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M. Sabatelli · T. Mignogna · G. Lippi · S. Servidei
G. Manfredi · E. Ricci · E. Bertini · M. Lo Monaco
P. Tonali

Autosomal recessive hypermyelinating neuropathy

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Abstract We studied three patients from two kinships, affected by early onset hereditary motor and sensory neuropathy with probable autosomal recessive inheritance (HMSN type III). Morphological studies of sural nerve biopsies revealed an abnormal myelin proliferation. Two adult patients with long-term follow up, lost ability to walk at 28 and 22 years and showed severe involvement of the cranial nerves. Our observations suggest that "hypermyelination neuropathy" with early onset is a progressive disease with poor long-term prognosis. In one kinship the occurrence of the disease in two sibs of both sexes but not in parents, is consistent with an autosomal recessive inheritance. Familial cases of hypermyelination neuropathy have not been described in previous reports. Morphological aspects of this condition are compared with other forms of hypermyelination neuropathy.

Key words Polyneuropathy · Hereditary motor and sensory neuropathy · Demyelination · Myelin sheath foldings

Introduction

Hereditary motor and sensory neuropathies (HMSN) include a heterogeneous group of disorders. The most frequent forms are HMSN type I and II which are inherited as an autosomal dominant trait.

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M. Sabatelli (✉) · T. Mignogna · G. Lippi · S. Servidei
G. Manfredi · E. Ricci · M. Lo Monaco · P. Tonali
Neurological Institute, Catholic University, Pol. A. Gemelli, Largo Gemelli, 8, I-00168 Rome, Italy

E. Bertini
Department of Neuropediatrics, Hospital Bambino Gesu', Rome, Italy

HMSN type III is not a well-defined entity. Characteristic features are autosomal recessive inheritance, cogenital or infantile onset, variable expression and markedly decreased nerve conduction velocity. Pathological changes in sural nerve biopsy from typical forms are severe loss of myelinated fibers with hypo- and demyelination and frequent onion bulbs [4]. In recent years, however, some patients have been reported with a virtual absence of myelin sheath and absent or atypical onion bulb formations (hypomyelination neuropathy) [6, 8, 9, 11, 17] or with an abnormal myelin overgrowth (hypermyelination neuropathy) [5, 7, 15, 16, 19]. It is still unclear whether or not these conditions represent distinct clinico-pathological entities.

We describe three patients from two kinships, affected by early onset HMSN with probable autosomal recessive inheritance, showing the features of "hypermyelination neuropathy".

Case reports

Patient 1

This 30-year-old man was born normally at term after a normal pregnancy. His 53-year-old mother was normal at clinical and electrophysiological examination. His father was referred to as being healthy but was not examined by us. Parents were not consanguineous; they were from a little town of 1000 inhabitants, near Isernia, Italy. One sister, aged 33 years, was normal at clinical exmination. Another sister was affected by the same disease (patient 2).

The patient walked normally at 13 months. Around the age of 18 months the parents noticed that he walked with a waddling gait, on tip toes. When he was 11 years old a diagnosis of Charcot-Marie-Tooth was established in another neurological institute. At the time the patient showed bilateral foot drop, pes cavus with retraction of Achille's tendons, waddling gait, mild weakness of small hand muscles and areflexia; there was no sensory loss. Height was 123 cm (below 3rd centile). Routine hematological examinations and serum CK were normal. Electrophysiological examination revealed absent sensory action potentials and "severe" reduction of motor nerve conduction velocity.

During the following years progression of the disease was slow, but by the age of 26 the patient noticed progressive weakness of proximal limb muscles. At 29 he lost the ability to walk anaided. When first seen by us, the patient showed a severe and generalized weakness. Muscle power was F=0 (Medical Research Council scale) in the tibio-peronei, Triceps sura, extensor carpi, extensor digitorum communis and small hand muscles, F = 1–2 in the iliopsoas and glutei, F = 2–3 in the biceps brachii, triceps brachii and quadriceps, F = 4 in the deltoids and neck flexors. There was a moderate weakness of masticatory and facial muscles: forced closure of lids and of jaw could easily be overcome by the examinator's fingers. The patient could walk a few steps only with major assistance. Tendon reflexes were absent. Sensory examination showed mild loss of sensation distally in both legs and a marked acrocyanosis was also present. Intelligence was normal. Routine hematological exams were normal. Serum CK was 260 IU/l [normal value (n.v.) < 230], lactic acid was 1 mEq/l (n.v. <2.2). Brain CT scan, brain stem evoked potentials and audiometric examination were normal. Respiratory functional tests were low normal.

