

The presence of anti-CV2 antibodies was shown using immunohistochemistry on sections of rat brain and western blots of a soluble fraction of newborn rat brain proteins, as previously reported (figure, B).<sup>2</sup> The identity of the antibody was confirmed by immunoprecipitation of the CV2 protein,<sup>2</sup> and with an immunohistochemical competition assay in which preincubation of a section of rat brain with the patient's serum blocked the reactivity of a previously characterised biotinylated anti-CV2 antibody (data not shown).

Our patient is remarkable because she had several well characterised paraneoplastic antineuronal antibodies (anti-Hu, anti-Ri, and anti-CV2) in her serum, a finding that until now has not been reported. As anti-Ri antibodies react with neurons of the CNS in a pattern identical to the anti-Hu antibodies, they would have been missed without western blot analysis. This finding supports our view that antigen specificity should always be confirmed by western blot analysis.<sup>1</sup>

Anti-Hu are the best characterised antineuronal antibodies in paraneoplastic syndromes of the CNS.<sup>1,3</sup> Detection of these antibodies is almost always associated with small cell lung cancer, although a few other tumours, usually neuroendocrine related, have also been reported.<sup>1</sup> Low titres of anti-Hu antibodies (in general, orders of magnitude less than "paraneoplastic titres") are found in 16% of patients with small cell lung cancer without paraneoplastic syndromes.<sup>5</sup>

Although anti-Ri antibodies and Ri antigens have been well characterised,<sup>4</sup> many fewer patients have this antibody than other antineuronal antibody associated with paraneoplastic syndromes. Therefore the clinical range of neurological symptoms associated with anti-Ri antibodies is still expanding. As previously reported, the most frequent symptoms associated with anti-Ri antibodies are a predominant gait and truncal ataxia, usually accompanied by opsoclonus.<sup>1</sup> Other symptoms include myoclonus, axial and limb spasms, encephalomyelitis, and peripheral neuropathy.<sup>1</sup> Similarly, the range of tumours associated with anti-Ri antibodies is larger than what was previously suggested; it includes breast cancer and, less often, gynaecological cancers,<sup>4</sup> small cell lung cancer, and bladder cancer (Dalmau *et al*, unpublished data). The tumours of all these patients were found to express Ri antigen.

The serum of the patient contained another antibody, called anti-CV2, that has been identified in patients with paraneoplastic neurological syndromes (including cerebellar ataxia); the most commonly associated tumour is small cell lung cancer.<sup>2</sup> In a series of 11 patients with anti-CV2 associated paraneoplastic neurological syndromes, we identified another patient with small cell lung cancer who harboured both anti-Hu and anti-CV2 antibodies in his serum.<sup>2</sup>

We do not know which component of the immune response (anti-Hu, anti-Ri, or anti-CV2) either in combination or alone, was involved in the neurological dysfunction of our patient. The experience with anti-CV2 antibodies is too limited to draw conclusions about the role of this immune response in neurological symptoms. Patients with anti-Hu associated encephalomyelitis-sensory neuropathy complex do not usually improve with treatment, whereas symptoms associated with anti-Ri may respond to treatment.<sup>1</sup> The fact that our patient had high titres of anti-Hu antibodies, which until now have been invariably associated with

encephalomyelitis-sensory neuropathy complex, including predominant cerebellar symptoms, and that the neurological symptoms did not improve with chemotherapy, intravenous immunoglobulin, and steroids, suggest, but do not prove, that the anti-Hu immune response was involved in the patient's symptoms. However, the presence of both anti-Hu and anti-Ri antibodies, the second at titres also similar to those in patients with cerebellar dysfunction associated with anti-Ri, indicates that multiple immune responses against onconeural antigens may occur at the same time, and be involved in a specific neurological disorder.

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### Successful treatment of stiff man syndrome with intravenous immunoglobulin

Stiff man syndrome is a rare condition characterised by a progressive stiffness of the paraspinal and lower limb musculature with intermittent painful spasms often precipitated by startle responses.<sup>1</sup> It is associated with other autoimmune conditions and antibodies to glutamic acid decarboxylase (GAD) and other organ specific and non-organ specific autoantibodies.<sup>1</sup> The mainstay of treatment is with benzodiazepines and baclofen and attempts to treat patients with steroids or plasmapheresis have been undertaken with mixed results.<sup>2,3</sup> Our patient responded to intravenous immunoglobulin (IVIg).

A 43 year old man developed low back pain six years before admission. He then started to fall, initially with extreme exertion, due to sudden unexpected stiffness of the legs. This became progressively worse over a 12 month period such that it started to be apparent on walking. A diagnosis of agoraphobia was made and diazepam treatment resulted in dramatic improvement. His symptoms continued and he then started to

experience jerking of the legs when relaxing as well as an exaggerated startle response, which on occasions caused him to collapse to the ground. Four years into the illness he developed insulin dependent diabetes mellitus. His mother had thyrotoxicosis, his maternal grandmother had diabetes mellitus, and an uncle had pernicious anaemia.

