

## SHORT REPORT

## Histology of hereditary neuralgic amyotrophy

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We report the findings in five muscle and three sural nerve biopsies, and in one postmortem plexus specimen, from six patients with hereditary neuralgic amyotrophy (HNA). We found that the sensory nerves are definitely involved in HNA despite the mainly motor symptoms, and that lesions in nerves and muscles are more widespread throughout the peripheral nervous system than clinically presumed, but, simultaneously, very focally affect isolated fascicles within individual nerves.

Hereditary neuralgic amyotrophy (HNA), or hereditary brachial plexus neuropathy, is a rare autosomal dominant disorder (OMIM 162100) linked to chromosome 17q25 in a number of families.<sup>1</sup> Clinically, the picture is well defined and characterised by recurring attacks of acute and severe neuropathic pain, followed by paresis and marked muscular atrophy. Attacks involve one or both of the brachial plexuses but can also affect a lower cranial nerve, the phrenic nerve, intercostal nerves, or the lumbosacral plexus.<sup>2</sup> Sensory involvement is usually absent or not prominent clinically, but on electrophysiological examination patients do have sensory nerve abnormalities. In addition, we and others have the clinical experience that peripheral nervous system involvement is not restricted to the clinically affected nerves.<sup>3</sup> This suggests a more disseminated disorder of the peripheral nervous system, although there is no evidence for a generalised neuropathy in HNA.

The pathophysiology of HNA is still unclear and the underlying genetic defect is not yet known. Possibly it predisposes the patient's peripheral nerves to subsequent autoimmune attacks. The pain and multifocal, scattered affection of nerves suggest the phenotype of a mononeuritis multiplex. This raises the question whether the attacks in HNA could be a manifestation of an isolated peripheral nervous system vasculitis (NSPV).

Reports of histological findings in HNA are scanty; only seven nerve biopsies and four muscle biopsies have been described so far.<sup>3–9</sup> This is understandable in such a rare and non-life threatening disease, especially since a nerve biopsy is no longer required to make the distinction between HNA and its main differential diagnosis, hereditary neuropathy with liability to pressure palsies (HNPP). This can nowadays be done by electrophysiological or DNA studies.<sup>10 11</sup>

We re-examined five muscle and three sural nerve biopsies of six HNA patients, performed before DNA analysis of HNPP was available, and we revised the brachial plexus material obtained on postmortem examination previously described by Arts and co-workers.<sup>6</sup>

## METHODS

All patients fulfilled the existing criteria for HNA.<sup>12</sup> Their clinical details have already been described in more detail elsewhere<sup>2 6</sup> and are summarised in table 1.

The biopsy material, originally obtained to distinguish between HNA and HNPP at a time when DNA testing for diagnosis of HNPP was not yet available, was re-examined. In five patients a muscle biopsy was obtained for routine staining with haematoxylin-eosin, NADH-tetrazolium reductase, and myofibrillar ATPase. Three sural nerve biopsies were taken at mid-calf level and prepared for light and electron microscopic examination, including teased fibres studies, using standard techniques. In patient 1, additional immunohistochemical staining was performed to detect T helper and T suppressor lymphocytes, macrophages, and immunoglobulins.

New and existing paraffin sections of the cervical and brachial plexus of patient II-7 described earlier by Arts and colleagues were systematically (re-)examined.<sup>6</sup>

In three patients (1–3) an electrophysiological examination, including nerve conduction studies and electromyography, was performed using standard techniques.

RESULTS  
Muscle

Four out of five muscle biopsies were abnormal. In two biopsies (from patients 1 and 3) type grouping of type I and II muscle fibres was present, indicating previous reinnervation (fig 1A). The biopsy from patient 5 showed many (20%) so called target fibres, suggesting recent de- and reinnervation (fig 1B). In the biopsy of patient 4, mean muscle fibre size diameter was different for various fascicles, which also indicates a neurogenic condition. In none of the biopsies were cellular infiltrations or signs of vasculitis observed.

## Nerve

Biopsies of two of the clinically unaffected sural nerves showed no abnormalities. The density of myelinated fibres in the clinically affected sural nerve was also within normal limits. Occasionally a degenerating axon was seen. Two small fascicles showed a remarkable loss of large myelinated fibres (fig 1C) and an occasional cluster. Immunocytochemistry of this nerve did not show any inflammatory cells or immunoglobulin deposition.

Light microscopic examination of paraffin sections of the postmortem cervical and brachial plexus, which have not been reported on previously, showed a number of fascicles embedded in loose connective tissue. Fascicles of the cervical plexus showed no abnormalities. In the brachial plexus all but one fascicle also showed a normal density and a normal diameter distribution of myelinated fibres. However, one large fascicle was different. The density of myelinated fibres was markedly decreased and fibres were mainly of small diameter, often grouped in clusters. In some segments of this

**Abbreviations:** HNA, hereditary neuralgic amyotrophy; HNPP, hereditary neuropathy with liability to pressure palsies; NSPV, peripheral nervous system vasculitis

**Table 1** Features of HNA patients with nerve and/or muscle biopsy

Patient	1	2	3	4	5	6*
Sex, age at biopsy	Male, 53 years	Male, 29 years	Male, 19 years	Female, 9 years	Female, 8 years	Female, 72 years (postmortem)
Age at first attack	17 years	28 years	3 years	9 years	8 years	21 years
No. of attacks	3	1	2	1	1	5
Muscle	Soleus	Deltoid	Soleus	Soleus	Deltoid	–
Clinically affected?	Yes	Yes	No	No	Probably yes	–
Sural nerve	+	–	+	+	–	(Brachial plexus)
Clinically affected?	Yes	–	No	No	–	–
Time between biopsy and last attack	Muscle: 2 weeks Nerve: 2 years	6 months	1 year	Acute†	Acute†	>30 years †
Clinical features of last attack	Bilateral BP +right LSP	Bilateral upper BP	Right upper BP +posterior cord	Right upper BP	Right upper BP	Upper and medial BP