Electromyographic studies revealed fibrillation potentials and pseudomyotonic discharges in all muscles. No voluntary activation was detected in the tibioperonei, small hand muscles, extensor carpi and digitorum communis, while in deltoid, biceps brahii and quadriceps few high frequency giant motor unit potentials were observed. Sensory action potentials were absent recording from radial, median and sural nerves. No muscle action potentials could be elicited from electrical stimulation of peroneal, median and ulnar nerves. Motor latency from Erb's point to deltoid and biceps brachii were markedly prolonged: 13.5 ms (n.v. < 5.1) and 10 ms (n.v. < 5.7), respectively.

Patient 2

This 28-year-old-woman was the sister of the patient 1. Early motor and intellectual milestones were normal: she could walk unaided at 13 months. Since the age of 14–15 month she developed progressive difficulty in walking. When she was 4–5 years old wasting and weakness of hands was observed. At around 15 years of age dysphonia, dysphagia and difficulty in chewing appeared. Progression was more severe than in her brother and at 22 years she lost the ability to walk.

Clinical examination revealed severe weakness and wasting of tibio-peronei (F=0), quadriceps (F=2) and iliopsoas (F=1). In upper limbs, motor power was F=0 in flexor and extensor carpi, extensor digitorum communis and small hand muscles, F=2–3 in deltoid, biceps and triceps brachii and neck flexors. Moreover, there was marked dyshonia due to vocal cord palsy, dysphagia, weakness of masticatory muscles and of facial muscles; the face was amimic and the patient was not able to close her eyes completely. She was not able to walk and could stand only with assistance. Respiratory muscles were spared. Tendon reflexes were absent. There was mild loss of sensation distally in both legs. Routine blood examinations were normal. Brain CT was normal. Serum CK was 266 IU/l (n.v. < 230). Electromyographic changes were similar to those observed in the brother. Sensitive action potentials were all absent. Compound muscular action potentials were not evocable from peroneal, ulnar and median nerves stimulation.

Patient 3

A 4-year-old boy was admitted to our hospital because of clumsy gait and frequent falls since the age of 2 years. He was the only child of healthy and unrelated parents. Both parents were normal at clinical and electrophysiological examination. Pregnancy and delivery were normal. The patient had normal early motor milestones and he walked at 11 month.

Neurological examination showed mild bilateral facial weakness, moderate weakness and atrophy of distal limb muscles and neck flexors. He used the Gowers' manoeuvre to rise from the floor. All deep tendon reflexes were absent. There was bilateral pes cavus with retraction of Achille's tendons. Intelligence was normal.

Electrophysiological examination demonstrated absence of sensory action potentials on testing the median, radial and sural nerves. Motor conduction velocities were 16 m/s and 14 m/s in the right ulnar and median nerves, respectively; no action potential was elicited from electrical stimulation of the right peroneal nerve. Electromyographic examination was performed only in the quadriceps femoris and was unremarkable. The following tests were normal: full blood count, fasting blood glucose, serum electrolytes, creatine kinase, lactic acid, urinary organic acids, serum and urine carnitine, EEG, ECG and liver echography.

Materials and methods

Nerve

A whole sural nerve biopsy specimen was fixed in 2.5% glutaraldehyde in phosphate buffer and post-fixed in 1% phosphate-buffered osmium tetroxide. The tissue was dehydrated, infiltrated and embedded in Spurr resin. Sections, 1 μm thick, were stained with toluidine blue. Thin sections were stained with uranyl acetate and lead citrate prior to examination in a Philips EM 400 electron microscope.