On examination he walked with a stiff gait punctuated by excessive startle responses causing him to fall forward to the ground on some occasions. He had a lumbar hyperlordosis with pronounced paraspinal, abdominal, and lower limb rigidity, normal power and coordination in his lower limbs, brisk lower limb reflexes, and flexor plantar responses. Sensory examination was unremarkable, apart from the excessive startle response to sensory stimuli.

He had a normal full blood count, erythrocyte sedimentation rate, and biochemical profile with a glycosylated haemoglobin of 6.5%. His autoantibody screen was negative apart from a weakly positive antiparietal cell antibody and a positive serum anti-GAD antibody at a titre of 1:500. Analysis of CSF and brain MRI were normal. Neurophysiological examination showed continuous motor unit activity in his paraspinal and lower limb muscles with exaggerated exteroceptive reflexes. Nerve conduction study was normal.

His symptoms were improved but not controlled by baclofen (60 mg/day), diazepam (15 mg/day), and buspirone (15 mg/day). He was given three courses of intravenous immunoglobulin (Alphaglobulin; 0.4 g/kg/day for five days) about a month apart and his progress was assessed on a timed walking task off treatment during the week he received IVIg.

The initial benefit from the IVIg was small, but the first symptomatic improvement reported by the patient was a reduction in the startle response and associated falls. Subsequently his walking improved both subjectively and objectively. Six weeks after his final course of IVIg there had been a reduction in his walking task time from 29 to 20 seconds (normal subject on same task; 15 seconds) and on EMG there was no evidence of continuous motor unit activity off treatment. This improvement in his condition has occurred even though his benzodiazepine and baclofen doses were reduced by a third after his final course of IVIg.

The significant response to IVIg is in agreement with earlier studies, in which six patients in total have received between one and three courses of IVIg.<sup>4,5</sup> Interestingly some of the patients in these studies responded to IVIg having only had a partial or no response to steroid treatment or plasma exchange.

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### Increase of flexor reflex latency in patients with amyotrophic lateral sclerosis treated with riluzole

Recently, riluzole has been reported to increase life expectancy in patients with amyotrophic lateral sclerosis.<sup>1</sup> Pharmacologically, riluzole is an inhibitor of glutamate release and a non-competitive antagonist at N-methyl-D-aspartate receptors.<sup>2</sup> Glutamate antagonists are also undergoing clinical trials for several other diseases. It is known that the H reflex and flexor reflexes in experimental animals are mediated by different subtypes of ionotropic glutamate receptors<sup>3</sup>; the flexor reflex by NMDA receptors and the H reflex by non-NMDA receptors. Therefore, spinal reflexes may provide an opportunity to investigate glutamatergic neurotransmission in humans *in vivo*. We investigated whether riluzole differentially alters the H reflex and flexor reflexes in patients with amyotrophic lateral sclerosis treated with the drug. From the natural course of the disease it is known that the density of the non-NMDA binding sites increases in the spinal cords of patients with amyotrophic lateral sclerosis.<sup>4</sup> We therefore expected that treatment with riluzole would maintain the latency of the H reflex and increase the latency of the flexor reflexes.

The study was approved by the Ethikkommission of the Humboldt-University.

The H reflex (recorded from M soleus) and the flexor reflex (recorded from M tibialis anterior) were investigated in 15 controls (nine men, six women, mean age 25 years) and 10 patients with amyotrophic lateral sclerosis, at onset and after three months of treatment with 50 mg riluzole twice a day (four men, six women, age range 35-75 years; less than 30 months since the onset of clinical symptoms). The H reflex was investigated in a sitting position<sup>5</sup> with stimulation of the nerve in the popliteal fossa. The flexor reflex was elicited in a sitting position with the foot mildly dorsally flexed. Stimulation was performed at the plantar aspect of the foot (20 ms duration, 50 Hz, 50 mA). The stimulus was recog-

nised as a sharp burning pain but was tolerated by all patients and controls. The differential electrode was placed 10 cm below the patella ligament, the indifferent 3 cm distal over the tibial bone. In controls, the mean latency of the H reflex was 29.2 (SD 2.0) ms and of the flexor reflex 80.1 (SD 7.1) ms. At the onset of treatment with riluzole, the mean latency for the H reflex in patients with amyotrophic lateral sclerosis was 31.0 (SD 3.3) ms. After three months of treatment with riluzole, the latency was unchanged at 30.4 (SD 3.0) ms. The respective values for the flexor reflexes were 72.5 (SD 6.6) ms at onset and 121.1 (SD 17.6) ms ( $P < 0.05$ ; fig 1) after three months of treatment with riluzole.

