Electrophysiological and biomechanical data before and after repetitive magnetic stimulation in 12 patients with multiple sclerosis (median range)

	Maximum voluntary contraction (Nm)		Stretch reflex amplitude (% M_{max})	Threshold of stretch reflex (%/s)
	Dorsi	Plantar		
Before treatment	15.5 (0–23.0)	19.0 (1.7–32.0)	1.23 (0–10.4)	22 (6.0–88.0)
After treatment	20.0 (1.4–48.0)**	26.0 (3.2–44.0)**	0.88 (0.002–10.5)*	33 (12.0–88.0)*

* $p < 0.05$; ** $p < 0.01$.

values in 12 patients with clinical definite multiple sclerosis.¹ All had spasticity of the lower extremities, a preserved capability of continuous walking for at least 30 meters, and a clinical stable condition during the six months before study. Eight patients had not been treated recently for spasticity and four patients stopped drug treatment one week before the study. The magnetic stimulus has a biphasic waveform with a pulse width of 400 μ s, a rise time of 200 μ s, and a maximum magnetic field of 2.1 Tesla. The oil cooled coil was placed in the midline at the midthoracic level with the caudal part of the coil positioned at the eighth thoracic vertebra. The patients were stimulated in a relaxed supine position for 30 minutes with stimulation for eight seconds at 12 Hz followed by 22 seconds of rest. The range of stimulation intensity was 40–65% of maximal stimulator intensity. At the start of the study and 24 hours after the last magnetic stimulation clinical, electrophysiological, and biomechanical performances were registered. The same physician evaluated the spasticity at both knee and ankle joints by an Ashworth's score (0–4)² with a total maximum score of 32 arbitrary units (AU) as well as the patellar and Achilles tendon reflexes according to conventional clinical grading (0–4) with a maximum score of 16 AU.

For the electrophysiological and biomechanical measurements the patients were seated in a chair with the foot strapped to a pedal rotated by a strong motor.³ Spasticity was electrophysiologically evaluated by the threshold and amplitude of the stretch reflex by EMG of the soleus muscle and expressed as a percentage of the supramaximal direct muscle response (M_{max}). The short latency stretch reflex was elicited by rotating the platform at different stretch velocities in the range from 7.5 to 120°/s.⁴ Stretches and releases of 4° were delivered with a duration of 500 ms and were applied randomly with an interval of 4.0 (SD 0.2)s. The amplitude of the stretch reflex was measured at a stretch velocity of 90°/s. Maximum voluntary contraction of dorsi and plantar flexion of the foot was measured as the highest value the patient could maintain for one second out of three attempts. The patients self scored the ease of daily activities (0–10) with a score of 5 as the preset level. Group values and delta difference values between the pretreatment and post-treatment condition are given as median values and ranges. Differences were tested by Wilcoxon signed rank test with a 5% limit of statistical significance.

Self score of ease of daily day activities improved significantly ($p = 0.01$) by 2 (4–0) AU pretreatment and post-treatment group values were 5 (5–5) AU and 7 (9–5) AU. The clinical score of spasticity decreased significantly by 1.5 (8–(-1)) AU ($p = 0.03$); pretreatment and post-treatment group values were 9.5 (17–1) AU and 5.5 (10–2) AU. The score of hyper-reflexia decreased signif-

icantly by 1.0 (3–(-1)) AU ($p = 0.03$); pretreatment and post-treatment group values were 6.5 (11–4) AU and 6.5 (11–2) AU. Electrophysiological measures of spasticity improved. The table shows a significant decrease of EMG amplitude of the stretch reflex of 28% ($p = 0.04$) and an increase in the threshold of the stretch reflex of 50% ($p = 0.03$). Maximum voluntary contraction of plantar and dorsiflexion of the foot strengthened significantly, by 27% and 29% respectively ($p = 0.008$ and $p = 0.009$).

No major side effects of magnetic stimulation were found. All patients reported a tight feeling as if wearing a narrow ring around the midthoracic level during stimulation. One patient had a single episode of brief dizziness but otherwise magnetic stimulation was well tolerated. By contrast, con-

ventional pharmacotherapy often induces side effects including loss of muscle strength, drowsiness, dizziness, and nausea. A double blind and sham stimulation controlled study of the effect of repetitive magnetic stimulation on spasticity is under way.

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Patients with clinically definite multiple sclerosis, white matter abnormalities on MRI, and normal CSF: if not multiple sclerosis, what is it?