Muscle

For histochemical studies, the biopsies were frozen in liquid nitrogen-cooled isopentane, cross-sectioned at 7- to 8-μm thickness in a cryostat, and processed for routine histochemical analysis as described [3]. Assays of mitochondrial and β-oxidation enzyme activities and of carnitine were performed as described [18].

Results

Sural nerve biopsy

Pathological changes on sural nerve biopsy were similar in all three cases and they will be described together.

Light microscopy

On semithin transverse sections there was severe reduction in the number of myelinated fibers, more remarkable in patients 1 and 2 (Figs. 1, 2). The most striking finding, in all cases, was the presence of marked overgrowth of the myelin sheath in the majority of myelinated fibers. Some fibers showed a thin myelin sheath with respect to axonal diameter. Onion bulbs were frequent in patients 1 and 2, while they were rare in patient 3.

Teased fiber analysis

One hundred fibers from patient 3 were teased, while only few fibers could be obtained from the biopsies of patients 1 and 2. All fibers showed abnormal myelin

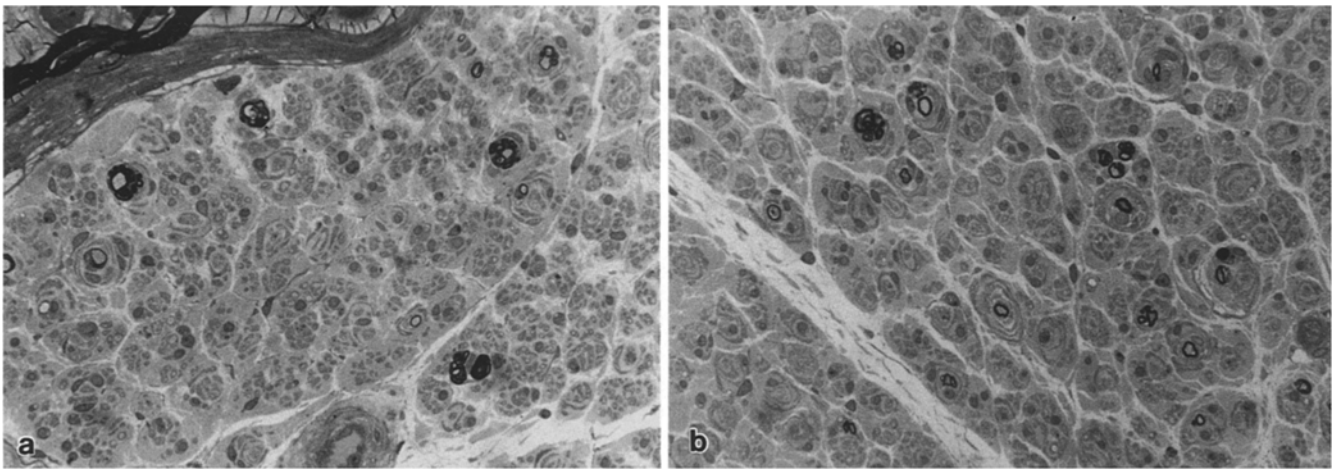

Fig. 1 a,b Semithin transverse section of sural nerve biopsy from patients 1 (**a**) and 2 (**b**). There is severe fiber loss, many fibers show abnormal myelin proliferation. Some onion bulbs are present. Toluidine blue, × 780

proliferation (Fig. 3). Segmental demyelination was present in 92 % of fibers in patient 3 and in most fibers of patients 1 and 2.

Electron microscopy

Ultrastructurally, redundant loops and folds of the myelin sheath were very irregularly arrayed next to the axons disclosing highly variable figures (Fig. 4). In patients 1 and 2 myelin proliferation was less florid than in patient 3. Occasionally intramyelinic vacuoles were evident. Some axons seemed to be compressed by myelin proliferations (Fig. 4c). In some instances the axoplasm extended into the myelin folds. There were neither active axonal degeneration nor signs of active demyelination. In some cases, demyelinated axons showed reduced diameter with increased density of neurofilaments and neurotubules and were surrounded by abnormal myelin (Fig. 4d). Onion bulb formations were composed of flattened Schwann cell processes containing few unmyelinated fibers (Fig. 4a, b). Unmyelinated fibers were moderately reduced in patients 1 and 2 and relatively spared in patient 3.

