bilateral ALO. To the best of our knowledge, no patients have been reported to have unilateral ALO. The unilateral lesion for ALO was not always in the same side. Namely, it was in the non-dominant hemisphere in some patients and in the dominant hemisphere in others. One of our patients had a lesion at the non-dominant hemisphere. A few patients with ALO had large ischaemic lesions in the middle cerebral artery territory in the non-dominant hemisphere.[1] Furthermore, the right (non-dominant) hemispheric supranuclear area controlled the bilateral levator palpebrae superioris.[5] In contrast, two of four patients with ALO showed significant hypometabolism at the dominant-side basal ganglia,[4] and one of our patients had a lesion at the dominant side. Based on these arguments, we cannot make any conclusion about the laterality about a lesion for ALO.

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Non-paraneoplastic limbic encephalitis associated with NMDAR and VGKC antibodies

INTRODUCTION

Limbic encephalitis (LE) is characterised by seizures and impairment of short-term memory as well as behavioural and psychiatric symptoms such as anxiety, depression, personality change and hallucinations. Onset of these symptoms is typically subacute over a few weeks or months but may also evolve over a few days. In many patients, limbic encephalitis is a paraneoplastic syndrome usually preceding diagnosis of the malignancy. Associated tumours are most commonly small-cell lung cancer (SCLC), breast cancer, testicular tumour, teratoma, Hodgkin lymphoma and thymoma.[1] Antineuronal autoantibodies can be detected in the sera of about 60% of patients. These autoantibodies are classically directed to intracellular antigens (eg, anti-Hu, anti-Ma1/2, anti-CRMP5/CV2, anti-amphiphysin). However, LE is now being recognised frequently in the absence of malignancy and can be associated with antibodies to voltage-gated potassium channel (VGKC-ab). More recently, a new type of immunotherapy-responsive severe LE was described by Dalmau and colleagues that is associated with antibodies to the *N*-methyl-D-aspartate-receptor (NMDAR) and ovarian teratoma. In rare instances, these NMDAR-ab also occur in men with testicular teratoma or SCLC.[2 3] For the first time, we describe a male patient with non-paraneoplastic limbic encephalitis and with serum antibodies to both NMDAR and VGKC.

CASE REPORT

This previously healthy 56-year-old man reported the first signs of disease in 2007 when he recognised hypersomnia and progressive generalised myoclonus while sleeping. Additionally, he developed short-term memory loss, concentration deficits and disorientation. All these symptoms evolved over 6 months. At this point of time, the patient experienced his first epileptic seizure. However, there was no evidence for neuromyotonia.

Neuropsychological testing revealed severe verbal amnestic syndrome. MRI of the brain showed bitemporal T2- and fluid-attenuated inversion recovery-hyperintense lesions. There was no evidence of contrast enhancement in the T1-weighted sequences (figure 1). EEG showed diffuse slowing and focal epileptic activity in the left temporal lobe. Repetitive cerebrospinal fluid (CSF) investigations revealed normal values for lymphocytes and protein. Serum and CSF revealed the same oligoclonal IgG bands. Serum analysis showed slight hyponatraemia (129 mmol/l), which resolved completely during the following weeks. Blood cell count, thyroid function test including thyroid autoantibodies, antibodies to double-stranded DNA, and SSA/Ro and SSB/La were unremarkable. Paraneoplastic antineuronal antibodies (Hu, Ri, Yo, Ma1, Ma2, Recoverin, CRMP5/CV2), tumour markers and screening for infectious disease such as, herpes simplex virus IgG and PCR were all negative. Limbic encephalitis was diagnosed according to reviewed diagnostic criteria.[4] Oral methylprednisolone therapy (1 mg/kg body weight) followed by oral tapering to 5 mg per day led to a marked clinical improvement during the following weeks. Therefore, steroid therapy was continued with this dosage. Seizures were treated with levetiracetam (1 g twice daily) successfully.

One year after onset of symptoms, he was seen in our institute for the first time. We obtained positive results for VGKC-ab at a level of 392 pM (normal <100 pM) as well as for NMDAR-ab (scoring 2 on a range from 0 (negative) to 4 (highly positive) (Irani S, Vincent A unpublished results)). Repetitive testing 3 months later confirmed both of these positive results (NMDAR-ab 2; VGKC-ab 281 pM). An extensive tumour search including positron emission tomography with fluor-desoxyglucose in combination with CT (FDG-PET/CT) of the whole body did not reveal an underlying neoplasm. Urological examination including ultrasound of the testis gave no evidence for testicular cancer.

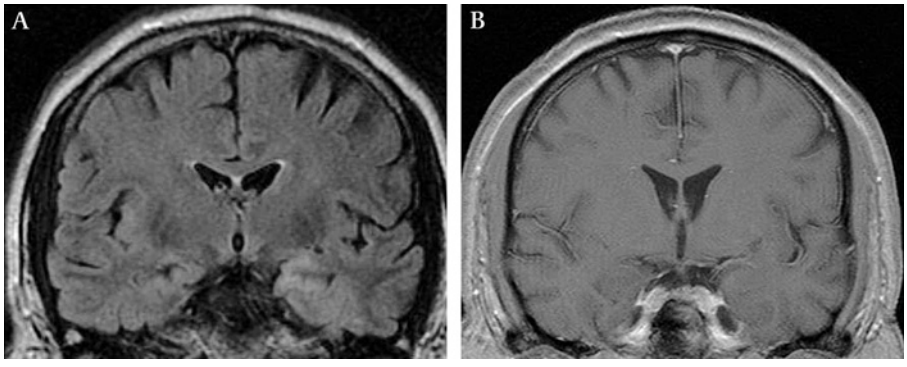

Figure 1 Brain MRI findings at onset of symptoms. (A) Fluid-attenuated inversion recovery showing hyperintensity asymmetrically involving both medial temporal lobes. (B) Contrast-enhanced T1 images. No gadolinium uptake was shown.