Clinical overdiagnosis of multiple sclerosis may occur in as many as 10% of patients according to Hendon and Brooks.¹ Whereas diagnosis has been facilitated by the use of MRI,^{2,3} the detection of focal disease scattered throughout the CNS in young adults is not specific for multiple sclerosis (table).

We therefore estimated the proportion of diagnostic mistakes still found in our large cohort of clinically diagnosed patients with multiple sclerosis.

Four hundred and five new patients were studied between 1988 and 1992. Three hundred and fifty two patients of our cohort met the Poser criteria for "clinically definite multiple sclerosis" and 184 had a complete CSF examination. Of these 184 patients, 166 had positive immunological findings for multiple sclerosis. The remaining 18 had no CSF abnormalities. These eighteen patients

had a duration of disease of at least one year, an upper age limit below 45 at onset, and the presence of multiple white matter lesions on MRI and they were given repeat CSF and MRI examinations between January and April 1993, together with a variety of tests screening for mitochondrial encephalomyopathy, adrenoleukodystrophy, Lyme disease, AIDS, coagulopathy, vasculitis, sarcoidosis, and cardiac embolic sources.

The MRI characteristics of multiple sclerosis are "multiple small lesions mainly involving white matter with asymmetric distribution that have optimal specificity if the following three features are present: size > 6 mm, abutting ventricular bodies, infratentorial location".⁴

We defined the MRI as: (a) "typical" and (b) "compatible" when not all the three features for optimal specificity were present.

In 16 of these 18 cases, the MRI was typical for multiple sclerosis, but four had a final diagnosis that was not multiple

Differential diagnosis of brain MRI mimicking multiple sclerosis

Multiple sclerosis-variants: Charcot type, Devic type, Schilder type, Marburg type, isolated syndromes
Normal aging*
Alzheimer's disease*
Migraine
Subcortical arteriosclerotic encephalopathy or Binswanger's disease*
Multiple metastases
Vasculitis: Sjögren's syndrome, polyarteritis nodosa, systemic lupus erythematosus, Behçet's disease, giant cell arteritis
Sarcoidosis
Leucodystrophies
Encephalitis:
Viral: HTLV-I myelopathy, progressive multifocal leucoencephalopathy (Papova), subacute sclerosing panencephalitis (measles), acute disseminated encephalomyelitis
Bacterial: tuberculosis
Spirochaetal: syphilis, neuroborreliosis, or Lyme disease
Chronic demyelinating inflammatory polyneuropathy
Subacute combined degeneration of the spinal cord

*Excluded by age.

sclerosis. In two more cases the neuroradiologist used the expression "compatible". For these two patients, the final diagnoses were Lyme disease and vasculitis. Hence, six of 18 patients with normal CSF had a final diagnosis other than multiple sclerosis. The methodological details along with the clinical and laboratory characteristics of our patients will be the subject of a full paper. Here we describe the six patients with an alternative diagnosis.

Case 1 was a 42 year old woman who had right optic neuritis and a mild deficit of the seventh cranial nerve in February 1989. Symptoms improved a month after steroid treatment. In March 1991 she experienced paraesthesia and mild hypoesthesia in her left leg, which remitted spontaneously in 10 days. An antinuclear antibody test was positive. A skin rash developed after her inclusion in our study and biopsy of this confirmed the diagnosis of systemic vasculitis.

Case 2, a 50 year old woman, experienced multiple episodes of diplopia and ataxia between January 1986 and September 1989 remitting in a few days without treatment. In June 1990 she developed weakness in her lower limbs with severe ataxia, lasting two months and partially improving after steroid treatment. Repeated MRI was typical. In December 1992 a progressive worsening of gait disturbance began. The MRI performed showed severe olivopontocerebellar atrophy. Some punctate hyperintense areas in the white matter were still present. A diagnosis of olivopontocerebellar atrophy was made on clinical and MRI findings.

Case 3, a 46 year old woman, had several episodes of left facial paraesthesia and dysarthria between June 1972 and June 1986. In September 1989 she developed weakness in her left side and in March 1992 she experienced vertigo and ataxia. All episodes were mild, lasting a few days and remitting without treatment.

Echocardiography showed an aneurysm of the atrial septum.

Case 4 was a 40 year old man who reported dysarthria and weakness in his left limbs, lasting about three weeks in September 1986. In April 1991 he developed severe weakness in his right limbs, remitting in two months. Steroid treatment was efficacious in both episodes. A repeated CSF examination in February 1993 showed high concentrations of lactate, without any other abnormalities. A diagnosis of mitochondrial encephalomyopathy was made after skeletal muscle biopsy.

