

A Case of Progressive Hypertrophic Neuropathy in Childhood with Facial Diplegia (Dejerine-Sottas Disease)

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Due to unknown underlying biochemical disorders, the delineation of Dejerine-Sottas disease has been subject to recent controversy. This is a case of a 9 year-old Korean female with the clinical manifestations of sporadic occurrence, chronic severe and symmetrical motor sensory polyneuropathy, thickened palpable peripheral nerves, facial diplegia, areflexia and abnormal pupillary reactivity to light. The electrophysiological studies are indicative of chronic demyelination neuropathy showing markedly slowed motor NCV, low and dispersed CMAPs and extreme dispersion of a SNAP. The pathology of the sural nerve reveals prominent hypomyelination and onion bulbs characterized by whorling, concentric proliferations of the cytoplasmic processes of Schwann cells. The nosological problems of hypertrophic neuropathy in childhood are discussed.

Key Words: Dejerine-Sottas disease, Onion-bulb neuropathy, hypomyelination

Hypertrophic neuropathy is characterized by a whorling, concentric proliferation of Schwann cells around axons which is perhaps the most striking among the reactions encountered in peripheral nerve pathology (Austin 1956; Webster *et al.* 1967). This process referred to as 'onion bulb formation' has long been considered to be specific for Dejerine-Sottas disease and certain dysmetabolic neuropathies such as Refsum's disease, but the lesion is now known to be the nonspecific consequence of repeated demyelination and remyelination and is encountered in a wide-range of inherited and acquired disorders (Pleasure and Towfighi 1972).

Among hypertrophic neuropathies, Dejerine-Sottas disease is one of the rare heredo-degenerative disorders of peripheral nerves, is also known as progressive hypertrophic interstitial neuropathy of childhood and belongs to Dyck's hereditary motor sensory neuropathy (HMSN) type III (Satran 1980).

Most cases of Dejerine-Sottas disease are isolated

or, if multiple, confined to a single sibship, suggesting autosomal recessive inheritance, and occur usually in childhood. The consistent clinical manifestations include symptoms of severe symmetrical sensori-motor peripheral neuropathy with areflexia, which involves all peripheral nerves of the upper and lower extremities with the tendency of worsening in distal limbs. The thickened peripheral nerves are easily palpable. The sensory loss may be severe, usually affecting touch, position, and vibration sense more than pain and temperature (Dyck and Lambert 1968). The peripheral nerve conduction velocities are markedly slow and nerve biopsies reveal characteristic onion bulbs and hypomyelination (Weller 1976). The cerebrospinal fluid protein level may be increased. Ataxia, kyphoscoliosis, hearing loss, facial weakness, nystagmus and abnormal pupillary responses to light can be seen but are inconsistent (Gathier and Bruyn 1970).

There have been many reports on Dejerine-Sottas disease with considerable recent controversy about the delineation of this disease in the literature, including a case of a 6 month old Korean male reported in the USA (Moss *et al.* 1979). But in this country, there was one case report with the title of Dejerine-Sottas disease in 1971 (Kim *et al.* 1971), which looked, in fact, like a case of neuroma of the hand. This may be, to the authors' knowledge, the first case of Dejerine-Sottas disease in Korea.

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CASE REPORT

A nine year-old girl presented at Severance Hospital in Jan. 1987 because of quadripareisis and facial diplegia for several years.

She was the first child of 3 children with healthy parents. She was delivered by Caesarean section due to breech presentation at full-term with a body weight of 3.0kg. She was fed by breast and vaccinated as scheduled. She began to toddle around one year of age and her mother did not observe any psychomotor retardation up to 4 years when the patient entered a kindergarten. Compared with other children, her mother noticed that she could not run or jump, and her facial expression on smiling and crying was poor. In retrospect, however, she had never seen the patient run before. These handicaps have a tendency of slow progression without any fluctuation. Recently she had difficulty in walking and hand movements, and easily fell down. Her mental functions developed normally, and her school performance was excellent. There was no specific past history except pneumonia and febrile convulsions at 1 year of age. All other family members including her younger brother and sister were healthy on history and by examination.

The temperature was 36.6°C, the pulse was 95, and the respiration was 23. The blood pressure was 130/80mmHg.

The height was 118cm (25 percentile) and the weight was 25 Kg(90 percentile). On examination there was no rash, lymphadenopathy, abnormal pigmentation or evidence of neurofibromatosis. The lungs were clear and the heart was normal. Abdominal examination was negative.