Brain MRI revealed complete remission of the right temporal lobe lesion and partial remission of the lesion in the left temporal lobe. In order to reduce steroids, persistent cognitive deficits, and still raised antibody titres, treatment with azathioprine was initiated. With this therapy, the patient has remained stable until now with slight residual memory deficits but returned to work recently. During therapy with levetiracetam, there is no evidence of seizures. However, long-term follow-up is needed.

DISCUSSION

Here, we report a male patient with non-paraneoplastic VGKC-ab and NMDAR-ab associated limbic encephalitis. While the mere occurrence of NMDAR-ab in male patients is relatively rare and limited to a few cases worldwide, to our knowledge this is the first patient to harbour both VGKC-ab and NMDAR-ab.

In patients with VGKC-ab associated LE, clinical improvement is associated with titre reduction. Since first testing for both antibodies occurred 1 year after the onset of symptoms and 6 months after the start of steroid therapy, we cannot determine the decline of the antibody titre after therapy. However, both antibodies were still present at this time and also detectable 6 months later.

While most patients with VGKC-ab-associated limbic encephalitis present with a subacute amnesic syndrome, seizures and REM sleep behaviour disorder and do not have an underlying malignancy,[5] NMDAR-ab-associated limbic encephalitis usually affects young women with an ovarian teratoma.[2 3] These patients usually present with acute, severe psychiatric symptoms including personality change, paranoia, anterograde amnesia, agitation and/or catatonic stupor. Autonomic symptoms and central hypoventilation as well as seizures may also be present in NMDAR-ab positive cases. Most of these patients have lymphocytes in CSF, while VGKC-ab-associated LE usually lacks CSF changes.

The majority (85%) of previously described patients suffering from NMDAR-ab associated LE had prodromal flu-like illness;[3] however, our patient did not have such symptoms, had a more insidious disease progress and had no evidence for the presence of an underlying tumour. Clinical presentation was more similar to VGKC-ab associated LE than NMDAR-ab associated LE. In our experience, none of the 60 control patients were positive for antibodies to NMDAR, and all patients with these antibodies have an encephalitic illness (Irani and Vincent unpublished results), so this test seems to be specific.

This case emphasises the importance of testing for antibodies in patients with subacute onset of encephalopathy and suggests that the clinical spectrum of NMDAR-ab and VGKC-ab associated LE may turn out to be broader than initially described. Since both types of LE are associated with excellent treatment responses, and since the extent of residual symptoms correlates with time of treatment initiation, it is important to recognise and treat autoimmune limbic encephalitis early during disease course.

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Elevated phosphorylated tau pT-181 in a possible *PRNP* codon 129 MV vCJD case

CASE REPORT

A 30-year-old man died of a progressive neuropsychiatric illness of approximately 17 months' duration with a clinical picture strongly suggestive of variant Creutzfeldt–Jakob disease (vCJD).[1] His initial symptoms, at the age of 28, were of personality change with anxiety and irritability. Lower abdominal and leg pain were troublesome early symptoms. At about 12 months of illness, he developed tremor and unsteadiness, leading to progressive walking problems. Increasing social withdrawal and behavioural problems were complicated by the development of progressive memory and general cognitive impairment. Visual hallucinations and paranoid delusions occurred in the later parts of his illness. During the course of his illness, he developed the following neurological signs: cognitive impairment, limb and gait cerebellar ataxia, mild dysarthria and mild pyramidal signs. Extensive neurological investigations revealed no cause other than prion disease, including consideration of a wide variety of inflammatory, neoplastic, immunological and neurodegenerative illnesses. The EEG showed diffuse slow activity without periodic complexes. The cerebral MRI showed changes suggestive of vCJD but did not show the characteristic pulvinar sign.[2] No tonsil biopsy or neuropathological examination was performed. Sequencing of the *PRNP* gene showed no pathogenic mutation and revealed the patient to be heterozygous (methionine (M)/valine (V)) at codon 129 and heterozygous for the common synonymous substitution at codon 117. The final formal case classification of this patient was of possible vCJD,[3] but the clinical opinion is that this is very likely to have been the first instance of vCJD in a *PRNP* codon 129 non-MM individual.

Cerebrospinal fluid (CSF) analysis was performed as part of the routine investigations, no abnormalities were found in white cell count, total protein or glucose concentrations, and no bacteria were grown on culture. In light of the normal white cell count and lack of bacterial growth, the CSF sample was considered to be sterile, and no further investigations were carried out. CSF was sent to the National CJD Surveillance Unit for the analysis of 14-3-3 and other brain-specific proteins. CSF 14-3-3 was detected using western blotting with chemiluminescent detection,[4 5] while CSF S-100b,[4] tau protein[5 6] and tau protein phosphorylated at threonine 181 (pT-181)[6] were measured using enzyme-linked immunosorbent assays (ELISAs). The results are shown in table 1.

Table 1 Cerebrospinal fluid brain-specific protein results

Analyte	Result
14-3-3	Positive
S-100b	0.67 ng/ml (reference range: <0.41)
Tau protein	2110 pg/ml (reference range: <500)
Phosphorylated Tau (pT-181)	124 pg/ml (reference range: <120)