Congenital hypomyelinating neuropathy

YADOLLAH HARATI,* IAN J BUTLER†

From the Department of Neurology, Baylor College of Medicine and Veterans Administration Medical Center, and the Departments of Neurology and Pediatrics, University of Texas Health Science Center Medical School at Houston,† Houston, Texas, USA*

SUMMARY Two patients with congenital hypomyelinating neuropathy are reported with details of sural nerve pathology. The resemblance of this condition to the hypomyelinating neuropathy of Trembler mice is discussed and the pertinent medical literature reviewed.

Congenital hypomyelinating neuropathy is a severe polyneuropathy of early infancy manifesting as hypotonia, areflexia, distal muscle weakness and atrophy, and exceedingly slow nerve conduction velocities, usually leading to early death or severe disability. The pathogenesis of this neuropathy is not clear. It has been stated that this neuropathy may differ from inherited hypertrophic neuropathy of Dejerine-Sottas type and from chronic inflammatory polyneuropathy by the absence of typical onion bulb formation and inflammation in peripheral nerve biopsy.

crutches and was unsteady on sitting unsupported. There was rigid thoracic scoliosis, marked wasting of all muscles and hyperextensibility of all limb joints (fig. 1). Muscle weakness was moderately severe, particularly in the legs. Sensation to pinprick and light touch appeared intact, deep

Case 1

A male child aged 3 years 10 months was evaluated for muscle weakness and wasting associated with delayed motor development. He was born after a normal pregnancy and delivery and is the only child of Mexican parents. His development appeared normal until the onset at 5 months of a febrile illness associated with diarrhoea and dehydration and although the diarrhoea persisted for several months, he did not require hospital care. Routine vaccinations had been performed, including triple vaccination against poliomyelitis. At 2½ years, he was evaluated in a rural clinic for inability to crawl and walk. He was able to sit unsupported but upper and lower limbs were flaccid and there was marked hyperextensibility at the joints without any contractures. He was encouraged to ambulate with long leg braces and crutches and 6 months later he could stand and walk with assistance. At age 3 years 10 months he was referred to a medical centre for diagnostic studies.

He was an alert Spanish speaking child who cooperated readily during the examination. He walked with the aid of

Fig 1 Case 1. Able to stand with support.

Address for reprint requests: Yadollah Harati, MD, Department of Neurology, Baylor College of Medicine, 6501 Fannin, Houston, Texas 77030, USA.

Received 11 December 1984 and in revised form 2 May 1985.
Accepted 10 May 1985

Fig 2 Sural nerve. Case 1. Longitudinal sections stained for modified Gomori's trichrome. Note hypercellularity and absence of myelinated nerve fibres. ($\times 195$).

tendon reflexes were absent and plantar reflexes were flexor. Muscle and tongue fasciculations were not observed and peripheral nerves were not palpably enlarged. Neither parent was available for examination or historical details. Routine blood and urine analysis was normal. Cerebrospi-

Fig 3 Sural nerve. Case 1. Note a few thin myelin (short arrows) and amyelinated axons (long arrows). 1 μ m epoxy section, stained with toluidine blue. ($\times 360$).

nal fluid analysis showed no red or white cells, glucose was 40 mg/dl and protein was 58 mg/dl. Motor nerve conduction velocity determinations for right median and peroneal nerves were 2.6 and 2.1 m/s and terminal conduction latencies were 18 and 23 ms respectively. Sensory action

Fig 4 Sural nerve. Case 1. Electron micrograph. Normal size axons with no or very thin myelin sheath enclosed by empty basement membrane (thin arrows). Double arrow points to a normal unmyelinated fibre. ($\times 1700$).

Fig 5 Sural nerve. Case 1. Electron micrograph showing concentric layers of basement membrane around a very thin myelinated fibre. ($\times 1660$).

potentials were unobtainable in right ulnar, median and sural nerves. Electromyography of right first dorsal interosseus and tibialis anterior muscles showed no positive sharp waves or fasciculations but motor unit potentials were broad and of low amplitude.

Sural nerve biopsy

During the surgical procedure, only a thread-like structure could be seen in the usual location of the sural nerve proximal to the lateral malleolus. No visible branch arose from it. A 3 cm length of the thin nerve was removed and divided into three segments for light microscopy, teased nerve fibre preparation and electron microscopy. Longitudinal and transverse frozen unfixed sections were stained with H and E, modified Gomori trichrome, PAS, and cresyl violet. A segment was fixed in 2.5% glutaraldehyde, post-fixed in 1% osmium tetroxide, dehydrated in alcohol and then embedded in Epon. Transverse sections, 1 μ m thick, were stained with toluidine blue and 1,4-phenylenediamine for light microscopy. Ultra-thin sections were stained with uranyl acetate and lead citrate and examined by electron microscopy.

