Chronic inflammatory demyelinating polyneuropathy in two siblings

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SUMMARY A familial occurrence of chronic inflammatory demyelinating polyneuropathy is reported. The diagnostic problems in distinguishing the progressive form of this disease in childhood from hereditary motor and sensory neuropathy types I and III are discussed. Criteria for a definite diagnosis of chronic inflammatory demyelinating polyneuropathy are proposed.

Chronic inflammatory demyelinating polyneuropathy is a disorder in which clinical and laboratory investigations suggest a primarily inflammatory demyelinating process. The following diagnostic criteria of chronic inflammatory demyelinating polyneuropathy have been proposed:^{1,2}

- (1) presence of a sensorimotor polyneuropathy involving proximal as well as distal limb structures,
- (2) a slow onset and a steadily progressive or relapsing-remitting course,
- (3) elevated cerebrospinal fluid (CSF) protein content without an increase of mononuclear cells,
- (4) marked slowing of nerve conduction velocity,
- (5) sural nerve biopsy showing segmental demyelination with or without onion bulb formation and perivascular or diffuse infiltrates of mononuclear cells,
- (6) absence of evidence of any associated or systemic disease, intoxication, malignancy or monoclonal gammopathy.

There is evidence of disturbed humoral and cellular immunological mechanisms in chronic inflammatory demyelinating polyneuropathy,³⁻⁷ and therapy with corticosteroids or plasmapheresis has been shown to cause improvement.^{6,8,9}

Two investigations have suggested that HLA-linked genetic factors may influence susceptibility to chronic inflammatory demyelinating polyneuropathy.^{10,11} Nevertheless, a familial occurrence

of chronic inflammatory demyelinating polyneuropathy has not yet been reported. We present the occurrence of chronic inflammatory demyelinating polyneuropathy in two sibs.

Case reports

A normally intelligent girl, aged 9 years, eldest child of healthy unrelated parents, was admitted to our department because of difficulty in walking. Pregnancy, delivery and postnatal development were normal. She received the routine diphtheria, pertussis, tetanus and poliomyelitis vaccinations between the 3rd and 12th month without showing complications. At the age of 14 months she could walk without support, but gait was awkward. Gradually, she developed pes cavus and scoliosis.

On examination, muscle strength was poor in all limbs and muscle wasting was present. She had an equine gait. Slight sensory loss was detectable, particularly in distal lower limbs. Tendon reflexes were absent. Nerves were not palpably thickened. Muscle and nerve biopsy was performed. A follow-up study of six years revealed a slow progression of the polyneuropathy and an increasing scoliosis.

Two years later, a younger sister was admitted to our department. This girl, the third child, aged 4 years 9 months, suffered from the same walking difficulties as her sister. Pregnancy, delivery and postnatal development had been normal, and she received the normal vaccinations without complications. She could walk without support at the age of 14 months, but gait remained clumsy. On examination, she had poor muscle strength, wasting of muscle and a slight sensory loss in distal limbs. She had a slight scoliosis. Nerves were not palpably thickened.

Family investigation

There was no history of familial polyneuropathy. The mother showed slightly elevated arches but no muscle weakness or reflex changes. Father and the second (female) child

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Fig 1 Case 2. Sural nerve showing remyelinated axons (▲) and onion bulbs (△) (Ultrathin Epon section, bar = 5 µm).

had neither abnormalities on neurological examination. Maximal motor conduction velocities of both parents and the healthy sister were completely normal (table 1). Two maternal sisters had slightly high arches but they too showed no abnormalities on neurological and electrophysiological examination. A child of the sister of mother's mother had a scoliosis but she showed normal muscle strength and normal reflexes. Nerve conduction velocity studies and electromyography yielded no abnormalities. Autoimmune diseases occurred in the paternal family as well as in the maternal family. Two relatives suffered from rheumatoid arthritis, one relative suffered from ankylosing spondylitis and regional enteritis.

Laboratory investigations

Blood and urine of both patients were investigated but no abnormalities were found. There were no signs of metabolic or endocrine disorders, nor signs of intoxication or deficiency. Muscle enzymes were normal. Lysosomal enzymes were also normal. Serological and bacteriological investigations all were negative. CSF protein content of patient 1 was increased (630 mg/l, normal up to 350) without an increase in cells. CSF of patient 2 was not examined.

Electrophysiological examination

Both girls showed decreased maximal motor conduction velocities, especially in the lower limbs (table 1). Sensory potentials of the sural nerve could not be elicited.

