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Hypertrophic Neuropathy with Complete Conduction Block

-Hereditary motor and sensory neuropathy type III-

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Hypertrophic neuropathy is a non-specific consequence of repeated demyelination and remyelination, encountered in a wide range of inherited and acquired disorders. We report an 11-year-old boy with HMSN III, a kind of hypertrophic neuropathy, with clinical, electrophysiologic and pathologic data. The electrophysiologic studies show complete conduction block in the upper and lower extremities with severe abnormal spontaneous activities. The pathologic findings of sural nerve reveal prominent hypomyelination, onion bulb formation, and severe endoneurial collagenization. Complete conduction block with the preservation of fair to good grade muscle strength is an unusual finding in hypertrophic neuropathy and other peripheral neuropathies, in general.

Key Words: Hypertrophic neuropathy, HMSN III, onion bulb, conduction block

The term "hypertrophic neuropathy" is used to describe a nerve thickening related to the concentric proliferation of Schwann cells around axons. It is now recognized that hypertrophic neuropathy is a non-specific consequence of repeated demyelination and remyelination, encountered in a wide range of inherited and acquired disorders. Hypertrophic changes are usually observed in ongoing demyelinating neuropathies such as hereditary motor and sensory neuropathy type I and III (HMSN I and III), Refsum's disease (HMSN IV), and chronic inflammatory demyelinating polyneuropathy (CIDP). Hypertrophic changes have also been seen in a variety of experimental demyelinating neuropathies, including lead neuropathy, recurrent compression, experimental animal model using trembler mouse, and experimental allergic neuritis (Ayers and Anderson 1972; Thomas *et al.* 1992; Dyck *et al.* 1993).

HMSN III, which is also known as Dejerine-Sottas disease, is a severe demyelinating neuropathy with an early age of onset. This relatively rare disorder includes clinical findings of generalized muscle weakness and atrophy, with the greatest severity in distal limb muscles, areflexia, and sensory loss. The disease is characterized histologically by segmental demyelination and remyelination of the peripheral nerves, and onion bulb formations due to supernumerary Schwann cells (Dyck *et al.* 1993). HMSN III have a unique electrophysiologic profile. It was reported in a recent study that the typical features were motor nerve conduction velocity less than 6 m/sec, distal latencies greater than 3 times normal, markedly increased stimulus thresholds, and dramatic temporal dispersion without con-

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duction block (Benstead *et al*, 1990).

We present an 11-year-old boy with HMSN III, whose electrophysiologic studies show complete conduction block with the preservation of fair to good grade muscle strength. These findings are unusual in hypertrophic neuropathy as well as in other hereditary or acquired peripheral neuropathies.

CASE REPORT

The patient is an 11-year-old boy presented to us for the evaluation of stumbling gait since his early childhood, with associated deformities of claw hands and toes. He is an only son and his mother has a history of four spontaneous abortions since his birth. The family history is unremarkable for the neuromuscular diseases. His father side uncle died of unknown disease in early childhood. His mother reports that the pregnancy was uncomplicated and the vaginal delivery was normal. His birth weight was 3.2 kg and the postnatal period was uncomplicated. At 7 months of age, he suffered from an intestinal intussusception and had an operation at the local hospital. His parents first noticed his claw hands at birth. Acquisition of all motor milestones was delayed: sitting without hands support at 15 months and independent walking at 28 months. At 28 months, he was presented at the local hospital for his delayed development and was diagnosed with cerebral palsy. After mastering independent walking, he stumbled easily, and could not run or jump. It was difficult for him to perform fine digital manipulation (e.g. grasping coins or turning keys in locks) due to weakness. His mental functions developed normally and school performance has been average.