The third segment of the biopsy specimen was post-fixed

in 1% osmium tetroxide for 12 hours and placed in a mixture of glycerine and water for teasing.

Vastus lateralis muscle biopsy

For histochemical studies, tissue was frozen with liquid nitrogen, and sectioned in a cryostat and stained with the following methods: modified Gomori trichrome, NADH-TR, ATPase and pH 9.4 and succinic dehydrogenase..

Results

No myelin was visualised on H and E and modified Gomori trichrome stain. Marked hypercellularity of endoneurium was present (fig. 2). No abnormal deposits were present. In semi-thin sections the total number of myelinated fibres were strikingly reduced and only a few very thinly myelinated axons were seen scattered throughout the fascicles (fig. 3). There was no apparent loss of axons and the diameter of most axons was normal. Electron microscopic examination showed the absence of myelin in practically all fibres (fig. 4). Exceptionally there was a thin

Fig 6 Sural nerve. Case 1. Single teased nerve fibre showing an axon (long arrow) devoid of myelin sheath and several Schwann cells faintly stained with osmium tetroxide (short arrows). ($\times 970$).

myelin sheath composed of two to four lamellae. Atypical onion-bulbs formed only by a concentric arrangement of double-layered basement membranes separated by a narrow space were seen (fig 5). These onion bulbs did not enclose Schwann cell cytoplasm. The axons in the centre of onion bulbs were of normal diameter and showed no structural alterations. There was no evidence of myelin breakdown. Schwann cell nuclei were normal. Unmyelinated Remak fibres were of normal diameter and shape and their density appeared normal.

On teased fibre studies no myelin was detected but several Schwann cells, faintly stained with osmium tetroxide were seen attached to the amyelinated axons (fig. 6). Muscle histochemistry revealed denervation atrophy, hypertrophy of fibres and fibre type grouping indicative of reinnervation (fig 7). No intramuscular nerve or muscle spindles were seen.

Case 2

A male child aged 3 years 11 months was evaluated for delayed motor development and weakness. He was born to a healthy 24-year-old mother after a normal pregnancy and delivery and had no neonatal problems. He was slow to crawl and unable to walk until 22 months. His parents became concerned at age 3½ years when his 2-year-old brother surpassed him in motor development. The parents stated that he could appreciate hot and cold sensations. His psychosocial and mental development were normal. He had chronic constipation requiring enemas. Routine vac-

nations had been performed. His 2 year and 4 month old brothers were normal and parents were healthy with no evidence of neuromuscular disorders. He had normal mentation and cranial nerve examination, but he was markedly hypotonic. He could stand while supported and walked with a waddling gait. His proximal and distal muscle strength were 3/5. There were no muscle fasciculations or tongue fibrillations and peripheral nerves were not palpably enlarged. Mild distal muscle atrophy was present. Deep tendon reflexes were absent in lower extremities and 1+ in upper extremities. Hot and cold sensation was intact.

Fig 7 Vastus lateralis muscle biopsy. Note central fascicle composed of type I (darkly stained) fibres (fibre type grouping) and enlarged type I and II fibres. NADH-TR. ($\times 200$).

All laboratory tests including muscle enzymes, EKG, lipoprotein electrophoresis, and arylsulfatase A were normal. CSF protein was 13 mg/dl. Sensory and motor nerve conductions of lower extremities could not be measured, but right ulnar nerve motor conduction velocity was 7.9 m/s. EMG of upper and lower limbs showed denervation with fibrillations and positive waves and broad motor units noted most prominently in the distal muscles of the upper and lower extremities. His two brothers were examined and found to have no evidence of neuromuscular disorders. His parents were also normal on examination and by nerve conduction studies.

A left vastus lateralis muscle biopsy specimen revealed denervation change similar to those of Case 1. A sural nerve biopsy was performed and processed similar to Case 1. A marked decrease in the number of myelinated fibres with occasional middle-sized and small myelinated axons were seen (fig 8). No typical onion-bulbs were seen but a few atypical bulbs composed of layers of reduplicated basement membrane were present. A few axons had filamentous hyperplasia and decreased neurotubules and mitochondria.

