Clinical syndromes associated with tomacula or myelin swellings in sural nerve biopsies

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Abstract

Objectives—To describe the neuropathological features of clinical syndromes associated with tomacula or focal myelin swellings in sural nerve biopsies and to discuss possible common aetiopathological pathways leading to their formation in this group of neuropathies.

Methods—Fifty two patients with sural nerve biopsies reported to show tomacula or focal myelin swellings were reviewed, light and electron microscopy were performed, and tomacula were analysed on teased fibre studies. Molecular genetic studies were performed on those patients who were available for genetic testing.

Results—Thirty seven patients were diagnosed with hereditary neuropathy with liability to pressure palsies (HNPP), four with hereditary motor and sensory neuropathy type I (HMSN I) or Charcot-Marie-Tooth disease type 1 (CMT1), four with HMSN with myelin outfolding (CMT4B), three with IgM paraproteinemic neuropathy, three with chronic inflammatory demyelinating polyneuropathy (CIDP), and one with HMSN III (CMT3).

Conclusions—Most of these syndromes were shown to be related to genetic or immunological defects of myelin components such as peripheral myelin protein 22 (PMP22), myelin protein zero (P0), or myelin associated glycoprotein (MAG). These proteins share the HNK-1 epitope which has been implicated in cell adhesion processes. Impaired myelin maintenance may therefore contribute to the formation of tomacula and subsequent demyelination.

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The term "tomaculous neuropathy" generally refers to hereditary neuropathy with liability to pressure palsies (HNPP), which is most commonly associated with a deletion of chromosome 17p11.2-12 including the peripheral myelin protein 22 (PMP22). Although tomacula are the pathological hallmark of HNPP¹ focal thickening of the myelin sheath is also found in IgM paraproteinemic neuropathy,² hereditary motor and sensory neuropathy (HMSN) or Charcot-Marie-Tooth disease (CMT),^{3,4} HMSN with myelin outfolding,⁵ other forms of hereditary neuropathy with myelin outfolding or hypermyelination,^{6,7} and other clinical

syndromes.⁸⁻¹¹ Sausage shaped swellings of the myelin sheath were first described by Behse and Buchthal in 1972.¹ Madrid and Bradley¹⁰ subsequently gave the name tomaculous neuropathy (latin: tomaculum=sausage) and described several mechanisms that may lead to the formation of a tomaculum—for example, hypermyelination, redundant loop formation, the presence of a second mesaxon, transnodal myelination, two Schwann cells forming one myelin sheath, and disruption of the myelin sheath. Sural nerve biopsies typically show regions of myelin thickening as well as features of demyelination and remyelination. Electrophysiologically, these syndromes most often present as multiple mononeuropathy (sometimes with conduction block) or demyelinating sensorimotor neuropathy.

In this study we reviewed 52 patients showing myelin swellings on sural nerve biopsy. We describe the various clinical syndromes associated with focal myelin swellings, present their morphological findings, and discuss disease mechanisms.

Materials and methods

Samples were obtained by searching sural nerve biopsy reports mentioning tomacula or myelin thickenings. The reports were generated by three different observers performing clinical reports between 1976 and 1998. Each sural nerve biopsy reported to show tomacula or focal myelin swellings on teased fibre studies was subsequently examined. Only myelin thickenings measuring more than 50% of the fibre diameter were defined as tomacula.¹² A total of 52 sural nerve biopsies were analysed by light and electron microscopy.

HISTOLOGICAL TECHNIQUES

Sural nerve biopsy was performed according to standard techniques and prepared for light and electron microscopy as previously described.¹³ Teased fibres were prepared as described by Low *et al*¹⁴ and classified according to Dyck *et al*.¹⁵

QUANTITATIVE STUDIES

Diameter and length of tomacula were measured using an ocular micrometer. Twenty fibres per patient were analysed. Only patients with HNPP carrying a definite molecular diagnosis were included for quantitative analysis. Teased fibre preparations of one patient carrying a P0 mutation did not allow quantitative analysis.

MOLECULAR GENETIC TECHNIQUES

PMP22 deletion, duplication, and mutation analysis was performed as previously

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Figure 1 (A) Transverse section of toluidine blue stained epon embedded sural nerve from a patient with HNPP (top arrow, adaxonal myelin breakdown products; bottom arrow, hypermyelinated fibre). (B) Electron micrograph showing a tomaculum with active myelin breakdown.

described.^{16 17} P0 mutations were analysed according to Bort *et al.*¹⁸

Results

PATIENTS

Of 52 patients whose sural nerve biopsies showed focal myelin swellings, 37 were diagnosed with HNPP, four with HMSN type 1/CMT1, four with HMSN with myelin outfolding, three with IgM paraproteinaemic neuropathy and positive anti-MAG antibodies, three with chronic inflammatory demyelinating polyneuropathy (CIDP), and one with HMSN III/CMT3.