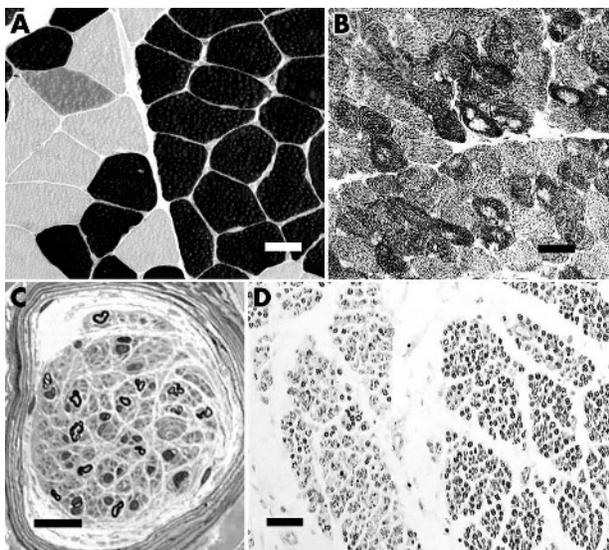
\*See Airaksinen *et al*;<sup>5</sup> †no further details available.  
BP, brachial plexus; LSP, lumbosacral plexus.

fascicle large fibre loss was more pronounced. The endoneurial collagen of this fascicle was substantially increased (fig 1D).

The blood vessels in all nerve specimens were unremarkable, and there were no signs of a tomaculous neuropathy (for example, HNPP) in any of the biopsies.

### Other studies

In three adult patients (1–3), extensive EMG and ENG examination revealed abnormalities compatible with scattered axonal lesions in the distribution of the brachial plexus, and in patient 1 also in the lumbosacral plexus. None had diffuse slowing of sensory abnormalities, prolonged distal latencies, or signs of nerve entrapment as are found in HNPP.



**Figure 1** Findings in HNA biopsies. Length of bars is 50 µm (A, B, and D) or 20 µm (C). (A) Myofibrillar ATPase (after pre-incubation at pH 4.2) stained section of the soleus muscle. The checkerboard pattern is slightly disturbed. Type I fibres (dark) are grouped together at the right and type II fibres are found on the left. (B) NADH-TR stained section of the deltoid muscle. Several fibres contain unstained circular regions in the middle or at the border of muscle fibres. These so called target fibres indicate decreased neuronal innervation. (C) Epon embedded 1 µm section of the sural nerve of patient 1 showing a fascicle with total loss of large fibres. (D) New paraffin section of the brachial plexus of patient II-7 from the family reported by Arts and co-workers.<sup>5</sup> Marked and variable loss of myelinated fibres within one fascicle of the brachial plexus can be seen.

### DISCUSSION

Here we report on the re-examination of unique histological material consisting of five muscle and three sural nerve biopsies, and a postmortem brachial plexus, from six HNA patients. This study allows us to characterise the histology of HNA more precisely.

### Focal involvement

Signs of neurogenic lesions in the two clinically unaffected muscles show that lesions during an attack of HNA are more widespread throughout the peripheral nervous system than is apparent on clinical evaluation. This is supported by the description of Arts and colleagues, who found that the biopsy of a clinically unaffected sural nerve showed a slight and focal decrease in the number of myelinated nerve fibres suggesting an axonal lesion in a few fibres.<sup>6</sup> We also found evidence that HNA causes very focal lesions *within* individual nerves.

Even though the sural nerve is not the most likely nerve to be involved in HNA patients, in whom the lumbosacral plexus is only affected in 12% of attacks,<sup>2</sup> the one clinically affected sural nerve of one of our patients was abnormal, but only in two small fascicles. Convincing evidence of focal involvement of nerves was also found in paraffin sections of the postmortem brachial plexus specimen. The Epon embedded 1 µm sections showed very few abnormalities, whereas one fascicle of the paraffin embedded section of the brachial plexus was definitely abnormal.

### Sensory involvement

Of the known total of 10 nerve biopsies in HNA, eight were taken from a sensory nerve, one from a proximal motor fascicle of the median nerve, and one was the postmortem plexus specimen. The finding of abnormalities in six out of eight of the sensory nerves confirms that, although clinically the deficit is mainly motor, the sensory nerves are definitely also involved in attacks of HNA.

### Pathophysiology

In our study and, except for one, in all other studies on nerve, muscle, or skin biopsies in HNA, signs of necrotising vasculitis were lacking. Klein and co-workers reported multiple microvessels with epineural perivascular mononuclear inflammatory cell infiltrates, and active multifocal axonal degeneration in two of the three radial sensory nerves. Although the inflammation did involve the vessel wall, there were no signs of fibrinoid necrosis.<sup>4</sup> Since the diagnosis of non-systemic NSPV requires histological demonstration of both vessel wall inflammation and necrosis, there is no definite evidence as yet that HNA is a limited form of NSPV.

## CONCLUSIONS

Summarising, the available histological data in HNA confirm that the disorder affects the PNS in a more widespread manner than is clinically presumed, and yet affects individual nerves very focally, with lesions restricted to isolated fascicles. Sensory nerves are definitively involved in HNA, even though patients often do not mention sensory symptoms other than pain. The retrospective nature of this study of historical biopsy material does not allow for further conclusions on the underlying etiology of HNA.

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