At the first presentation to us, he was 153 cm tall (over 97th percentile), weighted 38 kg (90th percentile), and head circumference was 53.5 cm (50-75th percentile). His facial features were not remarkably dysmorphic. He did not complain of night blindness. He had no rash, and no evidence of lymphadenopathy, abnormal pigmentation, or neurofibromatosis. Bilateral median and ulnar nerves were palpated in the wrist and ulnar grooves, respectively. Neurological examination revealed alert mental status, and equal pupil size with prompt light reflexes. He had nystagmus. There was no evidence of retinal pigmentation or optic nerve atrophy on ophthalmologic examination. He showed no spasticity or tremor. No deep tendon reflexes could be elicited and the plantar reflexes were flexor. Cerebellar functions looked normal. The facial muscle weakness was not obvious, though he had flat nasolabial folds. Mild calf muscle atrophy was noticed. He showed bilateral severe pes cavus, especially on the left side. Also, bilateral claw hands and toes were noticed. Sensory examination showed moderately diminished vibration sensation in the toes, but other sensations including pain, temperature, light touch, and position were normal. He showed generalized muscle weakness, especially in the distal muscles. He could ambulate independently but his gait showed steppage gait patterns with wide walking base. His muscle strength in the lower extremities was as follows: hip flexors G/F grade, hip extensor G/F grade, hip abductor G/F grade, hip adductor G/F grade, knee flexor G/F grade, knee extensor G/F grade, ankle dorsiflexor F/F grade, and ankle plantarflexor G/G grade. He could not perform heel gait and had great difficulty in toe gait, bilaterally. His hand strength was markedly reduced: hand grasp power 25/30 lb, three-point pinch power 5/6 lb, and lateral pinch power 8/9 lb.

The studies of urine, complete blood count and blood chemistry with muscle enzymes were all within normal range. The cerebrospinal fluid protein was elevated at 90.7 mg/dl with normal sugar and cell counts. Chromosome analysis of cultured peripheral leukocyte revealed a normal male karyotype, 46 XY. The brain MRI findings showed 0.7 cm × 0.3 cm sized, well-defined, focal bright signal in midpons level on T2-weighted image, bilaterally. These findings could be from previous hemorrhage or infarction but the clinical significance of these findings was uncertain. His IQ was at average level (total IQ 106, verbal IQ 110, performance IQ 100).

In peripheral nerve conduction studies, the

most striking findings were the absence of visible muscle contraction, and of compound muscle action potentials in all examined muscles, except in the left facial and right median nerves, on supramaximal electrical stimulations to the examined nerves. We used very slow sweep speeds up to 30 msec/division during the conduction study in order to pick up all potentials with very prolonged distal latency. Motor nerve conduction study for the right median nerve showed very prolonged distal latency (33.3 msec), low amplitude (0.42 mV), and markedly slow motor nerve conduction velocity in the right median nerve. Left facial nerve conduction study (Fig. 1) revealed very prolonged distal latencies (44.1 msec in the left orbicularis oris, 33.3 msec in the left frontalis), and low amplitude of compound muscle action potentials (0.56 mV in the left orbicularis oris, 0.64 mV in the left frontalis). Needle examination revealed severe abnormal spontaneous activities and reduced but partial recruitment patterns in many examined muscles, especially in distal muscles. Median and tibial somatosensory evoked potential study showed no responses. Electrophysiologic studies for his parents were normal.

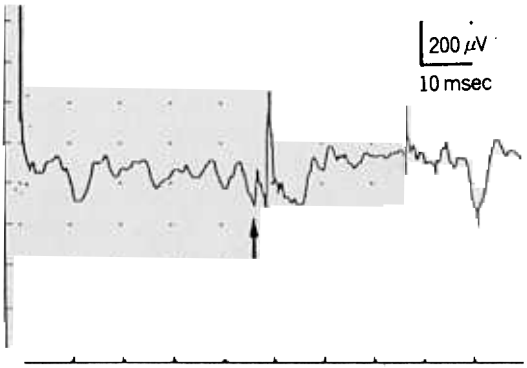

Fig. 1. *Response recorded from the left orbicularis oris muscle on stimulation of left facial nerve. Note very prolonged distal latency(44.1 msec).*