MOLECULAR GENETICS

Nineteen patients with HNPP were available for molecular genetic testing. A chromosome 17p11.2 deletion was detected in 17 patients, two showed frameshift mutations of the PMP22 gene¹⁷ causing a premature stop codon, the result of which is effectively the same as a deletion. Two out of four patients with CMT1 underwent genetic testing and showed the typical chromosome 17p11.2 duplication including the PMP22 gene. A myelin protein zero (P0) point mutation was demonstrated in the CMT3 patient. Three out of four patients with CMT4B were tested for

Figure 2 (A) Transverse section of toluidine blue stained epon embedded sural nerve from a patient with IgM paraproteinemic neuropathy. (B) Electron micrograph showing hypermyelination and redundant loop formation.

Figure 3 (A) Transverse section of toluidine blue stained epon embedded sural nerve from a patient with CMT4B (top arrow: fibre with myelin outpouchings; bottom arrow: hypermyelinated fibre with redundant myelin foldings). (B) Electron micrograph showing excessive myelin foldings.

P0 and PMP22 gene mutations. In one patient, exons 2, 3, and 4 of the PMP22 gene and exons 1, 2, 3, and 4 of the P0 gene did not show point mutations (exon 1 of the PMP22 gene and exons 5 and 6 of the P0 gene were not sequenced). Complete sequence analysis in the two remaining patients disclosed no mutations within the PMP22 nor the P0 gene.

MORPHOLOGY

Transverse sections (descriptive data)

Light microscopy—In sural nerve biopsies of patients with HNPP many fibres were found to be thinly myelinated, some showed profound hypermyelination or redundant myelin foldings

(fig 1 A) and occasional early onion bulb formations were visible. The average number of myelinated fibres was not greatly reduced. In the paraproteinaemic neuropathies (fig 2 A) and CIDP the degree of hypermyelination was less extreme compared with HNPP. By contrast with HNPP, in some patients marked fibre loss was evident. In HMSN with myelin outfolding (fig 3 A) the variation in myelin sheath thickness was most pronounced. Most fibres were very thinly myelinated, similar to those seen in Dejerine-Sottas syndrome, but there were also several fibres showing bizarre formations of myelin or many redundant myelin foldings. Biopsies from patients with HMSN I (CMT1)

Figure 4 (A) Transverse section of toluidine blue stained epon embedded sural nerve from a patient with CMT3 and a P0 mutation showing several onion bulb formations and a fibre with bizarre myelin outfoldings (arrow). (B) Electron micrograph showing bizarre myelin outfoldings.

Table 1 Classification of teased fibres

	Age (y)		A (% fibres)		B		C,D,F		E		G	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
HNPP	37.9	15.7	23.2	16.9	0	0	52.2	21.5	0.26	1.1	54	20.9
IgM PPN	64.3	14.2	11.7	12.6	20	30.4	65	40.9	0	0	52.7	9.3
CIDP	49	29.1	18.3	2.9	11.7	12.6	78.3	7.6	1.7	2.9	13.3	10.4
CMT1	28.4	24.4	8.8	17.5	16.3	32.5	67.5	39.5	0	0	18.8	8.5
CMT4B	4.19	1.6	0	0	0	0	100	0	0	0	100	0

Classification (Dyck *et al*¹⁵): A=normal; B=myelin wrinkling; C=demyelination; D=demyelination and remyelination; E=axonal degeneration; F=remyelination. HNPP=hereditary neuropathy with liability to pressure palsies; IgM PPN=IgM paraproteinemic neuropathy; CIDP=chronic inflammatory demyelinating polyneuropathy; CMT1=Charcot-Marie-Tooth disease type 1. CMT4B=Charcot-Marie-Tooth disease type 4B (HMSN with myelin outfolding).