Muscle biopsy

Muscle biopsy, performed in the left deltoid of patients 1 and 2 in the rectus femoris in patient 3, showed many atrophic and angulated fibers often in cluster and large type grouping, suggesting neurogenic atrophy. Moderate lipid accumulation was observed in case 3 by Oil red O and Nile red stains and it was confirmed by electron microscopy. On muscle homogenate biochemical studies for mitochondrial respiratory chain enzymes, β-oxidation enzymes and carnitine were within normal limits.

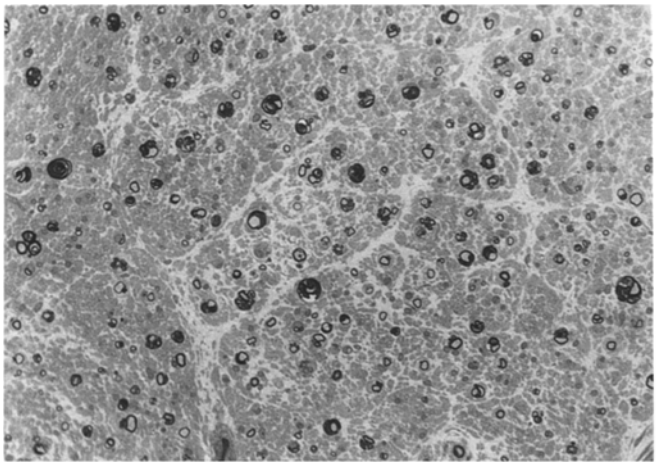

Fig. 2 Cross section of sural nerve from patient 3. Note the moderate reduction in the number of myelinated fibers and the marked myelin overgrowth. Toluidine blue, × 510

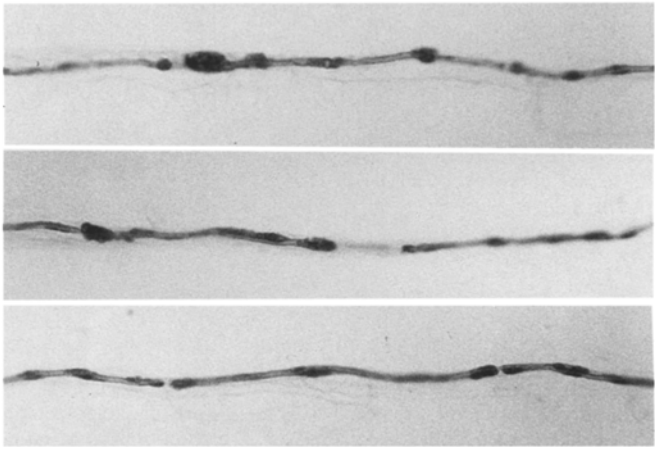

Fig. 3 Consecutive portions of a teased fiber from patient 3. Note segmental demyelination and focal areas of irregular myelin proliferation. × 317