The left sural nerve was biopsied and ex-

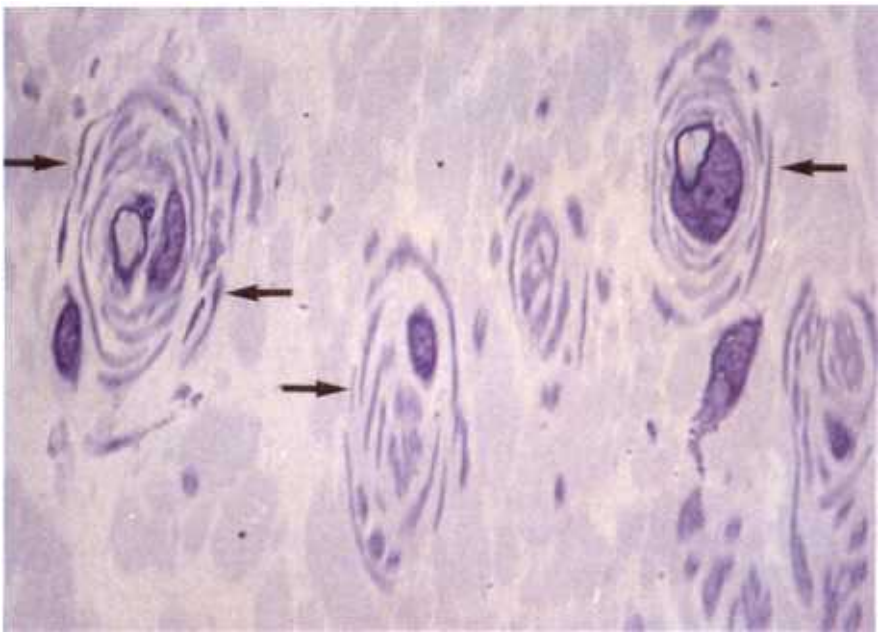

Fig. 2. *Transverse section of sural nerve. Note prominent hypomyelination, onion bulb formation(arrows), and severe endoneurial collagenization(asterisks). Toluidine blue(×1,000).*

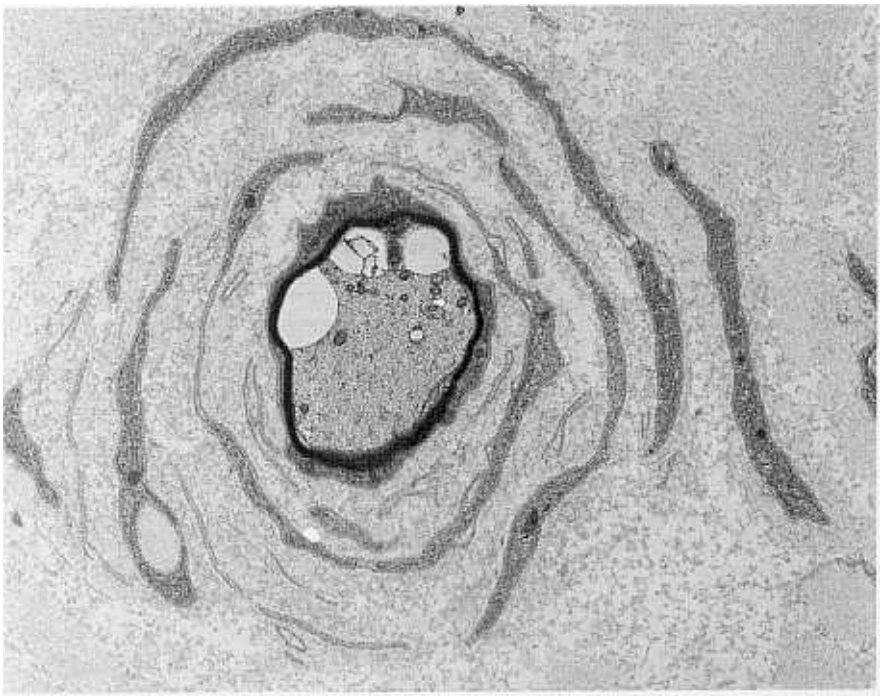

Fig. 3. Electron micrograph showing transverse section through an onion bulb. An axon with thin myelination is surrounded by concentric lamellae of Schwann cell processes(×5,000).

amined. Biopsied nerve showed marked hypertrophy. Transverse sections of sural nerve with toluidine blue stain showed that: the amount of endoneurial connective tissue was markedly increased, widely separated axons possessed very thin myelin sheath, and each axon was surrounded by concentric lamellae of Schwann cell processes - typical onion bulbs. The lamellae was separated by large amounts of connective tissue (Fig. 2). Endoneurial and perivascular inflammatory cells were not present. Electron micrograph revealed that axons with thin myelination were surrounded by concentric lamellae of Schwann cell processes (Fig. 3).