Case 5 was a 26 year old woman who reported right facial anaesthesia and dysphagia in September 1991, which lasted a week with spontaneous remission. In December 1991 she developed mild ataxia and paraesthesia in her right side; MRI was compatible with multiple sclerosis. Steroid treatment was started with complete remission in 30 days. A further CSF examination after inclusion in the present study showed a positive reaction for antibodies to *Borrelia burgdorferi*.

Case 6 was a 36 year old man who experienced vertigo and mild deficit of the seventh cranial nerve in July 1991, lasting a few days with spontaneous remission; MRI was compatible with multiple sclerosis. In September 1991 he developed vertigo, right facial hypoesthesia and mild ataxia. In our screening for alternative diagnoses we found autoantibodies to Ro (SS-A)/La (SS-B);

biopsy of a salivary gland confirmed the diagnosis of primary Sjögren's syndrome.

In our study, we attempt to estimate the proportion of diagnostic mistakes in our cohort of "clinically definite" multiple sclerosis with normal CSF, and to develop a rational approach to the diagnostic procedure leading to alternative, less common, diagnoses. Detailed reinvestigation of these patients proved that, when we considered all patients with multiple sclerosis with CSF examination, about 3.2% of them turned out to have some diagnosis other than multiple sclerosis, but when we evaluated only patients with normal CSF the diagnoses had to be revised in 33%. Even when the MRI picture is typical of multiple sclerosis, it is possible to find alternative diagnoses and a firm distinction based on MRI alone is often not possible. Especially in a busy clinical service—admittedly this is a self criticism—the level of alertness should be raised.

Currently, having a treatment such as interferon- β -1b which seems to alter favourably the course of multiple sclerosis⁵ emphasises the importance of making an early and correct diagnosis of multiple sclerosis so that treatment is given appropriately before the disease has progressed too far.

Assessment of a patient suspected of having multiple sclerosis requires (a) expertise in performing and interpreting MRI, combined with (b) a CSF study which, if normal, leads to (c) detailed tests for alternative, less frequent, diagnoses with particular attention to vascular disorders in young adults.

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Long term course of change in anti-Yo antibody content in paraneoplastic cerebellar degeneration

Female patients with paraneoplastic cerebellar degeneration (PCD) associated with breast or gynaecological cancers often have a characteristic antineuronal autoantibody (anti-Yo antibody).¹ To determine whether the anti-Yo antibody recognises the same

SDS-PAGE of the recombinant Yo-protein. (A) Lane 1: molecular size marker; lane 2: homogenates of transformed cells before isopropyl-p-D-thiogalactopyranoside induction; lane 3: homogenates of transformed cells after isopropyl-p-D-thiogalactopyranoside induction; lane 4: recombinant protein fused to the maltose binding protein purified on an amylose resin column. The molecular weight of the fusion protein is 62 kDa, consistent with the size expected from the DNA sequence. This protein gives triple bands (double bands under 62 kDa) that are thought to be its phosphorylated products. (B) Lane 1: molecular size marker; lane 2: Immunoblot of the recombinant Yo-protein that reacted with the patient's serum.

antigen epitope is important for detecting the origin of a cancer; therefore, we constructed recombinant Yo protein (r-Yo) and established an enzyme linked immunosorbent assay (ELISA) system that uses this protein as the antigen. With this system, we found a fallopian tube adenocarcinoma by testing for antibody to r-Yo in a patient with PCD that could not be detected by conventional methods.² We measured the antibody titre in serum samples taken serially during various times of treatment.

The details of this patient's case have been reported elsewhere.² Briefly, a 70 year old woman developed cerebellar ataxia that worsened rapidly, and she became bedridden within two weeks. An extensive malignancy survey showed no evidence of tumour. An immunohistochemical investigation showed that the IgG in her serum and in her CSF bound to the cytoplasm of Purkinje and other neuronal cells and reacted with the 58 kDa band on immunoblots of cerebellar homogenates. To determine whether this antibody really does recognise the Yo antigen, we produced r-Yo for use as the antigen in immunoblotting or ELISA.

Recombinant Yo protein was produced using the nucleotide sequence reported by Sakai et al.^{3,4} As the common epitope has the leucine-zipper motif,⁵ we designed a primer pair, nucleotide numbers 1 to 20 for the 5' site and 497 to 519 for the 3' site. The reverse transcription polymerase chain reaction (RT-PCR) was performed with RNA derived from adult human cerebellum as the template. The RT-PCR product with the leucine-zipper motif then was