Immunological examination

The concentrations of serum immunoglobulins and of the IgG subclasses were normal, in accordance with age. The percentages of B lymphocytes and T lymphocytes were normal. T cell subset analyses revealed a normal proportion of OKT₄/OKT₈ T cells. Results of lymphocyte stimulation *in vitro* with phytohaemagglutinin and pokeweed mitogen were normal, as were the total haemolytic complement contents.

Patient 1 had the following HLA phenotype A₂B₇DR₅/A₁₁Bw₁₆DR₄ and patient 2 A_w₃₀B₅DR₆/A₁₁Bw₁₆DR₄. The HLA phenotypes of the parents and the healthy sister were: father A₁₁B₂₇DR₁/A₁₁Bw₁₆DR₄, mother A₂B₇DR₅/A_w₃₀B₅DR₆, sister A₂B₇DR₅/A₁₁B₂₇DR₁. Thus our patients were haplo-identical for the haplotype received from the father.

Morphological examination

Midcalf sural nerve biopsy and soleus muscle biopsy of both patients were performed for light and electron microscopic examination, according to our previously described techniques.¹²

Cross sections of the sural nerve revealed sporadically demyelinated and occasionally remyelinated fibres, and slight onion bulb formation (fig 1). Some clusters of small regenerated and remyelinated axons inside onion bulb structures were seen, especially in the elder girl. Infrequently, fibres showed an increased myelin thickness, which in longitudinal section appeared to be local thickenings of the myelin sheath. Scattered foci of mononuclear cells were found, particularly around some endo- and epineurial blood vessels. In each biopsy, four or five infiltrates of lymphocytic cells could be distinguished in transverse and longitudinal sections randomly made of 1 cm of the sural nerve (figs 2 and 3). Teased fibre studies confirmed a process of segmental demyelination and remyelination (table 2).

Number and diameter of myelinated fibres were measured on electron microscopic photographs (× 1700) with a Zeiss TGZ-3 particle size analyser. The histograms of diameters of myelinated fibres showed a unimodal pattern, with nearly absent large fibres: 6% (patient 1) respectively 4% (patient 2) of the myelinated fibres showed a diameter of more than 8 µm (normal 18%, SD 6%). Density of myelinated fibres was decreased (patient 1) or low normal (patient 2), partly owing to an increase of total transverse fascicular area (TTFA) (table 2).

Muscle biopsy sections revealed in both cases a preponderance of type I fibres, which accounted for 90% of all the muscle fibres (normal 65%). Both cases showed some intrafascicular infiltration of mononuclear cells, which reacted partly positive with AcP-ase (histiocytes) and negative with AMP-ase (probably T lymphocytes).

Table 1 Motor conduction velocities (m/s) in median and peroneal nerve

	Case 1	Case 2	Mother	Father	Sister
Median nerve (N, 43–77)	34	41			
Peroneal nerve (N, 41–58)	23	27	47	45	52

N = normal.

Fig2 Case 1. Sural nerve showing mononuclear cell infiltration in endoneurium (paraffin section, Haematoxylin and Eosin, bar = 50 µm).

Fig3 Case 2. Sural nerve showing subperineurial mononuclear cell infiltration (cryostat section, Haematoxylin and Eosin, bar = 50 µm).

Discussion

The children described fulfil the diagnostic criteria of chronic inflammatory demyelinating polyneuropathy¹² mentioned in the introduction.

In the literature there are several reports of chronic inflammatory demyelinating polyneuropathy in childhood.^{2 8 13–22} Most of the described cases ran a relapsing course; some cases exhibited a chronic progressive course. Both forms are considered variants of chronic inflammatory demyelinating polyneuropathy.¹⁹ A relapsing/remitting course is a strong argument for the diagnosis chronic inflammatory demyelinating polyneuropathy, as other polyneuropathies which can exhibit a recurrent course²³ can generally be excluded by careful clinical, biochemical and/or morphological investigations. However, it may be difficult to assess a remitting course in young children because natural motor development can blur the course of the disease.

Special diagnostic problems arise if the illness starts early in life, with slow progression after an insidious onset. In these cases differentiation has to be made from hereditary motor and sensory neuropathy (HMSN) type III or HMSN type I.²⁴ An onset in the first decade of life is obligatory in HMSN type III²⁵

and occurs in the majority of HMSN type I cases,²⁶ even in the autosomal recessive form.²⁷

A raised CSF protein is common in HMSN type III.²⁵ In HMSN type I, although usually normal or only slightly raised CSF protein values are found, several reports have mentioned substantially elevated CSF protein levels.^{21 28}

Mononuclear cell infiltrates are considered pathologic hallmark in chronic inflammatory demyelinating polyneuropathy.^{1 29} As such, they can be the only sign in distinguishing chronic progressive cases of chronic inflammatory demyelinating polyneuropathy from HMSN type I or HMSN type III.³⁰ Theoretically, the possibility exists that mononuclear cell infiltrates could occur in hereditary demyelinating disease merely as an incidental response to the myelin breakdown. But neither in the literature to our knowledge, nor from our own experience covering 58 HMSN type I and 12 HMSN type III sural nerve biopsies, have inflammatory signs been found.