Discussion

In 1969 Lyon¹ reported a case of chronic progressive early infantile neuropathy whose nerve biopsy showed virtual absence of myelin sheaths of myelinated fibres. Clinically, the patient had marked delay of motor development, generalised muscle hypotonia, weakness and atrophy of lower limbs, areflexia, and normal mental development, sensory

and cranial nerve examination. His peripheral nerves were not palpably enlarged. The CSF protein was elevated and nerve conduction velocities were unmeasurable. He termed this condition "early infantile chronic neuropathy." Subsequently, other similar patients were reported using various terms such as infantile polyneuropathy with defective myelination,² hypertrophic interstitial polyneuropathy in infancy,³ congenital hypomyelinating neuropathy,⁴⁻⁸ chronic polyradiculoneuropathy of infancy,⁹ and Dejerine-Sottas disease.¹⁰ Although the clinical presentation of these cases were similar, the morphological abnormalities were not uniform. All showed severe loss of myelin sheath of myelinated fibres both in nerve biopsies^{1,4,10-12} or in necropsy material.^{2,9} In patients reported by Karch,² Ulrich,¹² Kasman,⁹ and Palix¹² there were practically no onion bulbs, but patients reported by Lyon,¹ Kennedy,⁴ Anderson,³ Moss,¹⁰ Towfighi,⁵ and Ono⁸ showed atypical onion bulb essentially composed of multiple layers of basement membrane with little or no Schwann cell processes. There was no myelin breakdown product, and the axons were preserved. In the first group, the children died in early infancy or early childhood while the second group, although severely handicapped, survived. Lack of evidence for an active myelin breakdown, preservation of axons, and absence of a well formed Schwannian onion bulb and a demyelination-remyelination process, suggested that the cases of congenital hypomyelinating

Fig 8 Sural nerve. Case 2. Longitudinal section. Note near total absence of myelinated fibres. Arrows point to a few remaining thinly myelinated axons. 1 μ Epoxy sections. ($\times 420$).

Table Congenital hypomyelinating neuropathy: Summary of reported cases

Reference	Age at onset	Motor development	Cranial nerves	Palpable nerves	CSF protein	Nerve conduction velocities (NCV)
1	Early infancy	Delayed, hypotonic	Normal	No	120 mg/dl	Unmeasurable
4	Birth	Delayed, hypotonic	Normal	Yes	90–190 mg/dl	Less than 2.6 m/s
2	12 weeks	Delayed, hypotonic	Normal	Not mentioned	Not measured	Unmeasurable
6	Birth	Hypotonic	Normal (?)	Not mentioned	78 mg/dl	“Extremely slow”
8	3 years 11 months	Slow hypotonic	Normal	No	29 mg/dl	Unmeasurable
5	Neonatal period	Delayed, hypotonic	Normal	Not mentioned	344–484 mg/dl	13–24 m/s
7: Case I	Birth	Delayed, hypotonic	Normal	No	120 mg/dl	Less than 5 m/s
Case II	Birth	Delayed, hypotonic, swallowing difficulties	Normal	No	97 mg/dl	Less than 5 m/s
Case III	Early infancy	Delayed, walked at 5 years	Normal	No	58 mg/dl	Less than 5 m/s
Case IV PRESENT REPORT	Early infancy	Delayed	Normal	No	54 mg/dl	Less than 5 m/s
Case I	5 months	Delayed, weakness and hypotonia	Normal	No	58 mg/dl	Less than 2.6 m/s
Case II	Early infancy	Delayed, hypotonic	Normal	No	13 mg/dl	Unmeasurable in legs. 7.9 m/sec of right ulnar nerve

neuropathy were different from typical Dejerine-Sottas disease. Based on these observations, it has been hypothesised that in congenital hypomyelinating neuropathy, there is a primary hypomyelination of peripheral nerves secondary to a defect in the Schwann cells.⁴ This is in contrast to the demyelination which occurs in Dejerine-Sottas disease. Our observation in two cases is in agreement with this hypothesis. Both patients had severe hypomyelination, atypical onion bulb, and preserved axons.

The concept of hypomyelination implies a congenital onset and a nonprogressive or slowly progressive course unless axon degeneration intervenes. In fact, the disease may start as early as the time of birth. A case reported by Hakamada⁶ was born with a low Apgar score and respiratory distress. He had extreme hypotonia with contraction of all four limbs. His sural nerve biopsy performed at one month of age showed absence of myelin sheath, well preserved axons, and no onion bulb formation or myelin debris. There were decreased fetal movements during the pregnancy suggestive of an intrauterine onset. The case reported by Karch² was evaluated at the age of 12 weeks because of feeding difficulties. He had mild initial improvement but

died at age 18 months of respiratory insufficiency. The necropsy revealed total absence of myelin in the cranial and spinal nerve roots distal to the glioschwannian junction. The brain was normally myelinated and the spinal cord showed no abnormalities. The other reported cases which are summarised in the table also had their onset in early infancy, and at the time of report, most were alive, although severely handicapped.

