relevant. On the one hand, flunarizine blocks dopamine receptors and might have a toxic effect on dopaminergic neurons.[4] On the other hand, its calcium channel antagonism leads to inhibition of dopamine neurotransmission.[4] In addition, the antihistaminic activity of flunarizine may also have some importance. The blepharospasm that occasionally follows the use of decongestants has been explained by the antihistaminic component of these drugs.[5] Whatever the mechanisms involved, the early development of blepharospasm in a young adult on a low dose of flunarizine would suggest that individual susceptibility played a part in its emergence. The present case would favour the inclusion of flunarizine among the causes of isolated blepharospasm.

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Expression of tenascin in astrocytic tumours: too much ado about nothing?

The stroma of astrocytic tumours has been investigated in the past years by various authors. Among the proteins of the extracellular matrix tenascin is considered a very important molecule because of presumed links with the malignancy of the tumours and with the angiogenesis[1 2] and also a possible target for therapy. To verify these opinions we have performed an immunohistochemical analysis of 10 astrocytic tumours of the cerebral hemispheres. The series of patients comprised six men and four women, ranging in age from 43 to 72 years; seven underwent gross total resection and three subtotal resection. The study focused on the following molecules of the extracellular matrix: tenascin, laminin, fibronectin, and type IV collagen. The results were evaluated in relation to the following indices: grading according to the St Anne/Mayo System,[3] proliferating cell nuclear antigen labelling index,[4] dimensions of the tumour evaluated radiologically (CT and MRI) and expressed according to the criteria of the manual for staging of cancer by means of the parameter "T".[5]

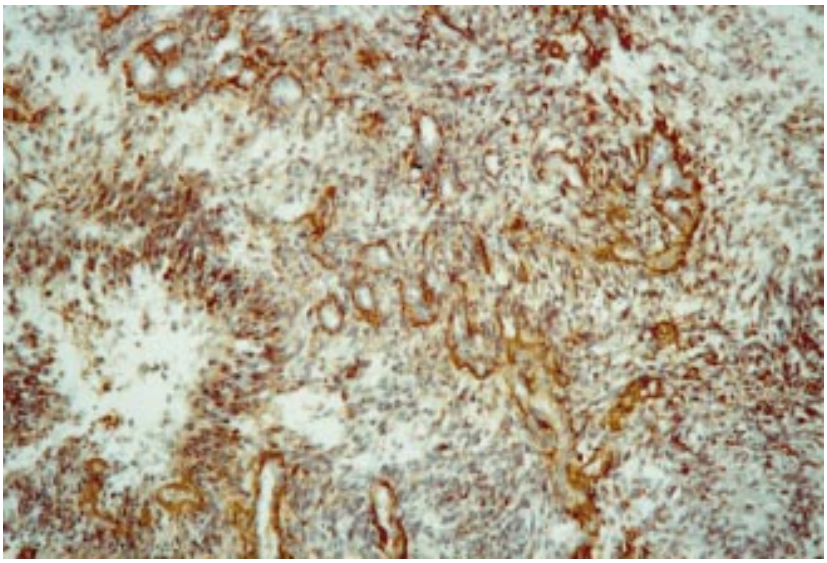
Primary monoclonal antibodies were purchased from Dako and staining was performed by the labelled streptavidin biotin staining method on 10% formalin fixed and paraffin embedded tissue.

The tumours were grade II in two cases (one gemistocytic), grade III in three cases, and grade IV in five cases. Tenascin was present in the extracellular matrix in all grade IV astrocytomas and in the gemistocytic astrocytoma. In two grade III astrocytomas and in all grade IV astrocytomas the basement membranes of the vessels with or without endothelial proliferation showed a positive immunohistochemical staining for tenascin (figure).Tenascin and fibronectin were detected in some neoplastic cells of grade IV tumours and also in the gemistocytes. Laminin, fibronectin, and collagen type IV were found around the vessels of tumours of all grades.The PCNA labelling index was <1% in tumours of grade II and grade III. In grade IV tumours the areas of highest PCNA staining did not correspond to the greater expression of tenascin on serial sections. In some areas with strong staining for tenascin the PCNA labelling index was <5%, whereas the total percentage in grade IV tumours ranged from 5% to 18%.