DISCUSSION

Hypertrophic neuropathy is encountered in a wide range of inherited and acquired disorders. Demyelination leads to Schwann cell proliferation; an excess of these Schwann cells results and those which are not involved in remyelinating the axon accumulate around the fiber. The profiles of the concentric proliferation of Schwann cells around axons are perhaps among the most striking of the reactions encountered in peripheral nerve pathology. They have been likened to cross-sections through an onion. Among inherited disorders, diffuse nerve thickening related to such 'onion bulb' formations is observed in HMSN I and III and in Refsum's disease. In acquired demyelinating neuropathies, it may be a feature of CIDP. Onion bulbs are now known also to occur in diabetic neuropathy, acromegaly, and metachromatic leukodystrophy (Kasman *et al.* 1976; Satran 1980; Thomas *et al.* 1992).

Refsum's disease, an inborn error of lipid metabolism with an autosomal recessive mode of inheritance, can be excluded by the normal

serum phytanic acid level and the absence of pigmentary retinopathy (Felice *et al.* 1994). To our knowledge, there has been no report of Refsum's disease without this ophthalmologic sign, and night blindness (Dyck *et al.* 1993). We could not check serum phytanic acid level in our patient but the ophthalmologic examination did not show retinal pigmentation or other abnormalities, and he did not have any history of night blindness.

Differential diagnosis from childhood CIDP may be difficult; the sural nerve biopsy is usually the most helpful diagnostic test. In addition to endoneurial inflammatory cells and perineural edema, sural nerve biopsy in CIDP usually reveals moderate myelinated fiber loss and only rudimentary onion bulbs (Felice *et al.* 1994).

The clinical symptoms of HMSN III are very similar to those of HMSN I, except for the degree of severity. For example, no one with HMSN IA and IB has been confined to a wheelchair, even late in life, but the two oldest patients with HMSN III have been confined to wheelchairs since the ages of 31 and 19, respectively (Dyck *et al.* 1993). In our literature review, we have not found any report on life expectancy of HMSN III, while a normal life expectancy can probably be expected in HMSN IA and IB. Children with HMSN III usually succumb to respiratory complications in the first year of life (Moss *et al.* 1979), while cardiopulmonary complications in adolescent and adult HMSN III patients are not considered a common feature. But there has been increasing awareness of respiratory involvement in adult HMSN III patients. As well, the clinicopathological description of phrenic nerve involvement in HMSN III has recently been reported. The patient was a 12-year-old girl who died suddenly in her sleep following the onset of mild flu-like symptoms. The autopsy revealed diffuse and severe axonal loss with prominent onion bulbs in all nerves including the phrenic nerve (Felice *et al.* 1994). As in other neuromuscular diseases, therefore, physical therapies for strengthening respiratory muscles, and effective pulmonary toileting are important for the rehabilitational management of HMSN III patients.

Dyck (1975) summarized the clinical features of 6 HMSN III cases as follows. In the majority of cases, hypotonia or delay in developmental milestones or both are noticed within the first year of life. Mean age of walking is often delayed beyond the second year and coordination is never fully normal. Ataxia is seen in all patients. Proximal weakness and deformity of the hands and feet are not frequent in early childhood but become increasingly more obvious with time so that by the second decade, proximal weakness is the rule rather than the exception. Clinical hypertrophy of nerves is present in most HMSN III patients; by contrast it is noticed in only a quarter of those with HMSN I. By the time adequate testing can be performed, the majority of patients have experienced moderate to severe sensory loss. Such sensory loss is rarely seen in HMSN I cases (Dyck, 1975; Ouvrier *et al.* 1987). We think that the clinical features and pathologic findings of our patient are closer to those of HMSN III than to those of HMSN I, when using the current Dyck classification.

