nied with no pupillary change, it was most probably realised through the activity of the oculomotor nerve although we did not perform EMG recording of the muscles.

The afferent limb of this reflex is probably attributable to proprioceptive impulses rising in the deep tissues of the arm such as muscles, ligaments, tendons and receptors participating in flexion of the arm. It is unlikely that pain receptors played a part, because the patients did not open their eyes to painful stimuli.

The "arm EOR" was accompanied by extension of the head and contralateral limbs suggesting a decerebrate response. Decerebrate response usually occurs in brainstem lesions with at least partial and bilateral midline pontine lesions, but occasionally in severe diffuse bilateral hemispheric damage due to posthypoxic encephalopathy. This response is interpreted as a release phenomenon of the brainstem activity from higher extrapyramidal control. It includes not only extension of the limbs and body, but also some pathological reflexes of the head such as clenching of the jaw ("a bulldog reflex", which was seen in our patient 1, or, on the other hand, jaw opening. These reflexes must require activity of the appropriate cranial nucleus and its efferent pathways. The "arm EOR" may be regarded as a component of the decerebrate responses involving the cranial nerves. It at least suggests preservation of the central caudal nucleus, which is thought to be responsible for the eyelids.

We report with confidence that there exists an EOR elicited by flexion of the arm. It may be a manifestation of decerebrate response, especially in diffuse bilateral hemispheric damage after acute hypoxic-ischaemic encephalopathy. This phenomenon may be mediated through the proprioceptive system, although it has been considered that the pain system has the most important role in occurrence of both decerebrate response and wakefulness.

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Association of antineural autoantibodies in a patient with paraneoplastic cerebellar syndrome and small cell lung carcinoma

Three autoantibodies have been well characterised in paraneoplastic neurological syndromes and proved to be helpful in the diagnosis. Anti-Hu (or ANNA-1) antibodies were reported in patients with encephalomyelitis-sensory neuropathy, complex and small cell lung cancer, anti-Yo (or PCA-1) antibodies were identified in women with paraneoplastic cerebellar degeneration and gynaecological tumours, and anti-Ri (or ANNA-2) antibodies were first reported in patients with opsoclonus/ataxia and breast cancers.

Our patient with paraneoplastic cerebellar syndrome and small cell lung carcinoma had circulating anti-Hu and anti-Ri autoantibodies. The serum samples and the CSF of this patient also contained anti-CV2, another autoantibody recently described in patients with paraneoplastic neurological syndromes.

A 56 year old woman with a 50 pack-year history of cigarette smoking had an unremarkable medical history until October 1994, when she developed acute vertigo. Brain CT showed no abnormalities. She then developed mild instability which remained stable until March 1995 when her gait became difficult with frequent falls. In June 1995, neurological examination showed bilateral horizontal nystagmus, dysarthria, and severe statokinetic cerebellar syndrome. The rest of the neurological and general physical examination was normal. Routine laboratory and immunological analyses were normal. Erythrocyte sedimentation rate was 40 mm. Cerebrospinal fluid contained 10 white blood cells/mm³ (40% lymphocytes and 60% neutrophils), 50 mg/dl protein (IgG 8.1 mg/dl, IgA 0.8 mg/dl, and IgM 0.4 mg/dl), and 43 mmol/dl glucose. Cytology was negative for malignant cells. Viral, bacterial, and fungal cultures from blood, CSF, and urine were negative. Serological studies of blood and CSF, including HIV, Lyme, syphilis and hepatitis B and C were negative. An EEG was normal. Brain MRI showed mild vermician and cerebellar atrophy. Compared tomography of the chest, abdomen, and pelvis disclosed two mediastinal lymphadenopathies and one nodule in the right adrenal gland. Bronchoscopy was normal. A mediastinoscopy showed several lymphadenopathies adhered to the trachea, the biopsy of which was consistent with small cell anaplastic carcinoma. Treatment included intravenous immunoglobulins (0.4 kg/day) and methylprednisolone (1 g/day) for five consecutive days, once a month, from July to September 1995. The patient received chemotherapy from July to December 1995 (cyclophosphamide, etoposide, cisplatin, and epirubicin) and after chemotherapy, she underwent bilateral lung hilus irradiation (44 grams) and mediastinal irradiation (16 grams). Clinical follow up was marked by progressive deterioration of cerebellar ataxia and, in February 1996, she was bedridden and totally dependent. There was tumour progression and the patient died suddenly in April 1996. Necropsy was not permitted.

Serum and CSF were examined for the presence of antineural antibodies, using immunohistochemical and western blot techniques with rat and human brain, as previously reported. Immunohistochemical studies showed the presence of antibodies which reacted with the nuclei, and to a lesser degree the cytoplasm of neurons, and with the cytoplasm of a subpopulation of oligodendrocytes in the white matter of the rat cerebellum, brainstem, and spinal cord as seen in patients with anti-CV2 antibodies. Western blot analysis of isolated Purkinje cells, recombinant HuD (an Hu antigen), CDR62 (a Yo antigen), and Nova (an Ri antigen) showed a high titre of both anti-Hu and anti-Ri antibodies (figure A).