Table 2 Diameter and length of tomacula

	Age (y)		Diameter (µm)		Length (µm)	
	M	SD	M	SD	M	SD
HNPP	37.9	15.7	16.3	2	83.7	14.4
IgM PPN	64.3	14.2	14.4	3.9	45.9	5.8
CIDP	49	29.1	18.9	1.2	56.3	10
CMT1	28.4	24.4	14.1	3.5	77.4	16.1
CMT4B	4.9	0.9	11.2	1.6	44.4	5.7

HNPP=Hereditary neuropathy with liability to pressure palsies; IgM PPN=IgM paraproteinemic neuropathy; CIDP=chronic inflammatory demyelinating polyneuropathy; CMT1=Charcot-Marie-Tooth disease type 1; CMT4B=Charcot-Marie-Tooth disease type 4B (HMSN with myelin outfolding).

occasionally exhibited tomacula. The appearance of these was similar to those seen in HNPP. The biopsy of one patient diagnosed with Dejerine-Sottas syndrome (HMSN III or CMT 3) who had a P0 mutation showed the typical findings of HMSN III, thinly myelinated fibres that were enclosed in well developed onion bulb formations (fig 4 A). In addition, occasional fibres showed redundant foldings or bizarre myelin formations similar to those seen in HMSN with myelin outfolding.

Electron microscopy—In HNPP, both hypermyelination—for example, an excessive number of myelin lamellae—and redundant loop formation were seen, the second being the

most frequent mechanism of tomacula formation. Adaxonal myelin breakdown products (fig 1 B) were most often seen in HNPP. The appearance of myelin sheath thickenings in CMT1 was similar to that seen in HNPP. In the paraproteinaemic neuropathies (fig 2 B) and CIDP, tomacula seemed less structured compared with HNPP or CMT1. Biopsies of patients with HMSN with myelin outfolding showed hypermyelination, redundant foldings, and bizarre myelin outpouchings (fig 3 B). The biopsy of one patient bearing a P0 mutation showed occasional swellings that resembled those found in HMSN with myelin outfolding (fig 4 B).

Teased fibre studies (quantitative data: tables 1 and 2)

HNPP—Teased fibre preparations showed features of demyelination and remyelination and tomacula in all cases; 23.3% of fibres were normal (A), 52.2% showed evidence of demyelination or remyelination (C,D,F); tomacula were found in 54% of the fibres (G). The range of tomacula was from 13.1 to 20.2 (mean 16.3 (SD 2) µm) in diameter and 71.3 to 117.2 µm (mean 83.7 (SD 14.4) µm) in length.

IgM paraproteinemic neuropathy —Teased fibre preparations showed a high percentage of

Figure 5 Single teased fibres of patients with HNPP, CMT1, CIDP, IgM paraproteinemic neuropathy (IgM PPN), and HMSN with myelin outfolding (CMT4B).

tomacula (52.7% of fibres); features of demyelination and remyelination were seen in 65% of fibres. The size of tomacula in biopsies of this group of patients ranged from 10.3 μm to 18 μm (mean 14.4 (SD 3.9) μm in diameter and 39.2 to 49.7 μm (mean 45.9 (SD 5.8) μm) in length.

CIDP—13.3% of teased fibres showed tomacula, and signs of demyelination or remyelination or both were seen in 78.3% of fibres. The diameter ranged from 17.6 to 19.2 μm (mean 18.9 (SD 1.2) μm), the length ranged from 46.4 to 66.4 μm (mean: 56.3 (SD 10) μm).

HMSN I/CMT1A—Tomacula were found in 10% to 30% (mean 18.8%) and 20% to 100% (mean 67.5%) of fibres showed signs of demyelination and remyelination. The tomaculum diameter ranged from 11.7 to 19.2 μm (mean 14.1 (SD 3.5) μm); the length ranged from 56.5 to 94.6 μm (mean 77.4 (SD 16.1) μm).

HMSN with myelin outfolding (CMT4B)—Teased fibres were all abnormal with features of extensive demyelination and remyelination and the formation of numerous small regions of myelin thickening. The size of these ranged from 10 to 13.1 μm (mean 11.2 (SD 1.6) μm) in diameter and 38.6 to 50 μm (mean 44.4 (SD 5.7) μm) in length.

HMSN III/CMT3—Teased fibres of this patient bearing a P0 mutation showed numerous small focal swellings comparable with those seen in HMSN with myelin outfolding. This specimen did not allow quantitative analysis.

Figure 5 shows typical tomacula of patients with HNPP, IgM paraproteinemic neuropathy, CMT1A, CIDP, and focal myelin swellings in CMT4B.

Discussion

Various demyelinating neuropathies are associated with the formation of tomacula in sural nerve biopsies. The frequency and size of these focal thickenings of the myelin sheath are not a specific feature, but they may assist in distinguishing different forms of peripheral neuropathy.

In our study, teased fibre preparations showed numerous small focal myelin swellings in all fibres of patients with HMSN with myelin outfolding and in one patient bearing a P0 mutation, a high frequency of tomacula in HNPP (54% of fibres), and in IgM paraproteinemic neuropathy (53% of fibres). Less often, tomacula were found in sural nerve biopsies of patients with CIDP (13%) and of four patients with CMT1 (19% of fibres).