Ouvrier (1987) reported that while the onion bulb lamellae in HMSN I contained generous amounts of cytoplasm with normal organelles, the onion bulb lamellae in HMSN III contained little cytoplasm and frequently consisted of apposed double basement membranes; but the pathological features of HMSN III cannot be absolutely differentiated from HMSN I, except by the degree of severity.

HNSM III appears to exhibit autosomal recessive inheritance in the majority of pedigree, or to arise as sporadic cases, therefore the recessive pattern of inheritance for HMSN III has allowed distinction from the dominantly inherited HMSN I (McCusick, 1986; Dyck *et al.* 1993; Roa *et al.* 1993). But, there have been reports of patients with a phenotype resembling HMSN III in which both parents were affected by HMSN I (Killian and Kloepfer, 1979), suggesting the possibility of genetic heterogeneity within HMSN III.

It is known that most HMSN IA results either from duplication of a 1.5-megabase DNA region in chromosome 17p11.2-p12 containing the peripheral myelin protein 22 (PMP22), or

from PMP22 point mutation (Mancardi *et al.* 1994). These findings suggest that alterations in the structure or level of expression of PMP22, an integral myelin membrane protein, are responsible for HMSN IA. Recently mutational analysis of the PMP22 coding region in two unrelated HMSN III patients identified individual missense point mutations present in the heterozygous state. These findings suggest that HMSN III can result from dominant point mutation alleles of PMP22 (Dyck *et al.* 1993; Hayasaka *et al.* 1993; Roa *et al.* 1993). P_0, also known as myelin protein zero (MPZ), is the major structural protein of peripheral nervous system myelin and is another integral membrane protein. P_0 is an adhesive glycoprotein of the immunoglobulin superfamily and is proposed to play a significant part in the compaction of myelin. Lately, the P_0 locus was mapped to chromosome 1q22-q23 in the region of the HMSN IB locus. A recent study shows that de novo dominant mutation of the P_0 gene is responsible for at least some sporadic cases of HMSN III (Hayasaka *et al.* 1993). One author describes the inheritance of HMSN III as autosomal dominant (McCusick, 1992). At the moment, differentiation between HMSN I and HMSN III on the basis of inheritance patterns seems to be impossible (Satran 1980; Sunwoo *et al.* 1988).

As a clinical entity, HMSN III has been a subject of considerable controversy. Westerberg (1982) suggested that "the designation of a special infantile hypertrophic HMSN III should be abandoned as being an artificial, and misleading concept." The basis for this viewpoint appears to be the proposition that cases of so-called HMSN III represent the more severely affected end of the spectrum of severity of HMSN I and that any proposed clinical or histopathological criteria which can be advanced as distinguishing features are merely the result of the selection of more severe cases for analysis. Thus, instead of being two completely distinct disease entities, HMSN I and HMSN III may more accurately represent different points in a spectrum of clinical findings due to allelic heterogeneity. Identification of the primary defect in the diseases enables us to classify the peripheral neuropathies based on their aetiologies and to advance an understanding of the physiological role of each myelin component (Hayasaka *et al.* 1993; Roa *et al.* 1993).

It was reported that electrophysiologic studies in 11 patients with HMSN III showed median and ulnar motor nerve conduction velocities of less than 6 m/sec in all but 1 patient. Marked temporal dispersion without conduction block was present in all patients (Benstead *et al.* 1990). The following histologic features of the nerves in HMSN III are known to be probably important factors in the mechanism of abnormalities of conduction: (1) myelin is absent for long distances along myelinated fibers; (2) when myelin is present, it is abnormally thin; (3) the distance of the largest axis cylinders are smaller than in healthy nerves; (4) the number of myelinated fibers probably decreased; and (5) there is an excessive separation of fibers by Schwann cell cytoplasm and collagen fibrils, which probably accounts for some of the decrease in the amplitudes of the action potentials in vitro(Dyck *et al.* 1971).