All reported cases, except the patient reported by Ono⁸ and our own case 2, had elevated CSF protein and very slow or unmeasurable nerve conduction velocity. Despite the extremely low nerve conduction velocity, the functional incapacity in these patients is less than might be expected. Both of our patients, for example, could walk with assistance.

The similarities of human congenital hypomyelinating neuropathy to the neuropathy of Trembler mouse is striking.¹³ The Trembler mutant mouse has a dominantly inherited neuropathy characterised by the presence of abnormally thin myelin sheaths, absence of axonal loss, and slow peripheral nerve conduction velocity. The deficit in myelination is limited to the peripheral nerves, is present at the time of birth, and is associated with an

Muscle biopsy	Nerve pathology	Prognosis	Other
Not performed	Absence of myelin, atypical onion bulbs, preserved axons	Alive at 30 months	—
Absent myelin of intramuscular nerves, Type I fibre predominance	Absent myelin sheath. Onion bulbs and empty basement membrane. Preserved axons. No myelin debris	Alive at 5.5 y	Slight reduced NCV in mother. 10-month old sister with slow development
Not performed	Necropsy: Absence of myelin, no onion bulb, axonal loss	Initial mild improvement. Died at 18 months	—
Type II fibre predominance and atrophy. Slight denervation	Near total absence of myelin sheath. Preserved axon. No onion bulbs. No myelin debris	Died at 4 months	—
Absent myelin of intramuscular nerves. Type II fibre predominance	Absence of myelin. Increased Schwann's cell nuclei. Preserved axons. No myelin debris	Alive at 5 years	—
Group atrophy	Sural nerve biopsy: Thinly myelinated axons. Preserved axons. Occasional atypical onion bulbs. Necropsy: Same findings for cranial nerves and spinal roots	Died at 39 months	Possible similar affected sibling. Normal NCV & EMG of parents. Presence of glial bundles at spinal and cranial nerve roots
Not examined	Absence of myelin. Reduplicated basement membrane (atypical onion bulbs). Rare typical onion bulbs. Preserved axons. No myelin debris	Alive at 30 months	—
Group atrophy	Same as Case I	Alive at 6 years	—
Normal	Absence of myelin in 50% of fibres. Very thin myelin in others. Atypical onion bulbs. Preserved axons. No myelin debris	Alive at 5 years	—
Group atrophy	Same as Case III	Alive at 9 years	—
Denervation—reinnervation	Absent myelin. Preserved axon. No onion bulbs	Alive at 5 years	—
Denervation	Myelin loss. Atypical onion bulbs. No myelin debris	Alive at 4 years	—

exaggerated rate of Schwann cell proliferation which persists into adulthood. The remarkable nerve transplantation experiments by Aguayo *et al.*^{13 14} have demonstrated that in Trembler mouse the neuropathy is due to a primary Schwann cell disorder. Segments of sciatic nerves from Trembler mice were grafted into sciatic nerves of normal mice and vice versa. In each instance, the regenerated axons took on the morphological appearance of the donor nerve. Thus, regenerating axons in the normal mouse growing into the segment grafted from Trembler nerve did not myelinate, whereas the Trembler axons growing into the segment grafted from normal nerve developed nearly normal myelination. A similar experiment, involving transplantation of nerve biopsy obtained from patients with congenital hypomyelinating neuropathy into the sciatic nerves of normal, immunosuppressed mice, have not been performed. Transplantation of a biopsy specimen of sural nerve of a patient with Charcot-Marie-Tooth disease into normal but immunosuppressed mice have shown failure of Charcot-Marie-Tooth Schwann cells to myelinate mouse axons.¹⁵ The same results may be predicted from studies on congenital hypomyelinating

neuropathy.