WHY DO TOMACULA FORM IN THESE DISORDERS ?

Most of these syndromes are associated with defects of myelin proteins or antibodies directed against myelin components such as peripheral myelin protein (PMP22), myelin protein zero (P0), myelin associated glycoprotein (MAG), or sulfoglucuronyl paragloboside (SGPG).¹⁹ In addition, all myelin components involved in these neuropathies share the HNK-1 epitope, which has been implicated in cell adhesion processes. Therefore, dysfunction

of these myelin components may lead to impaired maintenance of the myelin sheath with formation of tomacula and subsequent demyelination.

PMP22

HNPP most often involves a 1.5 Mb deletion of chromosome 17p11.2–12 including PMP22.²⁰ The same gene region is duplicated in CMT1A.²¹ PMP22 point mutations have been recognised in HNPP,¹⁷ CMT1A,^{22–23} and HMSN III/CMT3.²⁴

MYELIN PROTEIN ZERO P0

HMSN III/CMT3 and CMT1B have been shown to be associated with P0 mutations.^{25–27} Tomaculous neuropathy associated with P0 mutations was first reported by Thomas *et al*⁸ in a family with CMT1B. Gabreëls-Festen *et al*²⁸ described two divergent types of peripheral nerve morphology in seven patients with different P0 mutations. Three patients showed abundant formation of tomacula in their sural nerve biopsies.

MAG/SGPG

Anti-MAG antibodies are found in 50%–75% of patients with IgM paraproteinemic neuropathy¹⁵ and hypermyelination and focal myelin thickenings in IgM paraproteinemic neuropathy have been described.²

Chassande *et al*²⁹ found anti-MAG antibodies in 65% and anti-SGPG antibodies in 91% of patients with IgM paraproteinemic neuropathy. Occasionally, CIDP may be associated with anti-SGPG antibodies.³⁰

HMSN with myelin outfolding may be caused by defects of myelin components but no causative gene or protein has yet been identified, although an autosomal recessive form has been linked to chromosome 11q23.³¹

PMP22, P0, and MAG are, together with P2 and myelin basic protein (MBP) and connexin32, the major myelin proteins in the peripheral nervous system (PNS).

PMP22 accounts for 2–5% of PNS myelin protein,³² where it is localised to the compact portion of myelin.³³ PMP22 is predicted to be an integral membrane protein.^{34–36} It carries the HNK-1 epitope which has been implicated in adhesion processes.^{37–38} One of the possible functions of PMP22 may be that it serves as a structural component of myelin, responsible for adhesion between myelin membranes,³⁹ but it may also play a part in cell growth regulation⁴⁰; this might explain hypermyelination or hypomyelination in neuropathies associated with PMP22 gene defects. Martini and Schachner²³ propose that PMP22 is involved in controlling myelin sheath thickness and myelin integrity.

P0 is expressed in compact myelin and comprises about 50% of PNS myelin protein. It is a member of the immunoglobulin superfamily carrying the HNK-1 epitope and is thought to play a crucial part in the compaction and maintenance of myelin; Giese *et al*⁴¹ showed that in transgenic mice bearing a mutation of the P0 gene, P0 is essential for normal

spiralling, compaction, and maintenance of myelin and in Schwann cell-axon interactions.

In the PNS, MAG is expressed in the periaxonal and perinodal regions, the Schmidt-Lantermann incisures, the outer cytoplasmic aspect of the Schwann cell, and the Schwann cell basal lamina. It is an integral membrane protein with five immunoglobulin-like domains and, like PMP22 and P0, carries the HNK-1 epitope. MAG seems to be essential for myelin maintenance but not the formation of myelin.⁴² In MAG deficient 8 month old mice Martini and Schachner⁴² found degenerating axons that were associated with myelin sheaths too thick for the axonal diameter and tomacula.

Interestingly, CMTX, an X-linked form of Charcot-Marie-Tooth disease involving mutations of the connexin32 gene,⁴³⁻⁴⁵ is not associated with formation of tomacula on sural nerve biopsies. Although connexin32 is regarded as one of the major myelin proteins, it is not a structural component of compact myelin (like PMP22) and it does not carry the HNK-1 epitope. This and the fact that mutations of the PMP22 or P0 genes and antibodies to MAG have also been associated with widenings of myelin lamellae may further support the hypothesis that myelin proteins reacting with HNK-1 play an important part in adhesion mechanisms as well as in the formation of tomacula.

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