(A) Western blot analysis of the patient’s serum with immunoblot of Purkinje cells. Serum of the patient was used as dilutions of 1:2000 (lane 1). Lanes N, Hu, and Ri correspond to normal human serum, serum from a patient with anti-Hu antibodies, and serum from a patient with anti-Ri antibodies respectively (all at dilutions of 1:2000). The serum of the patient shows the pattern of bands characteristic of both Hu (35-40 kDa) and Ri (55 and 80 kDa) protein antigens. (B) Western blot analysis of the patient’s serum with immunoblot of the soluble fraction of newborn rat brain. Lane A corresponds to normal human serum (dilution 1:100), lane B to serum from a patient with anti-CV2 antibodies (dilution 1:300), and lane C to serum from the patient (dilution 1:800). Serum of the patient has a band of 66 kDa characteristic of CV2 antigen.
The presence of anti-CV2 antibodies was shown using immunohistochemistry on sections of rat brain with a western blot of a variable fraction of newborn rat brain proteins, as previously reported (figure, B). The identity of the antibody was confirmed by immunoprecipitation of the CV2 protein 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 characterized biotinylated anti-CV2 antibody (data not shown).

Our patient is remarkable because she had several well-characterized paraneoplastic antibodies (anti-Hu, anti-Ri, and anti-CV2) in her serum, a finding that is currently not shown. As anti-Ri antibodies react with neurons of the CNS in a pattern identical to the anti-Hu antibodies, they should have given rise to the western blot analysis. This finding supports our view that antigen specificity should always be confirmed by western blot analysis.\(^1\)

Anti-Hu are the best characterized anti-neuronal antibodies in paraneoplastic syndromes of the CNS. They are found in 16% of patients with small cell lung cancer without paraneoplastic syndrome.\(^2\) Although anti-Ri antibodies and Ri antigens have been well characterized,\(^3\) many fewer patients have this antibody than other neuronal antibodies associated with paraneoplastic syndromes. Therefore the differential 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 limb weakness, gait ataxia, and truncal ataxia, usually accompanied by opsinclonus.\(^4\) Other symptoms include myoclonus, axial and limb spams, encephalomyelitis, and peripheral neuropathy.\(^4\) Similarly, the range of tumors associated with anti-Ri antibodies is broader than what was previously suggested; it includes breast cancer and, less often, gynaecological cancers, small cell lung cancer, and thymoma.\(^4\) (Dalmau et al., unpublished data). The tumors of all these patients were found to express Ri antigen.

The serum of the patient contained both anti-Hu and anti-CV2, that has been identified in patients with paraneoplastic neurological syndromes (including cerebellar ataxia); the most commonly associated tumor is small cell lung cancer. 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.\(^5\)

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 syndromes. Patients with anti-Hu associated encephalomyelitis-sensory neuropathy,\(^4\) which do not usually improve with treatment, whereas symptoms associated with anti-Ri may respond to treatment.\(^7\) The fact that our patient had high titres of anti-Ri antibodies, which until now have been invariably associated with encephalomyelitis-sensory neuropathy complex, including predominant cerebellar symptoms, raises the question of whether the immunological syndromes did not improve with chemotherapy, intravenous immunoglobulin, and steroids, suggest, but do not prove, that the anti-Hu immune response is not involved in the patient's symptoms. However, the presence of both anti-Hu and anti-Ri antibodies, the second at titre also similar to those in patients with cerebellar dysynchrony 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.\(^6\) It is associated with autoimmune conditions and antibodies to glutamic acid decarboxylase (GAD) and other organ specific and non-organ specific autoantibodies.\(^7\) The mainstay of treatment is with benzodiazepines and baclofen and a proportion of patients with schizophrenia, or steroids or plasmapheresis have been undertaken with mixed results.\(^8\) Our patient responded to intravenous immunoglobulin (IVIG).

A 43 year old man developed lower back pain six years before admission. He then started to fall, initially with extreme exertion, due to sudden unexpected stiffness of the legs. He was treated conservatively with various intramuscular drugs over a 12 month period such that it started to be apparent on walking. A diagnosis of agranulocytosis 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 only improved when he had his Baclofen increased. Four years into the illness he developed insulin dependent diabetes mellitus. His mother had thyroiditis, 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 several occasions. He had no weakness, tremor, dysarthria with pronounced paraparesis, abdominal, and lower limb rigidity, normal power and coordination in his lower limbs, brisk lower limb reflexes, and flexor plantar responses. Sensation was unremarkable, apart from the excessive startle response to sensory stimuli.

He had a normal full blood count, erythropoietin and sedimentation rate and biochemical profile with a glycosylated haemoglobin of 6.5 % . His autoimmune screen was negative apart from a weakly positive antiparietal cell antibody and a positive serum anti-GAD antibody at a titre of 1:500. His chest X-ray 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 benzodiazepine (15 mg/day). He was given three courses of intravenous immunoglobin (Alpha-globulin; 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 the 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.\(^9\) 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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