The disparity between the degree of slowed nerve conduction and functional impairment in patients with congenital hypomyelinating neuropathy is not fully explained. It is possible that nodal and paranodal membrane specialisation required for normal saltatory nerve conduction is not fully developed in the peripheral nerves of these patients. In normal mature peripheral nerve, the freeze fracture techniques have demonstrated that the putative sodium channel particles, thought to participate in saltatory conduction velocity, are more confined to the nodes of Ranvier than the axolemma.¹⁵⁻¹⁷ Amyelination or demyelination may result in uniform distribution of these channels and development of continuous conduction along the axon. Although freeze fracture studies of the nerve biopsies of patients with congenital hypomyelinating neuropathy have not been performed, experiments in animals with primary myelin deficiency indicate that the absence of myelin affects the concentration of particles presumed to be sodium channels at the nodes of Ranvier.¹⁸ Finally, in view of the sporadic nature of most of the reported cases it is possible that like Trembler mice these cases are also a new dominant mutation.

Dr V Bagherian and D Armstrong assisted in electron microscopy of Case 1.

References

- ¹ Lyon G. Ultrastructural study of a nerve biopsy from a case of early infantile chronic neuropathy. *Acta Neuropathol (Berl)* 1969;**13**:131–42.
- ² Karch SB, Urich H. Infantile polyneuropathy with defective myelination: an autopsy study. *Dev Med Child Neurol* 1975;**17**:504–11.
- ³ Anderson RM, Dennett X, Hopkins IJ, Shield LK. Hypertrophic interstitial polyneuropathy in infancy: clinical and pathologic features in two cases. *J Pediatr* 1973;**82**:619–24.
- ⁴ Kennedy WR, Sung JH, Berry JF. A case of congenital hypomyelination neuropathy: Clinical, morphological, and chemical studies. *Arch Neurol* 1977;**34**:337–45.
- ⁵ Towfighi J. Congenital hypomyelination neuropathy: Glial bundles in cranial and spinal nerve roots. *Ann Neurol* 1981;**10**:570–3.
- ⁶ Hakamada S, Kumagai T, Hara K, Miyazakis. Congenital hypomyelinating neuropathy in a newborn. *Neuropediatrics* 1983;**14**:182–3.
- ⁷ Guzzetta F, Ferriere G, Lyon C. Congenital hypomyelination polyneuropathy. *Brain* 1982;**105**:395–416.
- ⁸ Ono J, Senba E, Okada S, *et al.* A case report of congenital hypomyelination. *Eur J Pediatr* 1982;**138**:265–70.
- ⁹ Kasman M, Bernstein L, Schulman S. Chronic polyradiculoneuropathy of infancy; a report of three cases with familial incidence. *Neurology (Minneapolis)* 1976;**26**:565–73.
- ¹⁰ Moss RB, Sriram S, Kelts KA, Forno LS, Lewiston NJ. Chronic neuropathy presenting as a floppy infant with respiratory distress. *Pediatrics* 1979;**64**:459–64.
- ¹¹ Palix C, Coignet J. Un cas de polyneuropathie périphérique neo-natale par amyelinisation. *Pediatric* 1978;**33**:201–7.
- ¹² Ulrich J, Hirt HR, Kleihues P, Oberholzer M. Congenital polyneuropathy. A case with proliferated microfilaments in Schwann cells. *Acta Neuropathol (Berl)* 1981;**55**:39–46.
- ¹³ Aguayo JA, Attiwell M, Trecarten J, *et al.* A binormal myelination in transplanted Trembler mouse Schwann cells. *Nature* 1977;**265**:73–5.
- ¹⁴ Aguayo JA, Perkins S, Duncan I, Bray G. Human and animal neuropathies studied in experimental nerve transplant. In: Canal N, Pozza G, eds. *Peripheral Neuropathies*. Elsevier/North Holland Biomedical Press 1978:37–48.
- ¹⁵ Livingston RB, Pfenninger K, Moore H, Akert K. Specialized paranodal and internodal glial-axonal junctions in the peripheral and central nervous system: a freeze-etching study. *Brain Res* 1973;**58**:1.
- ¹⁶ Rosenbluth J. Intramembranous particle distribution at the nodes of Ranvier and adjacent axolemma in myelinated axons of the frog brain. *J Neurocytol* 1976;**5**:731.
- ¹⁷ Schnapp B, Mugnaini E. The myelin sheath: Electron microscopic studies with thin sections and freeze fracture. In: Santini M, ed. *Golgi Centennial Symposium Proceedings*. New York: Raven Press 1975:209.
- ¹⁸ Rosenbluth J. Freeze fracture studies of nerve fibers: Evidence that regional differentiation of the axolemma depends upon glial contact. In: Aguayo AJ, Karpatis G, eds. *Current Topics in Nerve and Muscle Research*. Amsterdam: Excerpta Medica 1979:200–9.