PostScript

LETTERS

Immunotherapy responsive startle with antibodies to voltage gated potassium channels

Antibodies to potassium channels (VGKC-Ab) were first associated with acquired neuromyotonia and its variant with CNS involvement, Morvan's syndrome.¹ Recently, VGKC-Ab were found in patients with non-paraneoplastic limbic encephalitis (LE), characterised by personality changes, seizures and memory impairment.² These patients may respond to immunotherapies. Thus the association of VGKC-Ab and non-paraneoplastic LE established the concept of a potentially reversible autoimmune encephalopathy.² We describe a patient with startle syndrome and VGKC-Ab, without neuromyotonia or LE, who responded dramatically to plasma exchange (PE) and immunosuppression, adding to the spectrum of disorders associated with VGKC-Ab.

The patient was a 54-year-old female. Hypothyroidism was diagnosed at the age of 30 years. At the age of 52 years, sudden falls without loss of consciousness occurred. Two months later, massive muscle jerks appeared, spontaneously or elicited by auditory and

somatosensory stimuli. The frequency of jerks increased during the ensuing months, together with mild gait impairment and scanning speech. Brain MRI was normal; CSF was normal except for the presence of oligoclonal bands. Prednisone (50 mg/day), gabapentin and levetiracetam were prescribed without improvement. Low doses of clonazepam were poorly tolerated and not effective. She was admitted to our institution in December 2003. Physical examination showed spontaneous and stimuli induced massive limb jerking, very mild limb ataxia and scanning speech, increased deep tendon reflexes and mild gait disturbance. Neuropsychological tests were normal. Brain MRI showed a faint non-enhancing signal hyperintensity in the white matter of the middle cerebellar peduncles. No thymoma was found. CSF examination confirmed oligoclonal bands. Neoplastic markers (CA 15.3, CA 19.9, CA125, CEA, α -fetoprotein) were normal. Antithyroid peroxidase and antithyroglobulin-Ab were 278 (normal value <50 UI/ml) and 3096 (normal value <325 UI/ml), respectively. GAD and voltage gated calcium channel antibodies were absent; VGKC antibodies were 562 pM in serum and 46 pM in CSF (normal values <100 pM and <2pM, respectively).

Electroneuronography, long latency EEG, several episodes of sudden massive

jerking occurred, spontaneously or elicited by unexpected auditory and somatosensory stimuli (see supplementary data, video1, 2, 3.avi; the supplementary data can be viewed on the *J Neurol Neurosurg Psychiatry* website at <http://www.jnnpjnl.com/supplemental>). Jerks correlated with EMG bursts lasting more than 100 ms and did not show habituation even when stimuli were repeated at intervals lower than 30 s. A high amplitude slow EEG transient with a phase reversal with respect to Cz consistently followed the onset of EMG bursts (fig A₁). EMG recordings to evaluate the sequence of activation of different muscles in response to sudden stimuli showed an auditory blink on the orbicularis oculi (fig 1B, arrow), followed by a generalised reflex response with earliest activation of the sternocleidomastoid, followed by masseter, trunk and limb muscles. The latency between the onset of EMG bursts recorded on intrinsic hand muscles and those recorded on biceps brachii slightly exceeded 20 ms (fig 1B).

The patient was treated with PE with a rapid and dramatic improvement in startle, time related with the first set of four exchanges. Thereafter, she received periodic PE for 1 year (two sessions every 2-3 months) and regular doses of oral cyclophosphamide with stable improvement. Prednisone was slowly tapered from 50 mg/day until withdrawal after 2 years

Figure 1 (A₁) EEG polygraphic recording performed before plasmapheresis; EMG electrodes recorded repeated spontaneous jerks involving the proximal and distal muscles of the upper right limb; bilateral and diffuse EEG slow transients followed the muscle jerks. (A₂) EEG polygraphic recording performed after 1 year of immunotherapy. (B) Rectified EMG traces showing the activation sequence of muscle jerks in response to a sudden noise (single trial) (arrow: blink reflex recorded on orbicularis oculi). R APB, abductor pollicis brevis; R BB, right biceps brachii; R EC, right extensor carpi; R FC, right flexor carpi; R ORB OC, right orbicularis oculi; R SCM, right sternocleidomastoid; R TB, right triceps brachii; RECT AB, rectus abdominis.

and antiepileptic drugs considerably simplified. Video EEG performed after 1 year of PE and immunosuppression showed rare spontaneous jerks, clinically undetectable, appearing as occasional brief EMG bursts, followed by an EEG transient similar to that observed before immunotherapy (fig A₂).