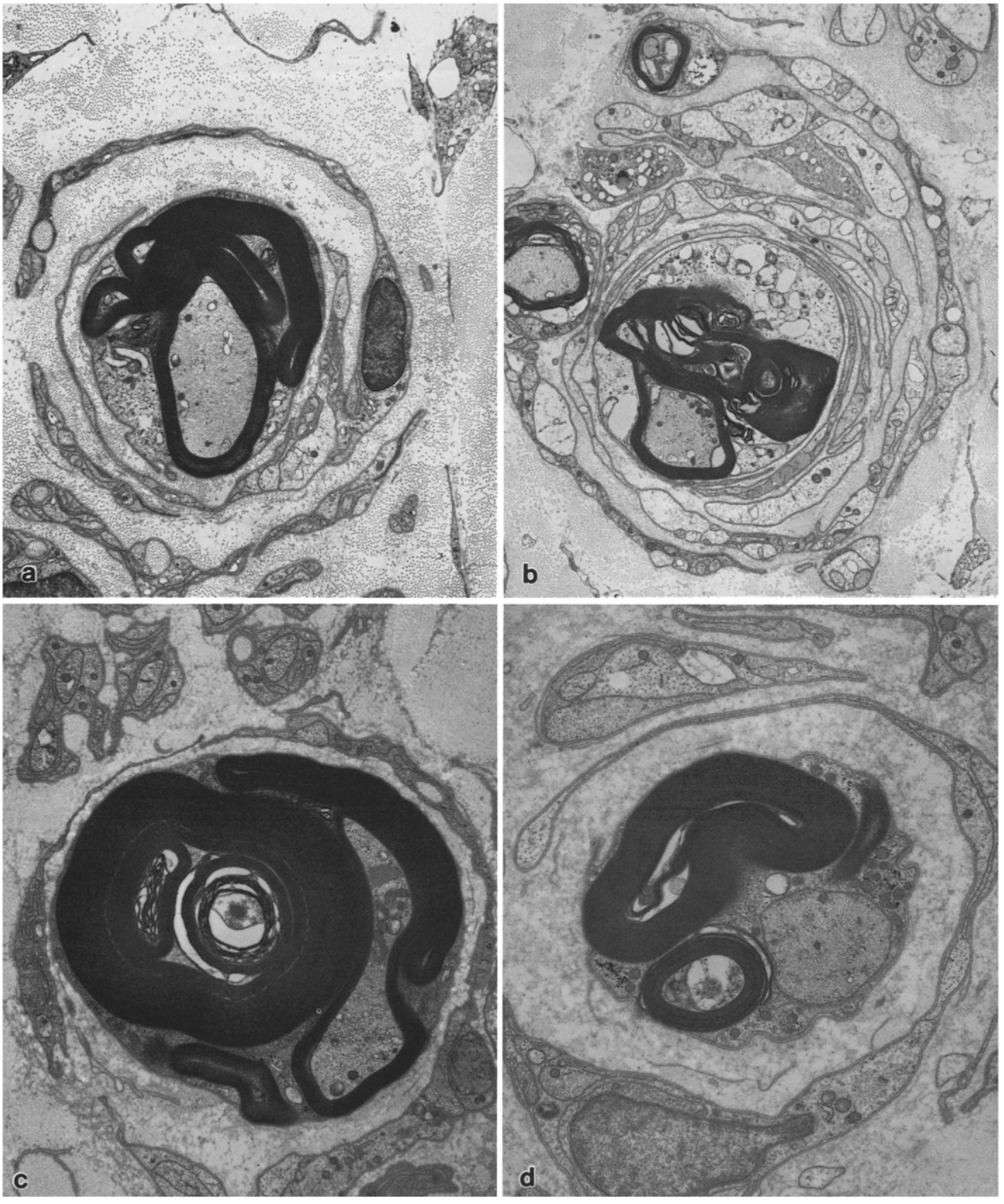

Fig. 4 Electron micrograph of sural nerve from patient 1 (**a**), patient 2 (**b**) and patient 3 (**c, d**). **a, b** Hypermyelinated fibers are wrapped by onion bulb formations. **c** The axon seems to be compressed by myelin foldings. **d** A demyelinated axon is partially surrounded by abnormal myelin. **a** × 5550, **b** × 4370, **c** × 8300, **d** × 9750

Discussion

Our patients showed clinical, genetic, and electrophysiological features of HMSN type III. However, sural nerve biopsy demonstrated highly unusual myelin

abnormalities characterized by complex redundant loops and folds of the myelin sheath.

Abnormal myelin proliferation is a prominent pathological feature in different forms of hereditary peripheral neuropathies. Hereditary liability to pressure palsies (HLPP) is, by far, the most frequent and best defined clinico-pathological entity. Cardinal features of the disease are: (1) autosomal dominant inheritance, (2) clinical presentation of a recurrent mononeuropathy simplex or multiplex related to trivial trauma, (3) sausage-shaped thickenings of the myelin sheath at sural nerve biopsy, and (4) mild to moderate reduction in conduction velocity, more marked over the points of compression [1, 12, 13].

