

Psychotic depression mimicking limbic encephalitis

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Autoimmune encephalitis may present with prominent neuropsychiatric symptoms, and is increasingly considered in the differential diagnosis of patients with altered mental state. Here, the authors navigate the muddy waters between neurology and psychiatry, describing the caveats of antibody testing with a misdiagnosed case of psychotic depression.

We met the patient, a retired 71-year-old gardener, following his transfer from a neurology ward. He had initially presented with an acute behavioural change and rapid cognitive decline associated with several generalised tonic-clonic seizures. From a highly functional individual going on holiday cruises with his wife, he had withdrawn from social life and developed difficulties with simple tasks, such as turning on the TV. On the emergence of agitated and paranoid behaviour, with a possible further seizure, he had been hospitalised. Following the detection of positive serum antibodies, he was treated for voltage-gated potassium channel (VGKC)-complex limbic encephalitis with several courses of methylprednisolone and plasma exchange. Little clinical improvement was observed, resulting in consideration of alternative diagnoses (including neurodegenerative or psychiatric disorders). At the time of transfer, low dose olanzapine and sertraline

were prescribed orally, but had been frequently refused.

Diagnosis and treatment

On examination the patient was rather unkempt, hypervigilant, deeply suspicious and guarded (refusing to shake our hand, a 'jibbering wreck'). It was impossible to establish a rapport, with a flat unreactive affect, and an irritable and dismissive manner (*'I know what you are going to say...just keep taking the tablets and you will get better'*). He felt hopeless (*'I can see into the past and into the future...it's bad'*) and slept poorly. Language and speech form appeared grossly normal. Delusions were present, with a sense of mood-congruency. These tended to be persecutory in nature or regarding contamination (*'this is all a set up and you are in on it'*, *'everyone is doing everything in reverse to fool me'*, *'I left the loo and the buzzer went off to show that I had done wrong [incidental nurse call bell]'*, *'I'll be beheaded at the weekend...you are in on it'*). He was often unshakably preoccupied with the notion that he was dirty and did not know how to use the toilet. A heightened sense of self-reference was observed, (reading special significance into butter being left on his table) and catastrophizing (*'I'll NEVER get it tuned again [when asked to turn the radio down]'*). At times it was thought that he was probably experiencing auditory hallucinations (*'I can hear talking about me you bastards'*) and visual hallucinations (attempting to point out figures walking past to

his family). He categorically denied suicidal ideation.

Examination demonstrated isolated mild left dysidiadochokinesia and fine tremor (maximal left with posture/intention). No extrapyramidal signs, visual deficit or myoclonus were observed. Psychomotor retardation was not present. Full cognitive examination was difficult; the patient remained highly negative and impersistent (*'oh I cannot do this...my brain won't work'*), or would become irritable and aggressive (*'I know what you're going to ask...we've done this all before... YOU try and do it!'*). Piecemeal assessment revealed full orientation in place and time, normal topographic orientation (finding his way to his room), excellent verbal fluency (naming animals), good visuospatial/constructional praxis (interlocking pentagons and reasonable clock drawing) and episodic memory (able to recall in detail conversations across several days and of recent events).

An extensive battery of investigations had been performed, including NMDA-receptor/paraneoplastic antibodies, an autoimmune antibody screen, serial lumbar punctures and MR brain imaging, which were unremarkable. One of the repeated EEGs had revealed transient runs of periodic slow wave complexes over the left frontotemporal region, of uncertain significance. In addition, whole-body PET imaging and an ultrasound scan of the testes failed to demonstrate any associated malignancy.

Revisiting the history, the only significant psychiatric history reported by his family was an episode of depression around 30 years ago, which was treated successfully in the community. Although not expressing hallucinatory or delusional symptoms this had a distinctly psychotic flavour (describing one episode where the patient laid down in the middle of his GP's reception area '*sprawled like a crucifix*'). There was no suggestion that he had misused alcohol. In addition, the initial 'seizures' had several unusual features, including prominent preceding personality/emotional changes many hours before attacks (irritability/crying out), the assumption of unusual postures (foetal position), and quick recovery with little post-ictal phase. While at least one 'generalised tonic-clonic seizure' was reportedly observed in A&E we were suspicious of non-epileptic attacks.

Treatment with significantly increased sertraline and olanzapine doses (initially given IM, then increasingly accepted orally) resulted in a dramatic improvement within weeks. Transformed, the patient became sociable, friendly and keen to visit his allotment with his family. He would greet us with a wave and smile on the ward. Psychotic symptoms abated. We continued to withdraw levetiracetam, preferring lamotrigine in view of its more favourable neuropsychiatric profile.

Discussion

The interface between neurology and psychiatry is increasingly blurred, as exemplified by autoimmune encephalitis. 'Learning the language' of both specialties and being competent to navigate both fields is essential for managing complex neuropsychiatric syndromes, and mutually rewarding for patients

and professionals.¹ In the present case, the combination of subacute behavioural disturbance, cognitive decline and seizures conformed to consensus diagnostic criteria for autoimmune encephalitis,² leading to treatment with immunotherapy in the context of positive VGKC-complex antibodies.

Recent guidelines have promoted the early use of clinical criteria in diagnosis in autoimmune encephalitis, in order to mitigate treatment delays engendered by a reliance on antibody testing.² Indeed, the utility of detected antibodies may be highly variable in diagnosis and cogent on the overall titre, presence across the serum and CSF, and specificity for target subunits within larger antigen complexes.² In regards to VGKC-complex antibodies, low detectable levels may be present in a heterogeneous spectrum of disorders, with questionable clinical significance (often with levels <400picomoles/litre).^{3,4} The pathogenic role of VGKC-complex antibodies in an autoimmune encephalitis syndrome is most strongly associated with antibodies targeted at the LGI1 and CASPR2 cell surface antigens, at levels >400picomoles/litre, and detectable in both the serum and CSF.³ Our patient possessed serum VGKC-complex antibodies only, at significantly lower titres (180–190picomoles/litre), which were unchanged on interval testing. The absence of CSF antibodies and lack of clinical or immunological response in levels to immunotherapy informed the consideration of alternative diagnoses. Unfortunately profiling of LGI1/CASPR2 antibodies was not performed. Advances in the range and availability of antibody testing presents the challenge of delineating 'normal' autoimmunity from autoimmune

disease. Although important not to miss, empirical treatment of limbic encephalitis may expose psychiatric patients with compatible symptoms to significant iatrogenic harm.

We found the present case interesting since the literature is littered with accounts of psychiatric presentations of autoimmune encephalitis, and almost none of the reverse. Was undue emphasis placed on the significance of equivocal immunological testing over clinical history? Were we guilty of being too timid with antipsychotic treatment when 'there's something medical going on'? We were prompted to reflect on the patient with psychotic depression languishing on a neurology ward for want of reasonably dosed antipsychotics, and the encephalitic patient languishing on a psychiatric unit psychotic for want of immunosuppression – how to design a service to better match these patients?

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Declaration of interests

No conflicts of interest were declared.

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