Limbic encephalitis and bipolar affective disorder: a slow awakening


There is increasing evidence for the role of autoimmune encephalitis in the aetiology of psychosis. Here, Dr Lilford and colleagues describe the case of a 74-year-old lady who presented as hypomanic almost a year previously and then developed bizarre stereotyped movements, periods of absences and became confused. She was admitted to an old age psychiatric ward and was subsequently diagnosed with non-paraneoplastic limbic encephalitis with high levels of voltage-gated potassium channel complex antibodies. The authors discuss her treatment with immunosuppressive drugs, which resulted in significant clinical improvement.

Autoimmune encephalitis is a disorder where autoantibodies target proteins involved in synaptic transmission, which results in a range of neuropsychiatric manifestations. Autoantibodies to N-methyl-D-aspartate (NMDA) and voltage-gated potassium channel (VGKC) complex antibodies are the two most common causes of psychiatric manifestations in autoimmune encephalitis. There is accumulating evidence for the role of autoimmune encephalitis in the aetiology of psychosis, and patients with first-onset psychosis who have seizure activity or unusual sensitivity to neuroleptic medication are more commonly being referred for a neurology opinion.

While initially it was thought that antibodies were targeting the actual ion channels, it has since emerged that the antibodies are against proteins associated with the ion channels. Depending on the channel, or protein affected, the clinical manifestations vary. The anti-VGKC-complex antibodies were initially recognised in patients with memory loss, seizures, confusion and hyponatraemia. The proteins associated with the VGKC channel include leucine-rich glioma inactivated protein 1 (LGI1), contactin-associated protein-like 2 receptor (CASPR2) and contactin-2. If LGI1 is targeted, seizures are predominantly faciobrachial and other symptoms include memory disturbance and hyponatraemia. With CASPR2-associated antibodies the clinical presentation differs with a picture of amnesia, insomnia, pain and autonomic disturbance. Interestingly, this may be explained by the different distribution of the two proteins, with LGI1 primarily expressed in the hippocampus and central nervous system, and CASPR2 in both the central and peripheral nervous system.

As well as psychosis, hallucinations and sleep disturbance, VGKC encephalitis can cause affective and neurotic symptoms, including depression, anxiety and obsessive-compulsive traits. Commonly, psychiatric symptoms are the most prominent, therefore psychiatrists should be aware of an atypical presentation or evidence of organic disease and include autoantibody-mediated encephalitis in their differential diagnosis.

Presentation

A 74-year-old lady received a routine review by her community psychiatrist. The impression was of a highly capable and active lady without cognitive impairment. While initially it was thought that antibodies were targeting the actual ion channels, it has since emerged that the antibodies are against proteins associated with the ion channels. Depending on the channel, or protein affected, the clinical manifestations vary. The anti-VGKC-complex antibodies were initially recognised in patients with memory loss, seizures, confusion and hyponatraemia. The proteins associated with the VGKC channel include leucine-rich glioma inactivated protein 1 (LGI1), contactin-associated protein-like 2 receptor (CASPR2) and contactin-2. If LGI1 is targeted, seizures are predominantly faciobrachial and other symptoms include memory disturbance and hyponatraemia. With CASPR2-associated antibodies the clinical presentation differs with a picture of amnesia, insomnia, pain and autonomic disturbance. Interestingly, this may be explained by the different distribution of the two proteins, with LGI1 primarily expressed in the hippocampus and central nervous system, and CASPR2 in both the central and peripheral nervous system.

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Cognitive Examination (ACE) III score declined from 82/100 on admission to 60/100 over the course of two weeks.

Her past medical history was of longstanding bipolar II disorder and she had no history of alcohol excess or illicit drug use. She had been seen by psychiatrists intermittently over the past 30 years and had received episodic treatment with psychotropic drugs, usually antidepressant medications, most commonly phenelzine. There was a strong family history of affective disorder with a maternal aunt and uncle suffering from bipolar affective disorder, and the same uncle died by suicide. Her father developed late onset Alzheimer’s disease and a cousin also suffered with depression and died by suicide. There was not a personal or family history of epilepsy. She was a high functioning individual who had a successful career and worked for most of her adult life.

**Investigations**

On admission to hospital, a detailed physical examination was unremarkable. Routine observations, including temperature, were normal. Analysis of full blood count, electrolytes, liver and hormone profile, and inflammatory markers showed no abnormality other than a persistently elevated thyroid peroxidase antibody at 219IU/ml (normal levels <100IU/ml) in the context of normal thyroid function. Her autoimmune profile was negative. There were no constitutional symptoms to suggest malignancy, and HIV and syphilis serology were negative.

An unenhanced computed tomography (CT) scan of the patient’s head revealed foci of low attenuation in the basal ganglia and thalami bilaterally, in keeping with established ischaemia. Subsequently, magnetic resonance imaging of the brain (standard technique with dedicated temporal lobe imaging) showed minor background small vessel ischaemic change with no evidence of acute ischaemic insult on diffusion weighted imaging. There was no evidence of an abnormal signal in the temporal lobes, or mesial temporal sclerosis.