On neurological examination, the patient was alert and her mental functions looked normal. Both pupils were reactive: comparing the pupillary response on near vision, the response to light tended to be sluggish and incomplete. Extraocular movements were intact. There was no optic atrophy, papilledema or retinal pigmentation on ophthalmoscopic examination. The facial muscle weakness was severe, symmetrical, and peripheral in type. Other cranial nerves appeared normal and no peripheral nerve was palpated on the head or neck. The muscles of all limbs and the upper back were somewhat wasted with claw hand deformities. There was, however, no kypho-scoliosis or deformity of the foot. The peripheral nerves were enlarged and palpated on the median nerve of the forearm, the ulnar nerve in the ulnar groove and

peroneal and posterior tibial nerves in the popliteal area. The Tinel sign appeared tapping the palpated peripheral nerves. The muscles of all limbs were moderately weak, worse in the distal part and in the lower extremities, with a steppage and waddling gait. On sensory function tests, the position and vibration senses were markedly diminished distally, but pain and temperature sensations were relatively preserved. No stretch reflexes could be elicited. The cerebellar functions looked normal.

The urine was normal. The hematocrit was 43.9%, the white-cell count was 5,700 with a normal differential count. The serum electrolytes and blood chemistries were all within normal range. The creatine kinase (CK) was 100 IU/L. The VDRL was nonreactive. An electrocardiogram and an x-ray film of the chest were reported normal. The cerebrospinal fluid was normal; protein was 22mg/dl and glucose 72mg/dl.

Because of clinical symmetry, the electrophysiological studies were performed on the right upper and lower extremities. The motor nerve conduction studies revealed markedly prolonged terminal latencies (8.9 msec in the median nerve, 7.9 msec in the ulnar nerve, 14.1 msec in the peroneal nerve and 10.0 msec in the posterior tibial nerve), very slow conduction velocities (10.4m/sec in median, 8.2m/sec in ulnar, 9.5m/sec in peroneal and 8.7m/sec in posterior tibial nerves) and low compound motor action potentials (2.3mV in median, 0.5mV in ulnar, 0.5mV in peroneal and 0.2mV in posterior tibial nerves) with dispersion. The SNAPs (sensory nerve action potentials) were not recordable by ordinary methods, but by the signal averaging technique, there appeared markedly dispersed potentials on the median nerve between the wrist and the elbow (Fig. 1). The needle EMG studies showed mild to moderate denervation potentials and neuropathic MUPs (motor unit potentials) with reduced interference. The electrophysiological studies of all other family members were normal.

The left sural nerve was biopsied and observed. Under light-microscopy the nerve trunk was normal to slightly enlarged in size with prominent epineurial fibrous tissue. Both cross and longitudinal sections were made, and prepared with Luxol-fast blue, Masson trichrome and Bodian stains along with routine Hematoxylin-Eosin stain. Cross sections were characterized by the loss of large and small myelinated fibers and interstitial fibrosis. Onion-bulb formation was seen in many areas. This structure was more easily seen with the trichrome stain. Interestingly the whorls were also seen with the Bodian stain (Fig. 2). Concentric layering was made of discontinuous curvilinear

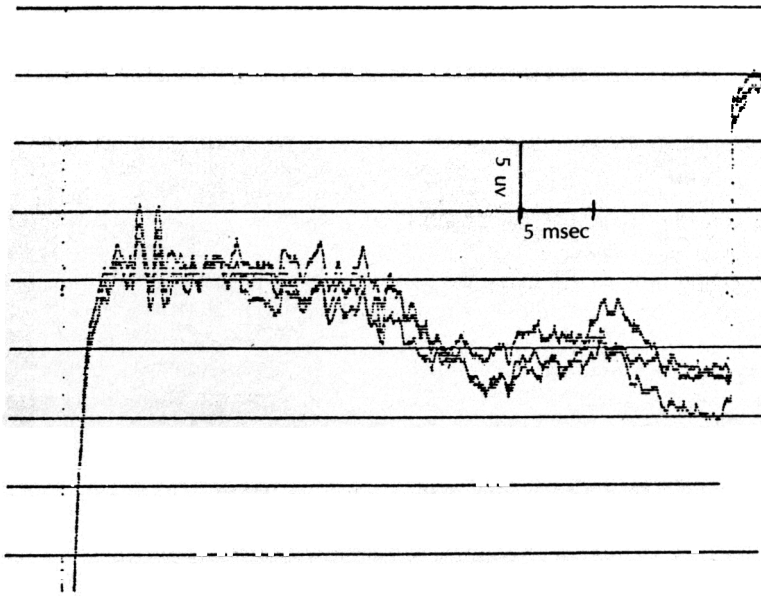


Fig. 1. A markedly dispersed SNAP in the median nerve of the right forearm.