Over the last few years a group of patients with "hypermyelination neuropathy" has been described whose clinical, electrophysiological and pathological aspects are quite different from HLPP [7, 15, 16, 19]. Clinically these patients had a peroneal muscular atrophy syndrome, usually with early onset. All reported cases were sporadic and genetic transmission was supposed to be autosomal recessive. Sural nerve biopsy showed very unusual myelin overgrowth which was clearly more irregular with respect to the tomacula observed in HLPP. Electrophysiological examination demonstrated severe and generalized slowing of conduction velocities.

It is difficult to make a nosological classification because only few patients have been described; moreover, clinical manifestations are quite heterogeneous among reported cases. Although the onset occurred within 3 years of age in most patients, Ohnishi et al. [15] reported two cases with first symptoms beginning at 7 and 47 years. All cases disclosed a HMSN-like syndrome, but some patients showed additional clinical features. Vallat et al. [19] observed psychomotor delay, Babinski sign and epileptic seizures in one of their two patients. Ouvrier et al. [16] described facial weakness, bilateral ptosis and ophthalmoplegia in their case. The patient reported by Jacob et al. [7] was affected by Waardenburg's syndrome and Hirschprung's disease.

Very little is known about the natural history of hypermyelination neuropathy. The patient described by Jacob et al. [7] showed severe clinical course with loss of deambulation at 8.5 years; coexistence of Hirschprung's disease might have influenced the outcome. The 7-year-old patient of Ouvrier et al. [16] disclosed mild proximal and moderate distal weakness. The patients reported by Vallat et al. [19] were 10 and 7 years old at the last examination, and showed reduction in muscular strenghth in the distal parts of all four limbs. Ohnishi et al. [15] observed moderate to severe weakness of proximal and distal muscles in the 15-year-old boy and moderate distal weakness in the 49-year-old woman. Gabreëls-Festen et al. [5] have recently reported six cases of HMSN type III with focally folded myelin sheath. The same authors, however, stressed that in these patients "the tomacula were similar to those depicted by Madrid and Bradley in HLPP". Progression of the disease was slow in all patients. Based on pathological and clinical findings, these cases should be considered a distinct clinico-pathological entity. Focal myelin thickenings have also been described by Dayan et al. [2], Lütschg et al. [10], and Nordborg et al. [14]. Pathological changes in these patients were not detailed enough to be compared with those of above-mentioned cases.

Our patients showed morphological changes similar to those reported by Jacob et al. [7], Onhishi et al. [15], Ouvrier et al. [16] and Vallat et al. [19]. On semithin sections and teased fiber analysis as well as at ultrastructural examination myelin abnormalities are of such complexity and variability that they are not comparable to the tomacula of HLPP. The rare occurrence of active myelin breakdown suggestes the hypothesis that the frequent observation of segmental demyelination on teased fiber analysis can be due to defective myelination more than to myelin breakdown.

The presence of lipid accumulation on muscle biopsy in patient 3 is of uncertain meaning and may be not specific. The most common causes of lipid storage, such as enzymatic disorders of mitochondrial and lipid metabolism, were in fact ruled out by biochemical studies. Moreover, lipid droplets were normal in patients 1 and 2.

Patients 1 and 2 had a very early onset of the disease at 18 and 14 months, and showed a severe degree of symmetrical muscular weakness of distal as well as of proximal muscles; they lost the ability to walk at 28 and 22 years of age, respectively. Cranial nerve function was abnormal with facial weakness, dysphagia and dysphonia. Patient 3 presented an early proximal lower limb involvement. These data suggest that hypermyelination neuropathy with early onset represents a progressive disease with poor long-term prognosis.

The occurrence of the disease in two sibs of both sexes but not in the parents, further supports an autosomal recessive inheritance. Familial cases of this condition have not been described previously. The available data are too scanty to establish whether the characteristic hypermyelination should be considered the pathognomonic feature of a single clinico-genetic entity with variable phenotypic expression or an epiphenomenon common to different diseases. However, the presence of the same myelin changes in two sibs, patients 1 and 2, suggests that this pathological finding is genetically determined.

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