The striking finding in the electrophysiologic study of our case is the preservation of fair to good grade muscle strength, despite complete conduction block on supramaximal electrical stimulations. This finding suggests that the proposition that HMSN III does not show conduction block should be reconsidered.

REFERENCES

Ayers MM, Anderson RM: Onion bulb neuropathy in the trembler mouse: a model of hypertrophic interstitial neuropathy(Dejerine-Sottas) in man. *Acta Neuropath (Berl.) 25: 54-70, 1973*

Benstead TJ, Kuntz NL, Miller RG, Daube JR: The electrophysiologic profile of Dejerine-Sottas disease(HMSN III). *Muscle Nerve 13: 586-592, 1990*

Dyck PJ, Lambert EH, Sanders K, O'Brien PC: Severe hypomyelination and marked abnormality of conduction in Dejerine-Sottas hypertrophic neuropathy: Myelin thickness and compound action potential of sural nerve in

vitro. *Mayo Clin Proc 46: 432-446, 1971*

Dyck PJ: *Inherited neuronal degeneration and atrophy affecting peripheral motor, sensory, and autonomic neurons.* In Dyck PJ, Thomas PK, Lambert EH, eds. *Peripheral neuropathy.* W.B. Saunders Company, *1975, 825-867*

Dyck PJ, Chance P, Lebo R, Carney A: *Hereditary motor and sensory neuropathies.* In Dyck PJ, Thomas PK, eds. *Peripheral neuropathy.* 3rd ed. W.B. Saunders Company, *1993, 1094-1136*

Felice KJ, Fratkin JD, Feldman EL, Sima AAF: Phrenic nerve involvement in Dejerine-Sottas disease: A clinicopathological case study. *Pediatr Pathol 14:905-911, 1994*

Hayasaka K, Himoro M, Sawaishi Y, Nanao K, Takahashi T, Takada G, Nicholson GA, Ouvrier RA, Tachi N: De novo mutation of the myelin P_0 gene in Dejerine-Sottas disease (hereditary motor and sensory neuropathy type III) *Nature Genet 5: 266-268, 1993*

Kasman M, Bernstein L, Schulman S: Chronic polyradiculoneuropathy of infancy. *Neurology 26: 565-573, 1976*

Killian JM, Kloepfer HW: Homozygous expression of a dominant gene for Charcot-Marie-Tooth neuropathy. *Ann Neurol 5: 515-522, 1979*

McCusick VA: *Mendelian inheritance in man.* 10th ed. Johns Hopkins University Press, *1992*

Mancardi GL, Uccelli A, Bellone E, Sghirlanzoni A, Mandich P, Pareyson D, Schenone A, Abbruzzese M, Ajmar F: 17p11.2 duplication is a common finding in sporadic cases of Charcot-Marie-Tooth type 1. *Eur Neurol 34: 135-139, 1994*

Moss RB, Sriram S, Kelts KA, Forno LS, Lewiston NJ: Chronic neuropathy presenting as a floppy infant with respiratory distress. *Pediatr 64: 459-464, 1979*

Ouvrier RA, Mcleod JG, Conchin TE: The hypertrophic forms of hereditary motor and sensory neuropathy. *Brain 11:121-148, 1987*

Roa BB, Dyck PJ, Marks HG, Chance PF, Lupski JR: Dejerine-Sottas syndrome associated with point mutation in the peripheral myelin protein 22(PMP22) gene. *Nature Genet 5: 269-273, 1993*

Satran R: Dejerine-Sottas disease revisited. *Arch neurol 37: 67-68, 1980*

Sunwoo IN, Kim JS, Chi JG, Suh YL: A case of progressive hypertrophic neuropathy in childhood with facial diplegia(Dejerine-Sottas disease). *Yonsei Med J 29: 278-285, 1988*

Thomas PK, Landon DN, King RHM: *Diseases of the peripheral nerves.* In Adams JH, Duchen LW, eds. *Greenfield's neuropathology,* 5th ed. Edward Arnold, *1992, 1158-1160*

Westerberg B: *Neuropediatric aspects of hereditary peripheral neuropathies in childhood.* MD Thesis, University of Gothenberg, *1982, 6-36*