A CT scan of her abdomen and pelvis seven months prior to the patient’s admission to investigate her persistent hyponatraemia had been normal. Of interest, despite a ‘seizure-type’ episode occurring during a routine EEG, the recording was reported as normal and her seizures remained resistant to antiepileptic medication. At this point, neurology opinion was that her condition was not characteristic of an epileptiform organic disorder and a psychiatric aetiology was questioned, although testing for antibodies to voltage-gated potassium channel and calcium channels and to the NMDA receptor were requested.

**Differential diagnosis**

The nature and rapid progression of the patient’s symptoms ruled out a common dementia cause, such as Alzheimer’s disease. Rapidly progressive dementias are rare but may be reversible, hence prompt investigation and diagnosis are essential. Infectious, toxic/metabolic, nutritional, vascular, structural and other causes of encephalopathy are more prevalent than autoimmune cases and so should be excluded. In this case, an infectious aetiology (herpes simplex, neurosyphilis) was considered unlikely in an immunocompetent adult due to lack of infective hallmarks and negative serology. Prion disease and toxic/metabolic causes (e.g. vitamin deficiencies, heavy metal toxicity and electrolyte abnormalities) were not considered likely diagnoses, and despite a slightly elevated thyroid peroxidase antibody, endocrine function was normal. There was no evidence to raise suspicion of a systemic autoimmune disorder.

**Treatment**

Subsequently, raised levels of voltage-gated potassium channel antibodies returned at 7979pmol/L (normal levels <100). A diagnosis of non-paraneoplastic limbic encephalitis was made and the patient was transferred to the neurology ward for management. Initial treatment was with high dose intravenous (IV) methylprednisolone for three days, followed by five days of IV immunoglobulin (Ig) G.

**Outcome and follow-up**

Immediately following treatment the patient showed a significant improvement in her mental state. She became more orientated to place and person, although her speech remained repetitive and she displayed restless, with exaggerated movements. She subsequently had further courses of steroids and another course of IV IgG. Her mood then appeared to become elated and she became irritable and aggressive. Her sleep became poor and she required 2:1 supervision for physical aggression towards others. She required intramuscular rapid tranquillisation and was placed under a Section 2 of the Mental Health Act.

Regular olanzapine and nitrazepam were started and her mood appeared to settle.

The patient was discharged from the general hospital to a neurorehabilitation unit. Her mobility and cognition gradually improved and she was able to hold coherent conversations, although her memory...
problems remained evident. However, she improved to a degree to be able to return home nine months later.

Now living at home, she described her time at the neurorehabilitation unit as an ‘awakening’. Currently, her language expression and understanding are significantly improved and she is managing to live independently. She does have some residual cognitive impairment. On ACE III cognitive testing she scored 83/100, losing points in particular for serial 7 subtraction and her delayed recall of a name and address was relatively poor. She remains on antiepileptic medication (sodium valproate 400mg daily and levetiracetam 500mg mane, 1000mg in the evening).

On repeat testing her VGKC complex antibodies had fallen considerably from 7979pmol/L to 893pmol/L. Her serum sodium had normalised and a repeat EEG showed no abnormalities. At home, she has been observed to occasionally have contorted facial expressions. LGI1 was positive and CASPR2 was negative, we suspected from her presentation that she had the LGI1 subtype due to hyponatremia, faciobrachial seizures and memory disturbance.

She is fascinated by limbic encephalitis and is enjoying reading ‘brain on fire’ by Susannah Cahalan and has attended local talks on the subject. Her mood has been euthymic since her return home, despite significant life stressors such as moving home, financial difficulties, and no longer taking psychotropic medication.

Discussion
The interface between neurology and psychiatry is a particularly fascinating one that is typified by conditions such as limbic encephalitis. This patient’s past psychiatric history appeared to help feed the narrative that her symptoms were of a psychiatric aetiology. Both nursing and medical staff documented on separate occasions that ‘her bipolar disorder appears to be manifesting in confusion’. Prior to the return of her voltage-gated potassium channel antibodies this patient was admitted to an organic old age psychiatry ward. She remained an inpatient there for five weeks, having daily seizures and experiencing progressive cognitive decline.

Graus and colleagues have recently proposed a set of guidelines to help clinicians to recognise suspected cases of autoimmune encephalitis, reducing reliance on antibody testing and thus treatment delay. Based on these criteria it is feasible to wonder whether our patient may have received more prompt immunotherapy, and potentially made a more complete recovery at this stage. On the other hand, the psychiatric symptoms of limbic encephalitis make diagnosis difficult, particularly in someone with an established psychiatric history when symptoms can often be explained by a relapse of the underlying illness. Moreover, there is growing evidence that common psychiatric illnesses such as schizophrenia may be driven by an underlying antibody-mediated encephalitis, further softening the boundary between psychiatry and neurology.

In their case study Newrick et al. discuss the ‘patient with psychotic depressive lenguishing on a neurology ward for want of reasonably dosed antidepressives’. Our patient reminds us of the ‘encephalitic patient languishing on a psychiatric unit for want of immunosuppression’. This makes us reflect on service design and whether, as the boundary between psychiatry and neurology blurs, our services with joint care between the specialities should similarly merge.

Declaration of interests
No conflicts of interest were declared.

Dr Lilford is a CT3 Psychiatry in Bristol, Dr Morrison is a ST3 Neurology at University Hospital Wales, Cardiff, Dr Morgan is a trust doctor in Bath and Dr Ward is a Consultant Old Age Psychiatrist in Bath.

References