Evaluation of the parameter "T" failed to provide a correlation between the size of the tumour and the presence of the molecules of the extracellular matrix. For instance, a grade IV tumour evaluated as T1 expressed the tenascin as well as a grade IV tumour evaluated as T4.

In conclusion, we have shown that tenascin does not correlate with the indices of malignancy we have studied—namely, grading, PCNA labelling index, and size of the tumour. The presence of tenascin in the extracellular matrix could only be a signal of progression of astrocytic tumours. This could explain its presence in the gemistocytic astrocytoma, which is well known as a tumour with a high probability of progression.

Furthermore, it is well known in oncology that the size of the tumour must correlate with neoangiogenesis.[6] Our hypothesis is that if the expression of tenascin does not correlate with the dimension of the tumour it cannot really correlate with the angiogenesis.



Glioblastoma. Immunohistochemical staining for tenascin is in the basement membrane zone of tumour vessels and also in the extracellular matrix (originally ×125).

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Multiple sclerosis associated with duplicated CMT1A: a report of two cases

The concomitant involvement of both the peripheral and central nervous system myelin is rare and may occur in the course of inherited lysosomal storage diseases. In inflammatory autoimmune diseases of the peripheral nervous system or CNS, a mild involvement of central or peripheral myelin has sometimes been reported.[1 2] In such conditions, a single pathogenetic mechanism has been tentatively considered as responsible for the nervous tissue damage and the association of peripheral nervous system and CNS demyelinating disorders due to different pathogenetic mechanisms has never been reported.

We describe two patients with definite multiple sclerosis and hereditary peripheral neuropathy of Charcot-Marie-Tooth type 1A (CMT1A).

Patient 1, a 38 year old woman, was admitted to hospital because of episodes of gait disturbances and optic neuritis. Neurological

examination showed ataxia, lower limb weakness, bilateral Babinski's sign, increased tendon reflexes, mild sensory loss in all four limbs, impaired bladder function, and bilateral pes cavus. Her CSF showed an IgG index of 0.89 and IgG oligoclonal bands. Electrophysiology disclosed features of CNS and peripheral nervous system demyelination (table).

Patient 2, a 30 year old woman, had had recurrent episodes of hemiparesis and paraparesis, optic neuritis, and facial palsy since the age of 22. When admitted to our department, she had spastic paraplegia, absent ankle tendon reflexes, bilateral Babinski's sign, distal loss of vibration in the legs, impaired visual acuity, internuclear opthalmoplegia, and ataxic speech. Bilateral pes cavus was found in the patient as well as in several members of her family. Her CSF showed an IgG index of 0.98 and IgG oligoclonal bands. Brain MRI showed diffuse foci of demyelination in the white matter of the cerebral hemispheres and in the spinal cord. Neurophysiological studies disclosed aspects of CNS and peripheral nervous system demyelination (table).

In both patients sural nerve biopsy showed loss of myelinated fibres and aspects of demyelination and remyelination with onion bulb formation.

Genetic molecular analysis was performed by CHEF-DRIII pulsed fields gel electrophoresis of the CMT1A Sac II junction fragment.[3] The detection of the novel junction fragment of 500 kb in both cases indicated the presence of duplication.

Both patients had clinically definite multiple sclerosis; in addition, the neurophysiological, neuropathological, and genetic analysis investigations disclosed a demyelinating and remyelinating neuropathy of CMT1A.

The involvement of the peripheral nervous system in the course of multiple sclerosis has been previously reported.[1 2] The authors suggested the diagnosis of chronic inflammatory polyradiculoneuropathy (CIDP) as the consequence of a peripheral nervous system invasion by the same pathological process affecting the CNS. Our patients did not fulfill laboratory criteria for CIDP. In addition, the anamnestic presence of foot abnormalities in family members suggested inherited neuropathy. Finally, the detection of characteristic genetic alterations in chromosome 17 confirmed the diagnosis of CMT1A.