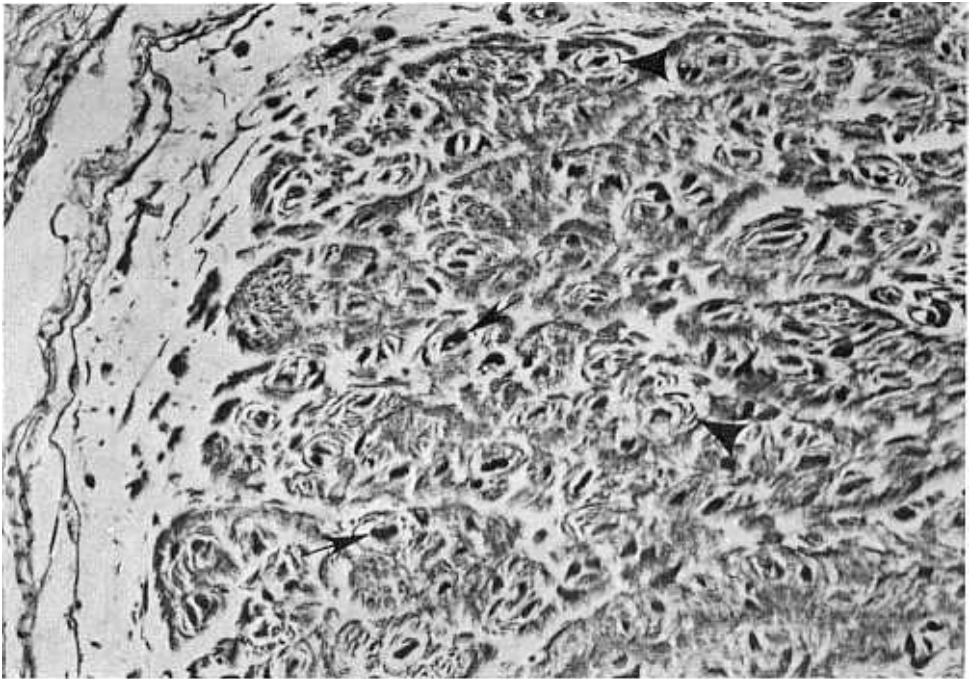


Fig. 2. Sural nerve showing "onion bulb" whorls with large axons (arrow) at the center. Concentric lamination is seen as a discontinuous line (arrowhead). Bodian stain ($\times 300$)

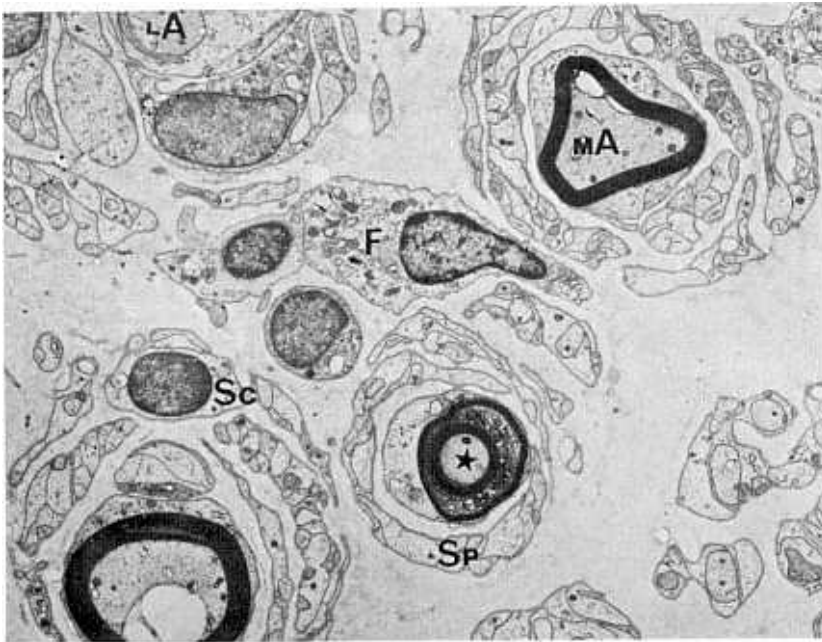


Fig. 3. The central thin-myelinated axon (asterisk) is surrounded by circumferentially arranged Schwann cell(Sc) processes (Sp) in which small axons are incorporated. Relatively large amyelinated (LA) and myelinated (MA) axons are seen. Fibroblasts (F) and an increase of collagen fibers are noted in the interstitium. Lead citrate-uranylacetate. (×8,750)

