

# Limbic encephalitis: a case report

Autoimmune limbic encephalitis is a rare but reversible cause of confusion or dementia that often evades diagnosis, leading to long-term neurological sequelae. It is becoming increasingly recognised and certain clinical features can be used to raise suspicion of the disease.

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This case report is of an 81-year-old woman who presented with falls, confusion, cognitive decline and seizures. She was eventually diagnosed with autoimmune limbic encephalitis.

## Case report

An 81-year-old woman, LJ, was admitted to a medical ward after a three day history of sudden collapses with a momentary loss of consciousness. Her past medical history was otherwise unremarkable; her examination revealed no physical or cognitive impairment and she was independent in all activities of daily living. She was not a smoker and did not abuse alcohol. Her telemetry revealed sinus rhythm with no arrhythmia and a short 1.76 second period of asystole (figure 1), strongly timed with a carotid sinus massage. Nevertheless, the patient was fitted with a dual-chamber permanent pacemaker, which may have been unnecessary.

There was an incidental finding of hyponatraemia, which

was attributed to syndrome of inappropriate antidiuretic hormone secretion (SIADH) although urinary sodium and osmolarity were normal. Her 9am cortisol levels and short synacthen test were also normal. A general screen of her hormone profile, liver profile, inflammatory proteins and other electrolytes highlighted no abnormality.

Whilst an inpatient, she began to have episodes of myoclonic jerks. Her CT head scan showed cerebral atrophy but no dilatation of the ventricles. An EEG recording revealed no evidence of generalised epilepsy but some left frontal slow-wave activity. Yet, she was started on clonazepam but continued to have occasional myoclonic jerks. The dose of the clonazepam was tapered and stopped and the patient was discharged when she began to mobilise without further risk of falling.

Seven months later, she was readmitted following a seizure and presented with a prevailing interim history of confusion, recurrent falls, intermittent

seizures and a decline in independence. She was found to be ataxic, had slurred speech and displayed a deterioration in cognition. Her Mini Mental State Examination (MMSE) was 23/30 when initially it had been 29/30. Her blood test revealed ongoing hyponatraemia. At this point, a differential list of either a paraneoplastic syndrome, encephalitis (infective or autoimmune) or degenerative condition such as Lewy-body dementia or prion disease was drawn up.

Examination of her CSF showed elevated protein of 1.01g but the tap was heavily blood-stained. Microscopy for microbiology and polymerase chain reaction (PCR) for virology were negative and there was no evidence of oligoclonal bands. The Creutzfeldt-Jakob disease (CJD) surveillance unit in Edinburgh sent a specialist registrar to review the patient and it was deemed that the clinical picture did not fit CJD. Thus, the CSF was not tested for protein 14-3-3.

In view of a possible

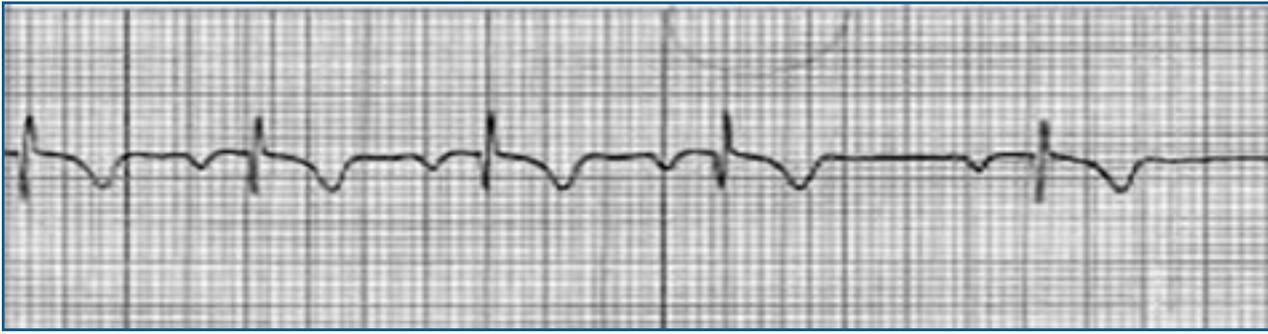


Figure 1. ECG trace showing the 1.76s delay used to diagnose the carotid sinus hypersensitivity. This was a point of contention in LJ's management.

paraneoplastic picture, a CT of the chest, abdomen and pelvis was requested but revealed no obvious tumour and a battery of serum paraneoplastic antibodies were proven negative. An autoimmune, vasculitis and complement screen did not unveil anything further. An MRI was not used to exclude evidence of CJD or autoimmune encephalitis as the permanent pacemaker could not be removed. The hyponatraemia responded slowly to strict fluid restriction (1L/day) and demeclocycline.

LJ's seizures became more generalised tonic-clonic fits and she was commenced on phenytoin, followed by sodium valproate and discharged. But eventually she had repeated admission for seizures, which were not controlled fully by varying combinations of anti-epileptics.

Eventually, her serum was assayed for voltage-gated potassium channel antibodies and titre value of 8000pmol/L (very high) was returned, suggesting a diagnosis of autoimmune limbic encephalitis. LJ responded well to steroids and plasma exchange but her condition quickly relapsed and was compounded by psychiatric

delusional symptoms and generalised weakness. She underwent further plasma exchange and the condition went into remission. Yet, she was left with residual physical and mental deficits that never fully recovered.

