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 hypoaesthesia 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. In 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 improved 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 hypointense 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 dyssarhythmia 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 aortal 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 immediately. 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. Spontaneous remission occurred. MRI was compatible with multiple sclerosis. In September 1991 he developed vertigo, right facial hypoaesthesia 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 non-specific clinical MRI 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-β1b which seems to alter favourably the course of multiple sclerosis’ 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). To determine whether the anti-Yo antibody recognised the same 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 fallapion tub adenosinocarcinoma by testing for antibody to r-Yo in a patient with PCD that could not be detected by conventional methods. We then measured the antibody titre in serum samples taken serially during various types of treatment.

The details of this patient’s case have been reported elsewhere. 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.14 As the common epitope has the leucine-zipper motif, 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
Plasmids were transformed into Escherichia coli DH5α. Production of the recombinant fusion protein was induced with isopropyl-β-D-thiogalactopyranoside. The DH5α cells were sonicated and centrifuged, after which the supernatant was applied to an amylase resin column and eluted with maltose to separate the Yo protein fused to the maltose binding protein (figure). For ELISA, the r-Yo was bound to immunoplates (0.5 μg/well). Non-specific binding was blocked with 0.5% buffered saline (TBS) containing 0.5% skimmed milk. The patient's serum then was diluted 1:5000 with the blocking solution and immunostained with avidin-biotin-peroxidase. Absorbance at 495 nm was measured with a spectrophotometer. The normal and disease control samples consisted of serum samples taken from 10 healthy young adults, from 10 patients with spinocerebellar degeneration (mean age 56 (SD 11)), and from seven patients with gynaecological cancer without neurological symptoms. The mean ELISA absorbance of serum samples from the young adult controls was 0.080 (SD 0.025) and that from the disease controls, 0.082 (SD 0.046). The absorbance for serum from the patient with PCD before treatment was 1.200. After three cycles of plasmapheresis, it rose to 1.764. On the basis of her clinical picture and the presence of the characteristic anti-Yo antibody, we did a test laparotomy with her informed consent because the conventional survey had found no tumour. A fallopian tube adenocarcinoma 1.5 cm in diameter was identified and successfully resected. Cancer chemotherapy was started 18 days after operation (cisplatin, adriamycin, cyclophosphamide, and 5-fluorouracil). Two more chemotherapy cycles were given at monthly intervals. The antibody titre of serum taken serially at various times during treatment and during the three year follow-up period showed a gradual reduction to 0.401. Only patients with PCD who have anti-Yo antibody have been found to have mostly breast or gynaecological cancers. More than half of these patients with PCD showed neurological symptoms only for several months, no underlying cancer being detected despite extensive surveys for malignancy. The detection of anti-neuronal antibodies, therefore, is important for the early detection of the underlying cancer. These autoantibodies can be detected from the staining distribution obtained by immunohistochemical means as well as by their molecular sizes on immunoblots. But, as there are many molecules of similar size, we constructed r-Yo to use as the ELISA antigen to group patients with PCD with an autoantibody that recognizes the same molecule.

In ELISA, our patient's serum and CSF both had a high titre for the anti-Yo antibody. This titre increased two weeks after plasmapheresis, indicative of rebound overproduction of the antibody. After tumour resection and subsequent anticancer chemotherapy, the patient's anti-Yo antibody titre gradually decreased. Her neurological symptoms showed mild improvement, suggesting that early tumour resection ameliorates neurological symptoms. Increases in antibody titre indicate the immunological state of the host, indirect evidence of tumour antigen stimulation. Therefore it is very important to follow up changes in specific antibodies in patients with PCD.
Long term course of change in anti-Yo antibody content in paraneoplastic cerebellar degeneration.

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