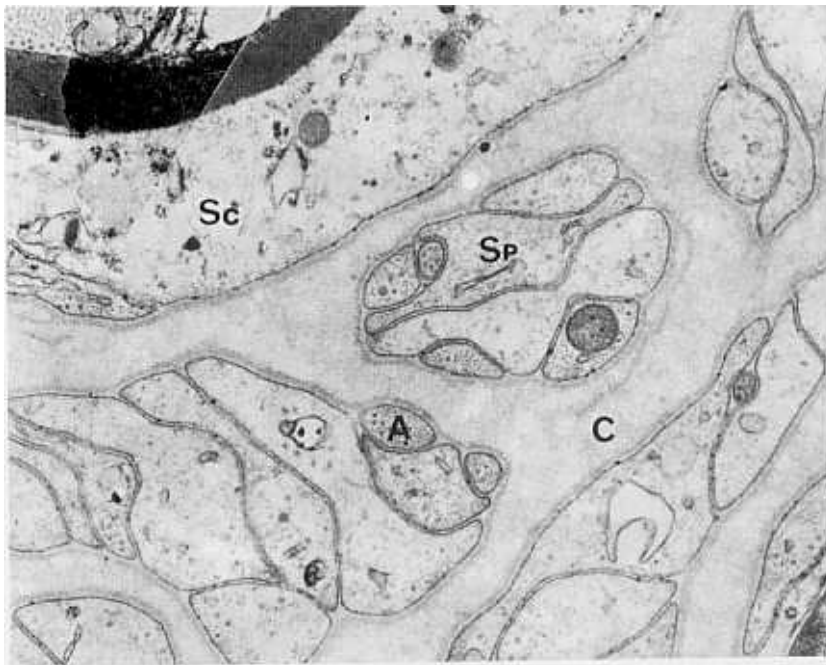


Fig. 4. The onion bulb formation of Schwann cell(Sc) processes (Sp) around a central hypomyelinated axon. The Schwann cell membrane layers in the whorl are separated from the central nerve fiber and from each other by longitudinally directed collagen fibrils (C). Small unmyelinated axons (A) are noted. Lead citrate-uranylacetate. (×42,500)

silver positive lines. No myelin digestion chamber was seen.

Electron-microscopically there was a striking loss of myelin in most areas, and in its place there was large number of onion bulbs composed of Schwann cell processes. Axons of large diameter are commonly devoid of myelin sheaths (Fig. 3). Schwann cell proliferation was also noted around the preserved axons. Multiple layers of imbricated cellular processes of Schwann cells were arranged concentrically around a central myelinated, or hypo- or amyelinated nerve fibers of large caliber. The axons located in the centers of these 'bulbs' were invested by one to several layers of Schwann Cell processes. Often small unmyelinated axons were seen in their cytoplasm and the basement membrane was tightly apposed to their surface membrane (Fig. 4). The cell layers in the whorls were separated from the central nerve fiber and from each other by longitudinally directed collagen fibers. Non-myelinated fibers were distributed throughout the nerve, either in small groups or within Schwann cells forming the whorls. Vacuolated fibroblast were not seen. Regenerating nerve sprouts and axonal degeneration were not seen.

DISCUSSION

Hereditary motor and sensory neuropathy (HMSN) is not a single disease, but a heterogeneous group of disorders. Because of unknown etiology and pathogenesis with the exception of Refsum's disease, the classification of disorders at this time can, at best, rest on the nature of inheritance, age of onset, symptomatology, populations of neurons affected and the pathologic nature of that involvement. The most commonly used classification at present is Dyck's (Dyck 1984) in which 7 types of HMSN are defined; type I is the dominantly inherited hypertrophic neuropathy (hypertrophic Charcot-Marie-Tooth disease), type II the neuronal type of peroneal muscular atrophy, type III the hypertrophic neuropathy of infancy (Dejerine-Sottas disease), type IV the hypertrophic neuropathy associated with phytanic acid excess (Refsum's disease), type V the HMSN with spastic paraplegia, type VI the HMSN with optic atrophy and type VII the HMSN with retinitis pigmentosa. However, the clinical and pathological spectrums of HMSN are so variable and overlapping (Hagberg and Westerberg 1983; Rossi *et al.* 1983), that strict applications are sometimes impossible (Bouldin *et al.* 1980), that some intermediate forms can be found, and that some authors (Salisachs *et al.* 1982) believe there is no clear separation of subtypes. In this situation, the typing of HMSN may be

