her mother said that she lacked discrimination for foods, but perspired normally and produced tears. On a single occasion she had bitten her fingers severely enough to cause bleeding. Her parents also reported that she had lost several of her primary teeth between the ages of 10 and 18 months. No significant trauma was known to account for this.

Examination revealed a fair-haired blue-eyed girl of 21 months with no trophic injuries, but with a moderate scoliosis, convex to the right. Temperature, pulse, and respiration were normal. Head circumference 45 cm (2nd centile), weight 11.3 kg (25th centile). Blood pressure recordings ranged from 110/60 to 120/60 mmHg, and there was no alteration in pressure with postural change. Tears could be produced but corneal reflexes were absent, and caloric stimulation with iced water failed to produce nystagmus. She ate salt and sugar and drank pure lemon juice without any apparent distinction in taste. The tongue was smooth. She was hypotonic and areflexic and though there was generalized lack of superficial pain and touch appreciation, she responded to deep pain stimulation. Her level of motor development was between 6 and 9 months, but language and social development were appropriate for her age.

Injection of 0.1 ml intradermal histamine acid phosphate 1:1000 produced a weal 1 cm in diameter and a flare 1.5 cm in diameter 5 minutes later. A control subject showed a weal and flare of 1.5 cm diameter and 9 $\times$ 5 cm, respectively.

Laboratory studies. Hb, white cells, platelets, serum creatine phosphokinase, and uric acid were normal. 2 ml 0.05% pilocarpine nitrate by iontophoresis produced a normal volume of sweat.

Electrophysiological studies. Motor conduction velocity of right ulnar nerve was 50 m/sec. No sensory potentials were obtained with stimulation of digital nerves. Electromyography of right anterior tibial and quadriceps muscle was normal.

Pathology. Specimens of skin from the ankle and quadriceps muscle were examined. Sural nerve biopsy was attempted but no neural tissue could be found by a surgeon experienced in this procedure.

No identifiable nerve endings were found with silver stains of the skin, though numerous nerve endings were seen in a similarly stained piece of skin from a normal control. Electron microscopy of the skin did not reveal any nerve endings. Adrenergic nerve endings innervating vessels and skin adnexae were shown when similar techniques to those used in Case 1 were employed.

Muscle biopsy showed a normal chequerboard pattern with 56% type 2 fibres. Muscle fibres were of fairly uniform diameter averaging 10.2 μm for type 1 and 13.3 μm for type 2. A nerve present within the specimen contained well-myelinated fibres and appeared normal.

Discussion

These infants fulfil the clinical criteria of congenital sensory neuropathy, i.e. they have a nonprogressive condition with gross impairment of pain and touch appreciation, hypotonia, and absent tendon reflexes, but apparently normal intelligence and the ability to sweat and produce tears. In Case 1 light and electron microscopy studies of the skin from peripheral sites failed to reveal evidence of free nerve endings, but cutaneous nerves of normal appearance were seen in skin from the thigh. Unmyelinated fibres with only an occasional small myelinated fibre were present in the sural nerve of Case 1, while no sural nerve tissue was found in Case 2. The presence of tears, the ability to sweat, and histological evidence of intact autonomic structures in the skin are evidence of normal autonomic function, this being a feature of this condition.

Although most reports emphasize the sporadic nature of congenital sensory neuropathy, Haddow *et al.* (1970) have reported two sibs with findings suggestive of this condition, thereby raising the possibility of autosomal recessive inheritance.

Both infants studied by us have generalized loss of superficial sensibility and are similar to the child reported by Linarelli and Prichard (1970). Before their report, other writers had found patchy areas of normal sensation over the trunk. However, as noted above, in Case 1 some nerve fibres were found

proximally and the clinical finding of generalized sensory loss may have been partly related to the difficulties associated with detailed sensory testing in early infancy. When last seen at the age of 22 months this boy had bitten the tips from both index fingers and the only evidence of superficial sensation was a suspicion of temperature recognition when placed in a hot bath. The effect of caloric stimulation has not been mentioned in previous reports, and the absence of nystagmus when this test was performed in Case 2 is further evidence supporting a generalized lack of superficial sensibility.

Although several conditions (Table) should be considered in the delineation of a sensory syndrome in which lack of response to pain in early life is a feature, it is our belief that a diagnosis of congenital sensory neuropathy can be made on clinical grounds. Normal autonomic function precludes a diagnosis of familial dysautonomia and congenital sensory neuropathy with anhidrosis. Hereditary sensory radicular neuropathy is manifest later in childhood, has a distal distribution, and is usually accompanied by deafness. The absence of touch and temperature appreciation excludes congenital indifference to pain and the clinical features of the Lesch-Nyhan syndrome, with gross self-mutilation and mental retardation, do not closely resemble congenital sensory neuropathy.

The only previous report on autonomic nervous structures and electron microscopical study of skin in congenital sensory neuropathy is that of Bourlond and Winkelmann (1966) when they reinvestigated Winkelmann *et al.*'s patient (1962). Our findings of normally staining autonomic nerves are similar and confirm the clinical impression of intact peripheral autonomic neural structures.