Perivascular or diffuse infiltrates of mononuclear cells are recognised in only a limited number of nerve biopsies of chronic inflammatory demyelinating polyneuropathy, ranging from 0% to 53.8%.¹ Inflammatory lesions are seen more often in the proximal parts of the nerve (nerve roots, trunks, plexuses)

Table 2 Quantitative findings in sural nerve

Case No	Age (yr, months)	Myelinated fibre density	TTFA† (mm)	Teased fibre preparations*			
				Number of fibres	A	E	CDF
1	9, 0	5,600	1.44	28	75.0	0	25
2	4, 9	8,600	1.18	72	91.7	0	8.3
Controls (n = 12)	4, 0–10, 0	13,000 (SD 1,700)	0.80 (SD 0.14)		>98	0	<2

*Capitals refer to the condition of the teased fibre: A = normal appearance; C = widening of nodal gap; D = segmental demyelination; E = axonal degeneration with linear rows of myelin balls; F = segmental or paranodal remyelination.

†TTFA = total transverse fascicular area.

only available by necropsy.^{1,30} So the chance of finding infiltrates in the distally located portion of the nerve taken by biopsy is limited. It is obvious that a number of chronic inflammatory demyelinating polyneuropathy will remain undiagnosed because inflammatory signs will not always be found.^{7,31}

Several indications exist that genetic factors may play a role in the pathogenesis of chronic inflammatory demyelinating polyneuropathy. Skeletal abnormalities and/or (sub)clinical signs suggestive of polyneuropathy have been mentioned in relatives of chronic inflammatory demyelinating polyneuropathy patients.^{18,22,32,33} Dyck *et al*³³ suggested a genetic susceptibility to inflammatory demyelinating processes in kindreds with hereditary motor and sensory neuropathy. Therefore, they recommended a therapeutic trial with prednisone for patients suffering from a HMSN type I syndrome with increased levels of CSF protein. Corticosteroid medication in patients who definitely have familial HMSN type I does not seem to be justified.³⁴

Steinman *et al*³⁵ have shown different susceptibility between inbred strains of rats to experimental allergic neuritis: the experimental model of acute and chronic inflammatory demyelinating polyneuropathy (among others Waksman *et al*³⁶). Stewart *et al*¹⁰ and Adams *et al*¹¹ demonstrated in preliminary studies that chronic inflammatory demyelinating polyneuropathy, like other organ-specific autoimmune diseases, is probably associated with certain antigens of the HLA system. In spite of these indications of a genetic factor, a familial occurrence of chronic inflammatory demyelinating polyneuropathy has not been described up to now. Instead, a kinship history of neuropathy has even been put forward as a criterion against the diagnosis of chronic inflammatory demyelinating polyneuropathy.⁹

The occurrence of chronic inflammatory demyelinating polyneuropathy in our two sibs strongly supports the view of a genetic disposition. It is unlikely that the maternal factor or some exogenous (such as infectious) agent is responsible for the disease in our patients, because there is a healthy sister between our two patients, and there is a gap of 5½ years in the times of disease onset. An autosomal recessive transmission is theoretically possible (healthy parents, two female sibs), but unlikely. Considering the nature of the disease, a multifactorial inheritance is most probable. HLA antigens could be one of the genetic factors in this polygenic disease. Our patients were haplo-identical for the haplotype received from the father, the healthy sister having a different haplotype.

Our patients did not receive prednisone therapy, azathioprine or plasmapheresis, because the neurological disability was judged insufficiently severe to justify the risks of such a prolonged treatment.⁹

The following criteria might be particularly useful in distinguishing childhood chronic inflammatory demyelinating polyneuropathy from other demyelinating polyneuropathies at young age: a relapsing/remitting course, remission directly related to pharmacotherapy, mononuclear cell infiltrates in nerve biopsy specimen. Presence of at least one of these criteria is obligatory for making a definite diagnosis of chronic inflammatory demyelinating polyneuropathy.

From our study it can be concluded that in chronic progressive demyelinating polyneuropathy of unknown aetiology with raised CSF protein a careful search should be made for inflammatory signs in nerve biopsy, even if there is a kinship history of polyneuropathy.

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