affected by the author's point of view and, as a result, nosological confusion may be inevitable at the present time (Dyck 1975; Hagberg and Westerberg 1983). This controversial problem of classification is especially true with regard to hypertrophic neuropathy.

According to the definition of Dyck (1984), there is no question that the disease of our patient is one type of HMSN. The heredity of our patient is uncertain, but suspected as autosomal recessive or sporadic; other family members are healthy on physical examination and electrophysiological studies. The very slow nerve conduction velocities (NCV) and dispersed CMAPs (compound muscle action potentials) and SNAP in this patient are indicative of chronic demyelinating neuropathy. The patient is not diabetic and chronic idiopathic demyelinating neuropathy can be excluded by clinical, electrophysiological and pathological features. The peripheral nerves are palpable, but there is no neuroma nor evidence of neurofibromatosis.

This is not a case of HMSN type IV (Refsum's disease), a neurolipidosis characterized by excessive storage of phytanic acid, clinically or pathologically; there is no ichthyosis, deafness or retinitis pigmentosa and no inclusions within Schwann cells demonstrated by electron microscopy. The possible HMSN types of our patient might be type I (hypertrophic Charcot-Marie-Tooth disease) or type III (Dejerine-Sottas disease). Usually it is known that Charcot-Marie-Tooth disease is inherited by autosomal dominant trait and Dejerine-Sottas disease by autosomal recessive or sporadic. Dejerine-Sottas disease appears earlier and presents a more severe and generalized sensorimotor polyneuropathy, and associates more diverse clinical manifestations than the classical Charcot-Marie-Tooth disease. However, the heredity and clinical criteria are frequently insufficient for this differentiation: HMSN type I may show variable autosomal dominant (Dyck *et al.* 1983), autosomal recessive (Harding and Thomas, 1980) or X-linked (Phillips *et al.* 1985) inheritance, and also infantile onset (Kasman *et al.* 1976, Vanasse and Dubowitz 1981). Therefore, some authors (Hagberg and Westerberg 1983) have suggested that the designation of HMSN type III (Dejerine-Sottas disease) be abandoned entirely.

The striking pathological feature of the sural nerve in our patient is the onion bulbs, formed by several concentric lamellae of Schwann cell processes containing many small unmyelinated axons, with a central amyelinated or hypomyelinated large axon. Sometimes the central axon is absent. Such onion bulb formations, originally recognized by Gombault and Mallet (1898), were considered to be a specific type

of pathological reaction and became associated with the names of Dejerine and Sottas (1898) who described these appearances in a pair of siblings with an inherited peripheral neuropathy (Satran 1980; Thomas *et al.* 1975). But it is now realized that the onion bulbs are the terminal phase of various neuropathic processes in which sequential stages of demyelination and remyelination are involved and may represent only one particular aspect of certain forms of chronic demyelinating neuropathy (Thomas and Lascelles, 1967). Dyck (1984) proposed the following sequence of events in onion bulb formation; (1) partial or complete segmental demyelination of an internode, (2) mitosis of a Schwann cell associated with the demyelinated internode, (3) capture of the demyelinated region by one of the two newly formed Schwann cells and outward displacement of the other, (4) circumferential orientation (influenced by the second order basement membrane, the one remaining from the old internode) and (5) successive outward displacement of layers of basement membranes and Schwann cells with repeated segmental demyelination and remyelination.

