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 ophthalmoplegia, 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.

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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 tibio-peroneal 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

Table 1 Neurophysiological studies

		Patient 1	Patient 2	Normal	
MNC	Ampl(mV)	0.5	12.0		
	DL (ms)	10.0	13.0		
	CV (m/s)	18.6	24.7		
Ulnar	Ampl(mV)	-	8.0		
	DL (ms)	-	9.0		
	CV (m/s)	-	20.1		
Peroneal	Ampl(mV)	1.0	NE		
	DL (ms)	8.7	NE		
	CV (m/s)	18.6	NE		
SNC	Ampl (µV)	4.0	NE		
	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
	Lat (ms)	105.0	150.0		
Left	Ampl (µV)	17.9	5.4		
	I (ms)	1.66	1.66		
	III (ms)	3.80	4.07		
BAERs:	V (ms)	5.56	NE	I	<1.72
	I (ms)	1.54	1.59	I-III	<2.37
	III (ms)	3.68	3.64	I-V	<4.30
MEPs:	V (ms)	5.48	NE		
	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.

recruitment was full but during prolonged maximal voluntary activation there was a pronounced reduction of the interferential pattern amplitude. Quantitative motor unit analysis showed a 20% reduced mean duration with 4% of polyphases. Repetitive stimulation at 3 Hz documented in the ulnar nerve-abductor digiti minimi system a 10% decrement whereas in the peroneal nerve-extensor digitorum brevis system the decrement was 33%. Amplitude CMAPs in the abductor digiti minimi after 15 seconds of maximal voluntary activation increased by 29%. A tensilon test, assessing strength in the tibio-peroneal muscles, was strongly positive. Sural nerve biopsy showed a loss of myelinated fibres. Anti-AChR antibody titre was 3.3 nM (normal value <0.8). Voltage operated calcium channel antibodies were negative. Antibodies (IgG and IgM) against gangliosides (GM1, GD1a, GD1b, GM2), SGPG, and sulphatides were negative. Chest CT excluded a thymoma or a lung cancer. A screening for breast, ovarian, and other gynaecological malignancies was negative. Tumorous markers were negative. Foot drop was greatly improved with pyridostigmine bromide and prednisone (75 and 25 mg every other day) and after three months the patient did not complain of paraesthesiae and could walk on her toes and stand on her heels.

By indirect immunofluorescence,¹ the patient's IgG strongly reacted with the cytoplasm of rat small size dorsal root ganglia neurons up to a dilution of 1:1280, whereas it did not react to large size dorsal root ganglia neurons (figure). With an indirect immunoperoxidase technique,¹ using sections of rat cerebellum, the patient's serum strongly immunostained the cytoplasm of Purkinje cells in a fine granular pattern up to a dilution of 1:2560. The patient's serum did not react with neurons of the molecular layer and Golgi neurons. To determine whether the binding to Purkinje cells and dorsal root ganglia neurons was due to the same antibody, the patient's serum was adsorbed either with whole cerebellum homogenate or with dorsal root ganglia homogenate. The pretreatment with each of the two homogenates removed the tissue binding activity, whereas liver homogenate was without effect. In the western immunoblot of whole human cerebellum homogenate, the IgG from our patient reacted with a 50 kDa protein band at dilutions up to 1:8000 (figure). Using whole dorsal root ganglia homogenate, the IgG from our patient reacted with a 50 kDa protein band at dilutions up to 1:1000. The pretreatment of serum either with whole cerebellum homogenate or with whole dorsal root ganglia homogenate removed the blot binding activity, whereas liver homogenate was without effect.

Clinical presentation in this patient pointed to a sensory-motor neuropathy. Neuropathological studies documented an axonal sensory neuropathy but normal motor conduction. Normal CMAP amplitudes and the borderline reduced mean duration value of motor unit potentials in tibialis anterior muscle indicated that the foot drop did not have a neurogenic origin. Repetitive stimulation showed an unequivocal decremental response in the peroneal nerve (whereas the ulnar nerve was still in the normal range) indicating a defect in neuromuscular transmission, more pronounced in leg muscles. The normal CMAP amplitudes, the absence of incremental response, and the negativity of voltage operated calcium channel antibodies ruled out a Lambert-Eaton myasthenic syn-

Top: binding of patient's serum at a dilution of 1:1280 to an unfixed frozen section of rat dorsal root ganglia by immunofluorescence microscopy. The patient's IgG intensely immunostains the cytoplasm of small size dorsal root ganglia neurons (arrows) but not with large size dorsal root ganglia neurons (arrowhead) (originally $\times 170$). Middle: control serum does not bind and stain the cytoplasm of rat dorsal root ganglia (originally $\times 170$). Lower: lane 1: immunoblot of human whole cerebellum homogenate shows that at a serum dilution of 1:8000 the patient's IgG (lane 1) binds to a 50 kDa protein. Lane 2: positive control with anti-Hu antibodies binding to a 40 kDa protein. Lane 3: negative control. Lane A: whole cerebellum homogenate; lane B: molecular weight standard. Lanes 1–3, peroxidase conjugated assay. Lanes A and B, amido black staining.

drome. Myasthenia gravis was confirmed by the raised titre of serum anti-AChR antibodies and the positive tensilon test. In myasthenia gravis distal limb muscles are reported to be almost never affected in absence of oculobul-

bar signs.² Peroneal nerve repetitive stimulation, as recently described by Oh *et al.*,³ was crucial to the confirmation of myasthenia gravis in this patient.

Clinical, electrophysiological, and histological findings also showed an axonal sensory neuropathy. Although there are no electrophysiological or morphological ways to distinguish between an axonal sensory neuropathy and a sensory neuronopathy, the reactivity of our patient's IgG against small size dorsal root ganglia (figure) suggests a primary, probably immunomediated, involvement of sensory neurons. The patient's serum strongly immunostained, in a fine granular pattern, the cytoplasm of Purkinje cells and in western immunoblotting the IgG reacted with a 50 kDa protein band present in whole cerebellum and dorsal root ganglia homogenates (figure). These immunostaining and immunoblot findings are clearly different from the features required for the identification of anti-Yo and anti-Hu antineuronal antibodies.^{4,5}

In conclusion this case is unique for several reasons:

(1) Clinical presentation pointed to a sensory-motor neuropathy but the foot drop was sustained by an atypical, distal presentation of myasthenia gravis.

(2) Peroneal nerve repetitive stimulation (not usually performed in EMG laboratories) played an important part in confirming myasthenia gravis.

(3) Myasthenia gravis has been reported to be associated with other autoimmune disorders but never to a sensory neuronopathy with antibodies reacting with dorsal root ganglia neurons and Purkinje cells.

(4) 50 kDa antineuronal antibodies reacting with small size dorsal root ganglia neurons and in a fine granular pattern with the cytoplasm of Purkinje cells have never been described previously.

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