Immunocytochemistry on rat brain slices with patient's IgG and CSF showed staining of cortical neurons (layer V) and apical dendrites with a pattern similar to that of commercial antibody to Kv1.6³ (see supplementary fig 2A–C; supplementary fig 2A–C can be viewed on the *J Neurol Neurosurg Psychiatry* website at <http://www.jnnpjnl.com/supplemental>).

Hyperplexia or exaggerated startle can be distinguished from the normal startle response by its lower threshold, greater extent and resistance to habituation, criteria that were fulfilled by the features of the reflex movement disorder of our patient. The sequence of muscle activation and delay between EMG bursts recorded on proximal and distal limb muscles indicated a slow conduction time compatible with the activation pattern found in pathological startle reactions.⁴

An exaggerated motor startle reflex is one of the main features of hereditary hyperplexia, but it has also been described secondary to other disorders involving the brainstem. In genetically transmitted startle disease, hyperexcitability probably results from a dysfunction of glycine mediated inhibition. In our patient, the excessive startle, which improved rapidly after PE, was associated with raised VGKC-Ab in serum and CSF, suggesting that an insufficient hyperpolarising effect might play a pathogenic role. To our knowledge, this is the first report on the association between startle and VGKC-Ab. The lack of neuromyotonia and of MRI changes of LE cannot be explained at present. The faint MRI changes observed in our patient may reflect the different distribution of VGKC within the CNS. The VGKC-Ab in our patients were mainly directed against the Kv1.6 subunit and these antibodies are less frequently observed in patients with LE.⁵

Jerks improved rapidly and dramatically after the first set of four PE. Improvement was then maintained with repeated apheresis and oral cyclophosphamide, with progressive tapering of prednisone up to withdrawal. The rapid response to PE suggests a role for humoral immunity in our patient.

Thyroid autoimmunity has been reported in patients with neuromyotonia or LE with VGKC antibodies.^{1–3} Our patient suffered hypothyroidism, and had positive TPO antibodies. However, the clinical features did not fulfil the diagnostic criteria for Hashimoto encephalopathy as they were not compatible with either the vasculitic or diffuse-progressive type presentation of Hashimoto encephalopathy. Moreover, there is still no evidence for the pathogenic role of thyroid antibodies.

The association of startle, thyroid antibodies, oligoclonal bands and response to plasmapheresis indicates an autoimmune pathogenesis in our patient and suggests that VGKC antibodies should be assayed in patients with CNS hyperexcitability.

Carlo Antozzi

Myopathology and Immunology Unit, Neurological Institute Foundation "C Besta", Milan, Italy

Simona Binelli

Clinical Neurophysiology Unit, Neurological Institute Foundation "C Besta", Milan, Italy

Carolina Frassoni

Experimental Neurophysiology Unit, Neurological Institute Foundation "C Besta", Milan, Italy

Claudia Ciano

Clinical Neurophysiology Unit, Neurological Institute Foundation "C Besta", Milan, Italy

Angela Vincent

Neurosciences Group, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford, UK

Francesca Andreetta

Myopathology and Immunology Unit, Neurological Institute Foundation "C Besta", Milan, Italy

Ferruccio Panzica, Silvana Franceschetti

Clinical Neurophysiology Unit, Neurological Institute Foundation "C Besta", Milan, Italy

Paolo Confalonieri, Renato Mantegazza

Myopathology and Immunology Unit, Neurological Institute Foundation "C Besta", Milan, Italy

Correspondence to: Dr Carlo Antozzi, Neuroimmunology and Muscle Pathology Unit, Neurological Institute Foundation "C Besta", Via Celoria 11, 20133 Milan, Italy; antozzi@istituto-besta.it

doi: 10.1136/jnnp.2006.098301

Competing interests: Professor A Vincent's department receives payments and royalties for VGKC antibody assays. The other authors have not received any financial support from manufacturers of drugs or products cited in this manuscript.

Supplementary data (video 1, 2, 3, avi and fig 2A–C) can be viewed on the *J Neurol Neurosurg Psychiatry* website at <http://www.jnnpjnl.com/supplemental>.