In nerve biopsies from patients with Dejerine-Sottas disease, Dyck and Gomez (1968) has shown that the transverse fascicular area is greater than it is in healthy nerves, that in severely affected nerves the frequency distribution of myelinated fibers is markedly abnormal, that there is an abnormally high ratio of axis cylinder diameter to total fiber diameter because of hypomyelination, and that the term Dejerine-Sottas disease should be restricted to this form (Dyck 1984). Recently, Ouvrier *et al.* (1987) tried to differentiate Dejerine-Sottas disease from the hypertrophic Charcot-Marie-Tooth disease. In addition to a significantly greater incidence of ataxia, areflexia and clinical nerve enlargement in Dejerine-Sottas disease, there was (1) significantly lower density for myelinated fibers 8 μ m or more in diameter, (2) a greater frequency of onion bulbs, (3) more lamellae per onion bulb and (4) a higher ratio of mean axon diameter to fiber diameter. They also found that the onion bulb lamellae in Dejerine-Sottas disease contained little cytoplasm and frequently consisted of apposed double basement membranes in contrast to hypertrophic Charcot-Marie-Tooth disease in which the lamellae consisted of cytoplasmic processes of Schwann cells (Low *et al.* 1978, Smith *et al.* 1980). However some authors (Karch and Urich 1975, Kennedy *et al.* 1977, Lyon 1969, Ono *et al.* 1982) prefer the term congenital hypomyelination neuropathy for similar pathological features with the proposals of defective myelination rather than the classical concepts of repeated

demyelination-remyelination processes of the hypertrophic neuropathy. Guzzetta *et al.* (1982) have demonstrated that congenital hypomyelination neuropathies show a higher frequency of axons totally devoid of myelin sheaths than cases with onset later in childhood. They also show a higher frequency of onion bulbs composed of double layers of basal lamina from which Schwann cell processes have presumably disappeared. At present, it is uncertain whether the childhood onset and congenital cases of hypomyelination neuropathy are genetically distinct (Luetschig *et al.* 1985), or what the nosological status of rapidly lethal cases of congenital hypomyelination neuropathy in which onion bulbs have not been present is (Seitz *et al.* 1986). In this respect, the delineation of Dejerine-Sottas disease (MHSN type III) and its nosological confusion with congenital hypomyelination neuropathy have been subject to considerable recent controversy (Joosten *et al.* 1974) and the resolution of this nosological problem will depend on the identification of the underlying enzyme defect (Karch and Urich 1975).

The pathological findings of our patient are confusing; the hypomyelination with little evidence of active myelin destruction is suggestive of Dejerine-Sottas disease or congenital hypomyelination neuropathy (Ono *et al.* 1982), but the onion bulb formations by the cytoplasmic processes of Schwann cells are more compatible with the hypertrophic Charcot-Marie-Tooth disease (Low *et al.* 1978; Ouvrier *et al.* 1987). There are, however, other opinions that the pathological differentiation between Dejerine-Sottas disease and the hypertrophic Charcot-Marie-Tooth disease is impossible (Anderson *et al.* 1973, Hagberg and Westerberg 1983), and that the electron microscopic findings of Dejerine-Sottas disease are heterogeneous (Joosten *et al.* 1974). The clinical manifestations of our patient with the sporadic appearance, childhood onset, severe neurological deficits, facial diplegia and abnormal pupillary reactivity to light are also more suggestive of Dejerine-Sottas disease rather than Charcot-Marie-Tooth disease. The NCV in this case is also too slow to be the hypertrophic Charot-Maries-Tooth disease (Low *et al.* 1978).

Marked slowing of the motor nerve conduction velocities has been a consistent finding in Dejerine-Sottas disease, in fact, the slowest among various peripheral neuropathies ever reported (Dyck and Gomez, 1968; Joosten *et al.* 1874). It is known that the sensory nerve action potentials (SNAP) are usually unrecordable. These electrophysiological abnormalities are related to the pathological features of peripheral

nerves including hypomyelinations and onion bulb formations (Dyck et al. 1971).

That a metabolic abnormality of lipid metabolism may underlie HMSN type III is suggested by the similarity of the histologic abnormality in nerve that is seen in Refsum's disease (Zacks et al. 1968). A decrease in the amount of cerebroside in peripheral nerves with increased ceramide monohexoside sulfate and low levels of other ceramide hexose sulphates in the liver, and other biochemical changes of peripheral nerves have been reported (Dyck et al. 1970), but not confirmed yet. The histology of hypomyelination in Dejerine-Sottas disease indicates that the site of the lesion may be mainly in the Schwann cells, but the finding of a marked abnormality of the axonal transport of dopamine beta-hydroxylase (Brimijoin et al. 1973) and the decreased diameter of axons (Nukada et al. 1983) in hypertrophic neuropathy is confusing, suggesting a role of axonopathy in secondary segmental demyelination and remyelination and hypertrophic neuropathy. At present, because the underlying biochemical disorder is yet to be defined, the concept of Dejerine-Sottas disease should be regarded as a provisional entity.

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