## Discussion

Limbic encephalitis was first described in the 1960s as a rare clinic feature of an underlying paraneoplastic syndrome. Non-paraneoplastic forms, associated with autoimmunity, are being increasingly recognised and should be considered as serious and potential differential diagnoses for dementia, confusion or any new-onset temporal lobe epilepsy in an adult.

## Clinical features

Patients often present with subacute confusion, disorientation and impaired memory. Seizures may become a prominent feature and typically begin in the medio-temporal lobe, becoming secondary generalised and responding poorly to anti-epileptics. Additional psychiatric features can include

hallucinations and disturbance in behaviour.<sup>1</sup> It has been argued that there is predominance in males with a 2:1 male to female ratio and patients are often above the age of 40 years.<sup>2</sup>

Important differential diagnoses include acute delirium; other causes of encephalopathy (infectious, toxic, drug-induced, inflammatory/vasculitic, Korsakoff's, cerebral neoplasia), as well as psychiatric disorders. Limbic encephalitis should also be weighed in any rapidly progressive dementias and there have been cases of autoimmune limbic encephalitis that would otherwise have been misdiagnosed as Creutzfeldt-Jakob disease according to WHO criteria.<sup>3</sup>

Hyponatraemia is said to be present in up to 59% of patients and responds poorly to fluid restriction or demeclocycline.<sup>4</sup> The mechanism leading to the hyponatraemia is not well understood but it could be related to hypothalamic inflammation. Images of the brain by CT may be normal but MRI imaging shows hyper-intense temporomesial signalling on T2-weighted sequences or fluid-attenuated inversion recovery MRI, which eventually progresses

to temporal lobe atrophy.<sup>5</sup> This useful investigation was made impossible in this case because the permanent pacemaker could not be removed.

Antibodies against voltage gated potassium channel complexes (VGKC) are typical and often occur in high titres (>400pmol/L) in the serum of patients.<sup>2</sup> Although other conditions (such as Morvan's syndrome and acquired neuromyotonia) may have relatively high titres, it is most frequently associated with limbic encephalitis.<sup>2</sup> Several other potential neuroreceptor targets for auto-antibodies have recently been identified.<sup>2</sup> Histopathology is normally a post-mortem investigation but sections would show a lymphocytic or micronodular inflammation of the hippocampus and temporomedial structures. With the combination of all the above clinical features and investigations, some study groups have suggested specific diagnostic criteria for paraneoplastic and autoimmune limbic encephalitis, but these have not formally been adopted by any guidelines as yet.<sup>6</sup>

## Management

Although largely associated with autoimmune limbic encephalitis, VGKC antibodies are known to be present in paraneoplastic forms and even titres of 300pM have been found to have underlying lung cancer.<sup>7</sup> Thus, there exists the argument that all limbic encephalitis patients should be investigated to exclude tumours. The "Bonn protocol"

proposes radiological and serum investigations according to the patient's age, sex, cancer risk factors and particular symptoms.

Treatment is through immunosuppression in autoimmune limbic encephalitis. This is largely unsuccessful in paraneoplastic forms although occasionally patients can show a degree of improvement.<sup>7</sup> Nevertheless it is more sensible to approach the cancer in the management of paraneoplastic forms.

Plasma-exchange, steroids and intravenous immunoglobulins have all been recommended for potential treatment and there appears to be a correlation between the VGKC antibody titre and clinical recovery in autoimmune limbic encephalitis.<sup>8</sup> Even the hyponatraemia tends to correct itself.<sup>2</sup> As mentioned, seizures may be refractory to anti-epileptic medication but they respond to immune suppression.<sup>8</sup> While limbic encephalitis is described as being largely monophasic—with treatment over a duration of months being curative—there are cases of relapses. Full recovery is uncommon and residual levels of cognitive impairment or physical change to the brain may exist.<sup>9</sup> In that respect, perhaps earlier recognition and treatment may reduce the amount of damage sustained by the brain.

## Conclusion

Autoimmune limbic encephalitis is a very real cause of subacute cognitive decline and should be considered as a potential differential diagnosis for delirium

or dementia, especially if coupled with pathognomonic features such as hyponatraemia and temporal lobe seizures. It is a very treatable condition and a delay in diagnosis may lead to the patient suffering permanent deficits.

The condition is amenable to immunotherapy. Interestingly, autoimmune forms of limbic encephalitis have been highlighted without evident VGKC-antibodies and these have responded well to immunosuppression.<sup>10</sup> Thus, there may exist an argument to trial steroids on patients presenting with such encephalitis (once infective causes have been excluded). VGKC antibodies may even be present in up to 3% of cases of encephalitis.<sup>11</sup> Moreover, other antibodies against neuronal proteins are being identified, expanding our understanding of the condition but perhaps clouding the criteria for making a definitive diagnosis or deciding to use immunotherapy.<sup>2,12</sup>

Although we could not MRI our patient, clinical and neuropsychological features and serum VGKC titres were sufficient to make a diagnosis.

**Conflict of interest: none declared**

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