The latencies of the H reflex in controls and untreated patients with amyotrophic lateral sclerosis are consistent with the medical literature. The latency and pattern of the flexor reflex is similar to the report from which the method was adapted.<sup>5</sup> Our results show that the H reflex and the flexor reflex are differentially affected in patients with amyotrophic lateral sclerosis treated with riluzole. The latency of the H reflex did not change in patients treated with riluzole, whereas the latency of the flexor reflex increased. This is consistent with the known pharmacological properties of riluzole as a non-competitive antagonist at NMDA receptors.<sup>2</sup>

We conclude that spinal reflexes can be used to investigate the differential modulation of glutamatergic neurotransmission *in situ* in humans. Possibly, these diagnostic tests can be used to evaluate pharmacological therapies with glutamate antagonists.

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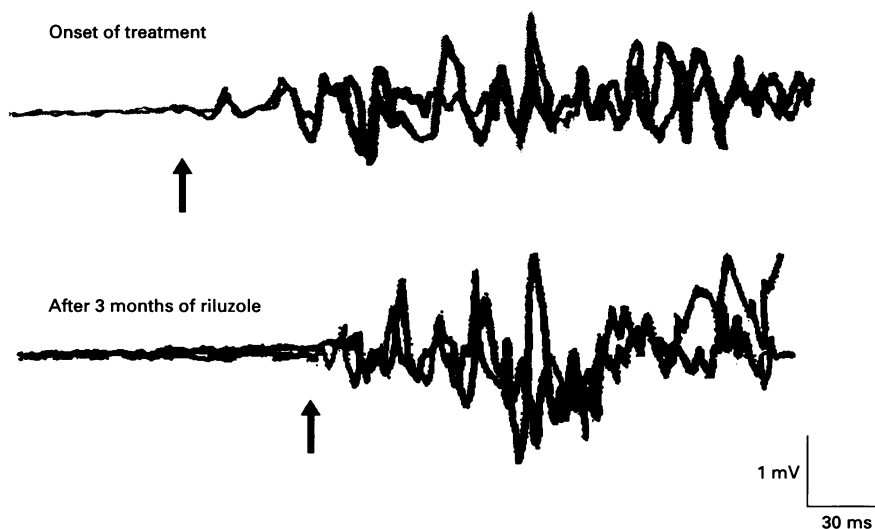
### Progressive multifocal leucoencephalopathy treated with cytosine arabinoside: 12 year follow up and postmortem findings

This patient was the subject of a previous report in 1975.<sup>1</sup> We now report follow up until her death in 1985 and the postmortem examination.

Sarcoidosis was first diagnosed in 1959, at the age of 38 years, after uveoparotitis and a left facial palsy. She had iritis in 1965 and evidence of pulmonary sarcoidosis in 1966. Treatment was then started with prednisolone (7.5 mg daily). In 1972 she had mumps in September and in October difficulty with the use of her right hand which slowly progressed to a right hemiparesis, associated with facial weakness and dysphasia. A diagnosis of progressive multifocal leucoencephalopathy was confirmed by cerebral biopsy and viral culture. Within a few weeks of starting treatment with cytosine arabinoside (2 mg/kg) in September 1973 definite improvement was seen. She returned to work as a nursing tutor in November 1973. By February 1975, at the time of the first report,<sup>1</sup> she was continuing with five day courses of cytosine arabinoside separated by intervals of three weeks, without complications. She continued to improve and there was at that time no evidence of speech disturbance. She had minimal right sided facial weakness, moderate spastic weakness of the right arm with quite dense cortical motor deficit in the hand, and obvious cerebellar ataxia involving the right arm and hand.

In May 1975 she developed intermittent lower abdominal colic with abdominal distension and tenderness associated with nausea, flatulence, and borborygmi. A barium meal and follow through showed uniformly dilated loops of bowel and coarse oedematous mucosal folds with an abnormal mucosal pattern. Further investigations showed malabsorption of B12, iron, and folate. Biopsy showed subtotal villus atrophy. In October 1975 further gastroenterological investigations gave similar results. These gastrointestinal abnormalities have not been described with cytosine arabinoside. Gluten sensitive enteropathy was confirmed by a response to a gluten free diet with considerable sustained improvement, apart from very occasional inadvertent gluten exposure, usually from gluten filler in tablets.

She had visual migrainous equivalents for many years, which only rarely proceeded to headache. Some of these attacks were associated with numbness of one or other hand, usually the right hand. In April 1976 she was having increasing attacks of migraine and found that if the right hand was affected, she became quite obviously dysphasic for an hour or more. If the numbness



Flexor reflexes in one patient at onset of treatment and after three months of treatment with riluzole (two recordings superimposed).