The pathogenesis of congenital sensory neuropathy is unknown; that the disease is peripheral rather than central is shown by absence of the axon reflex, absence of sensory nerve conduction

potentials, and absence of free nerve endings in skin. Yet a lesion which does not affect the motor or autonomic pathways could be placed in the dorsal root ganglia; at present, histological examination of this tissue has not been undertaken in this condition. Swanson (1963) reported a child with congenital sensory neuropathy and anhidrosis showing the absence of small primary sensory neurones in spinal ganglia, dorsal roots, spinal cord, and medulla, together with the absence of Lissauer's tract. However, the sympathetic preganglionic cell bodies in the intermediolateral column of the spinal cord appeared normal as did the autonomic ganglia. Examination of dorsal root ganglia by Denny-Brown (1951) in hereditary sensory radicular neuropathy revealed dendritic proliferation and the presence of nodules indicating loss of ganglion cells.

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REFERENCES

- Bourlond, A., and Winkelmann, R. K. (1966). Study of cutaneous innervation in congenital anesthesia. *Archives of Neurology*, **14**, 223.
- Dearborn, G. V. (1932). A case of congenital general pure analgesia. *Journal of Nervous and Mental Disease*, **75**, 612.
- Denny-Brown, D. (1951). Hereditary sensory radicular neuropathy. *Journal of Neurology, Neurosurgery and Psychiatry*, **14**, 237.
- Dyck, P. J. (1966). Histologic measurements and fine structure of biopsied sural nerve: normal, and in peroneal muscular atrophy, hypertrophic neuropathy, and congenital sensory neuropathy. *Mayo Clinic Proceedings*, **41**, 742.
- Ford, F. R., and Wilkins, L. (1938). Congenital universal insensitivity to pain. *Bulletin of the Johns Hopkins Hospital*, **62**, 448.
- Haddow, J. E., Shapiro, S. R., and Gall, D. G. (1970). Congenital sensory neuropathy in siblings. *Pediatrics*, **45**, 651.
- Hicks, E. P. (1922). Hereditary perforating ulcer of the foot. *Lancet*, **1**, 319.
- Johnson, R. H., and Spalding, J. M. K. (1964). Progressive sensory neuropathy in children. *Journal of Neurology, Neurosurgery and Psychiatry*, **27**, 125.

TABLE

Comparison of major clinical features in childhood sensory syndromes

	Inheritance	Manifestations in infancy	Touch appreciation	Temperature appreciation	Tears	Sweat	Mental retardation	Abnormal histology
Congenital sensory neuropathy	Mostly sporadic	+	—	—	+	+	—	+
Congenital sensory neuropathy with anhidrosis	Autosomal recessive	+	+	—	+	—	+	±
Congenital indifference to pain	Autosomal recessive	+	+	+	+	+	—	—
Familial dysautonomia	Autosomal recessive	+	+	±	—	+	±	—
Lesch-Nyhan syndrome	Sex-linked recessive	+	+	+	+	+	+	—
Hereditary sensory radicular neuropathy	Autosomal dominant	—	±	±	+	+	±	+

+, present; —, absent.

- Linarelli, L. G., and Prichard, J. W. (1970). Congenital sensory neuropathy. Complete absence of superficial sensation. *American Journal of Diseases of Children*, **119**, 513.
- McLean, J. R., and Burnstock, G. (1966). Histochemical localization of catecholamines in the urinary bladder of the toad (*Bufo marinus*). *Journal of Histochemistry and Cytochemistry*, **14**, 538.
- Naoumenko, J., and Feigin, I. (1967). A stable silver solution for axon staining in paraffin sections. *Journal of Neuropathology and Experimental Neurology*, **26**, 669.
- Ogden, T. E., Robert, F., and Carmichael, E. A. (1959). Some sensory syndromes in children: indifference to pain and sensory neuropathy. *Journal of Neurology, Neurosurgery and Psychiatry*, **22**, 267.
- Ortiz de Zarate, J.-C. (1955). Analgésie généralisée congénitale. *Encéphale*, **44**, 414.
- Pinsky, L., and Di George, A. M. (1966). Congenital familial sensory neuropathy with anhidrosis. *Journal of Pediatrics*, **68**, 1.
- Sandell, L. J. (1958). Congenital indifference to pain. *Journal of the Faculty of Radiologists*, **9**, 50.
- Swanson, A. G. (1963). Congenital insensitivity to pain with anhidrosis. *Archives of Neurology*, **8**, 299.
- Vassella, F., Emrich, H. M., Kraus-Ruppert, R., Aufdermaur, F., and Tönz, O. (1968). Congenital sensory neuropathy with anhidrosis. *Archives of Disease in Childhood*, **43**, 124.
- Wadia, N. H., and Dastur, D. K. (1960). Congenital sensory neuropathy. *World Neurology*, **1**, 409.
- Winkelman, R. K., Lambert, E. H., and Hayles, A. B. (1962). Congenital absence of pain. *Archives of Dermatology*, **85**, 325.

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