Aspects of CNS involvement have been reported in CMT1 and also in hereditary neuropathy with liability to pressure palsy,[4] the last being caused by a reciprocal deletion of the region duplicated in CMT1A; these changes have been tentatively attributed to an increased or decreased expression of peripheral myelin protein (PMP) 22 within the CNS. However, this is the first report describing an association of multiple sclerosis and CMT1A. CMT1A encompasses most of the cases of CMT and is associated with a duplication in chromosome 17 p11.2-12 where the PMP22 gene is located. PMP22 is mainly expressed in the peripheral nervous system, but it shares similarities with other proteins of the CNS such as the proteolipid protein. In duplicated CMT1A, myelin development is normal, but an overexpression of PMP22 may affect the maintenance of the peripheral nervous system myelin, which undergoes progressive destruction.[5]

The present finding raises the question whether the concomitant presence of CMT1A and multiple sclerosis represents a chance association or whether the genetic defect responsible for the peripheral neuropathy can play a part in triggering the autoimmune disorder of CNS myelin. We speculate that the PMP22 overexpression may also involve its antigenic properties, thus inducing modifications of self tolerance. In this context, the partial homology among peripheral nervous system and CNS proteins, such as the proteolipid protein, could account for the occurrence of autoimmune disorders targeted to the CNS myelin.

We suggest that patients with multiple sclerosis must be carefully evaluated for the presence of peripheral nervous system involvement. In such circumstances, neurophysiological, neuropathological, and genetic analyses may greatly contribute towards a correct diagnosis.

Table 1 Neurophysiological studies

		Patient 1	Patient 2		Normal
MNC	Ampl(mV)	0.5	12.0		
Median	DL (ms)	10.0	13.0		
	CV (m/s)	18.6	24.7		
	Ampl(mV)	−	8.0		
Ulnar	DL (ms)	−	9.0		
	CV (m/s)	−	20.1		
	Ampl(mV)	1.0	NE		
Peroneal	DL (ms)	8.7	NE		
	CV (m/s)	18.6	NE		
SNC	Ampl (μV)	4.0	NE		
Sural	DL (ms)	5.8	NE		
	CV (m/s)	26.0	NE		
SSEPS:					
Median		NE	NE		
Tibial		NE	NE		
VEPs:					
Right	Lat (ms)	151.0	149.0	P100	<118.0
	Ampl (μV)	14.7	6.4		>7.0
Left	Lat (ms)	105.0	150.0		
	Ampl (μV)	17.9	5.4		
BAERs:					
Right	I (ms)	1.66	1.66		
	III (ms)	3.80	4.07		
	V (ms)	5.56	NE	I	<1.72
Left	I (ms)	1.54	1.59	I–III	<2.37
	III (ms)	3.68	3.64	I–V	<4.30
	V (ms)	5.48	NE		
MEPs:					
Thenar	PCT (ms)	26.0	28.9		<14.5
	CCT (ms)	15.0	32.8		<10.0
Tibial ant	PCT (ms)	28.0	NE		<15.4
	CCT (ms)	32.0	NE		<18.0

MNC=Motor nerve conduction; SNC=sensory nerve conduction; Lat=latency; Ampl=amplitude; DL=distal latency; CV=conduction velocity; BAERs=waves I-III-V; VEPs=P100; MEPs=hand and leg muscles; PCT=peripheral conduction time; CCT=central conduction time; −=not performed; NE=not evoked.

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Distal myasthenia gravis and sensory neuronopathy with anti-50 kDa antibody mimicking sensory-motor neuropathy

Bilateral foot drop, paraesthesiae, and absent tendon reflexes in the lower limbs are, for the clinical neurologist, the hallmarks of a duration dependent sensory-motor neuropathy. We report a patient in which this clinical picture was sustained by the combination of an atypical distal presentation of myasthenia gravis with a probable immunomediated sensory neuronopathy.

A 69 year old woman presented with a three month history of progressive walking difficulties and paraesthesiae in the lower limbs. Examination showed bilateral foot drop with pronounced weakness of the tibioperoneal muscles (MRC= 2) and posterior leg muscles (MRC= 3), slight weakness in arm abduction (MRC=4+), tactile and pain distal sensory loss, and absent tendon jerks in the lower limbs. There were no oculobulbar symptoms and signs nor ataxia.

Motor conduction velocities and compound muscle action potential (CMAP) amplitudes were normal (ulnar= 57 m/s, 9.7 mV; peroneal= 44 m/s, 3.9 mV). Sensory conduction velocities were slowed with reduced amplitude sensory nerve potentials (ulnar=44 m/s, 5 μV; sural= 30.6 m/s, 1.8 μV). H reflexes were absent with normal latency F responses. Tibialis anterior muscle EMG did not show spontaneous activity and