References

- 1 Liguori R, Vincent A, Clover L, et al. Morvan's syndrome: peripheral and central nervous system and cardiac involvement with antibodies to voltage-gated potassium channels. *Brain* 2001;124:2417–26.
- 2 Vincent A, Buckley C, Schott JM, et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy responsive form of limbic encephalitis. *Brain* 2004;127:1–13.
- 3 Antozzi C, Frassoni C, Vincent A, et al. Sequential antibodies to potassium channels and glutamic acid decarboxylase in neuromyotonia. *Neurology* 2005;64:1290–3.
- 4 Brown P. Neurophysiology of the startle syndrome and hyperplexia. *Adv Neurol* 2002;59:153–9.
- 5 Kleopa KA, Elman LB, Lang B, et al. Neuromyotonia and limbic encephalitis sera target mature Shaker-type K⁺ channels: subunit specificity correlates with clinical manifestations. *Brain* 2006;129:1571–84.

Repetitive asystole in right insular haemorrhage

The insular cortex is known to be involved in central sympathovagal regulation. Both right and left insular lesions have been associated with cardiac derangements.

Previous stroke studies suggest that right insular lesions may cause reduced inhibition of sympathetic activity resulting in tachyarrhythmias, ECG changes, elevation of troponin T (TnT) and serum catecholamine levels, decreased heart rate variability, higher occurrence of sudden death and overall death rate within 3 months.

In contrast, recent data indicate a significant role of the left insula in mediating the

parasympathetic tone, and therefore lesions in this region may be associated with a shifted balance towards sympathetic activity.¹ In patients surgically treated for epilepsy, direct stimulation of the right insular cortex mainly resulted in sympathetic cardiovascular responses whereas stimulation of the left insula mainly caused parasympathetic reactions (bradycardia).² This is in agreement with the observation that barbiturate infusion into the human left carotid artery produced tachycardia whereas infusion into the right carotid artery generated bradycardia.³

Left insular lesions may be associated with decreased parasympathetic tone, shifting the balance towards enhanced sympathetic outflow and decreased heart rate variability.¹ Left insular strokes have been associated with adverse cardiac outcome, suggesting this mechanism.

Nevertheless, it is possible that both types of responses can be evoked from either insula. In the rat, prolonged left insular stimulation results in both cardiac sympathetic and parasympathetic activation.⁴ Cortical lateralisation of cardiac autonomic regulation has been suggested but the data are contradictory.

Case report

We report the case of a 51-year-old man with right insular haemorrhage who suffered from repetitive asystoles during his stay in our neurological intensive care unit (NICU). The patient had a history of treated arterial hypertension and presented with sudden onset left sided hemiplegia and somnolence. Cranial CT showed a right insular haemorrhage with intraventricular blood (approximate volume 22 ml). CT angiography did not show any arteriovenous malformation or aneurysm. The patient was treated within the 4 h window with activated recombinant factor VIIa (rFVIIa) and phenytoin because of left sided partial seizures. Because of the developing obstructive hydrocephalus, the patient was intubated, mechanically ventilated and an external ventricular drainage was inserted. The ventilator associated pneumonia was treated with ciprofloxacin and piperacillin with tazobactam, which were later changed to meropenem. Within the first 9 days, phenytoin, a beta blocker and propofol were administered without any complications for 8, 6 and 4 days, respectively.

After reduction of analgesedation on day 9, the patient suddenly developed asystole requiring cardiopulmonary resuscitation. Episodes of sudden asystoles without preceding bradycardia recurred up to five times with a duration of 10–50 s. At the time of the first asystole, the patient was on a low dose of beta blocker, phenytoin and propofol. These drugs were discontinued and phenytoin was substituted for levetiracetam. All asystole events were managed successfully with 0.5–1 mg atropine. A transthoracic cardiac pacemaker was placed temporarily. The observation was made that the asystoles were triggered by vagal stimulation (eg, the patient breathing against the ventilator, manipulation of the endotracheal tube or suctioning). The next day, the bradycardiac episodes ceased by minimal handling, deep analgesedation and after placement of a tracheotomy. No temporal relation of asystoles with any newly started medication was observed. Subsequent cardiological workup, including repeat ECGs, serum TnT and creatine kinase-MB levels and transthoracic echocar-