

# Anti-voltage-gated potassium channel complex antibody-mediated limbic encephalitis: a case report of a 53-year-old man admitted to intensive care psychiatric unit with psychotic mania

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## ABSTRACT

Limbic encephalitis represents a cluster of autoimmune disorders, with inflammation in the medial temporal lobe characterised by subacute onset of neuropsychiatric symptoms such as anxiety, affective symptoms, psychosis, short-term memory impairment as well as faciobrachial and grand mal seizures. We aim to present a case of a 53-year-old man with positive anti-voltage-gated potassium channel (VGKC) complex antibodies who initially presented with symptoms of psychotic mania. Six weeks post-psychiatric symptomatology, he presented with neurological symptoms such as faciobrachial jerking and tonic-clonic seizure. The patient had no previous psychiatric history and was initially treated with psychotropic medications. Our experience emphasises the fact that limbic encephalitis is not easy to identify as most patients initially present with psychiatric symptomatology than neurological symptoms. Furthermore, immunological and laboratory testing takes a rather long time to determine the diagnosis. What is more, few psychiatrists consider autoimmune nature of the neuropsychiatric presentation. Therefore, it is important to consider autoimmune encephalitis in patients with new-onset psychosis or mania who also present with neurological symptoms at some stage of their illness. Characteristic indicators of autoimmune encephalitis include neurological symptoms such as facial twitching, seizures, confusion and cognitive decline.

## BACKGROUND

The term limbic encephalitis was first used by the British neurophysiologist Corsellis and his colleagues who identified inflammatory changes in the medial temporal lobes and limbic structures of patients with progressive memory loss after being diagnosed with lung cancer. While limbic dysfunction is the single most consistent finding in autoimmune encephalitis, varying degrees of involvement are seen within the neocortex, striatum, hind-brain, spine and peripheral nervous system. We present the case of a 53-year-old man with

positive anti-voltage-gated potassium channel (VGKC) antibodies presenting with subacute polymorphic psychosis. Moreover, we aim to discuss the pathophysiology, clinical symptomatology and diagnosis of limbic encephalitis, an autoimmune disease that quite often manifests with psychiatric symptoms but can be easily overlooked or misdiagnosed within psychiatric settings.

## CASE HISTORY

### Vignette

A 53-year-old Caucasian man with no previous neuropsychiatric history was admitted to our local psychiatric intensive care unit (PICU) on 10 September 2017 following almost a 2-month deterioration of his mental health, physically aggressive, elevated in mood, paranoid-persecutory and grandiose delusions. Prior to his admission, he assaulted one of his neighbours. He presented with pressured speech and flights of ideas. He believed he had contact with politicians, including heads of states and powerful individuals. No cognitive deficit, no neurological symptoms. No significant medical history reported; no family history of mental disorders, no history of alcohol or substances reported as well as no previous forensic history reported. He was separated, lived on his own and worked until 2 weeks prior to his admission as a labourer. Initial routine investigations, including full blood count, renal, hepatic tests and inflammatory markers, were negative. Electroencephalography (EEG) and brain CT were normal. Psychosis was effectively treated with zuclopenthixol deaconate (600 mg/weekly) due to non-compliance with oral medication; as the psychotic symptoms improved, his aggressive behaviour also improved and on

25 October, after a month in the PICU, he was transferred to our open psychiatric ward with diagnosis of a persistent delusional disorder.

At the end of October and in the first week of November, the patient was observed to be having some twitching facial movements, thought to be anxiety-related and described as 'mini panic attacks'. On 10 November 2017, a 4min grand mal seizure was observed. On further assessment, cognitive decline and severe short-term memory were noted; Addenbrooke's Cognitive 55/100. CT, EEG and lumbar puncture were normal; however, MRI on 29 November 2017 demonstrated bilateral high signal around the temporal horn and diffusion abnormality, suggestive of encephalitis. Consequently, the patient was transferred to medical ward and zuclopenthixol decanoate was stopped. On further investigations, anti-VGKC complex antibodies were detected in his serum. The patient was effectively treated with levetiracetam and prednisolone, and after 52 days of admission in the medical ward he was discharged to the community on 19 January 2018. His psychiatric symptoms had resolved and he did not require further psychiatric treatment. However, he continued to receive treatment under the care of a neuropsychologist for his residual cognitive deficit.

At the last follow-up, in January 2020, he lives independently, performs his normal activities of daily living and works in his previous job. He, however, complained of mild cognitive deficit.

### limbic system

The limbic system is composed of a group of tightly interconnected brain areas that include the cingulate gyrus, the anterior thalamus, the hypothalamus and mammillary bodies; the hippocampus, and the amygdala. The functions of the limbic system are complex and include the establishment of baseline emotional state, addiction and motivation, appetite and eating behaviours, sleep and dreams, memory, sexual behaviours and social cognition. Disruption of limbic structures has huge clinical implications and is presented with a variety of neuropsychiatric disorders including epilepsy, dementia, anxiety and mood disorders, schizophrenia as well as attention deficit and hyperactivity disorder.<sup>1</sup>

### Clinical presentation

VGKCs are located on the membrane of neurons in both the central nervous system (CNS) and peripheral nervous system. They play an important role in a variety of cellular processes, including the functioning of excitable cells, regulation of apoptosis, cell growth and differentiation, the release of neurotransmitters and hormones, maintenance of cardiac activity and so on.<sup>2</sup>

A wide variety of clinical syndromes have been linked with antibodies to VGKCs. It has, however, been determined that patients do not have antibodies to potassium channels, nonetheless, to associated proteins, such as leucine-rich glioma-inactivated 1 (LGI1) and contactin-associated protein 2.<sup>3,4</sup>

LGI1 is a secreted protein, mainly present in the hippocampus and the temporal cortex. It is capable of binding to a disintegrin and metalloproteinase (ADAM) family of proteins. LGI1 connects presynaptic ADAM23 to postsynaptic ADAM22, which is essential for inhibitory signal transmission from the presynaptic potassium channels to the postsynaptic anti- $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor. Antibodies to LGI1 neutralise the LGI1-ADAM22 interaction and reduce postsynaptic AMPA receptors.<sup>5</sup>

Anti-LGI1 antibody-associated limbic accounts for most cases of anti-VGKC complex-associated encephalitis, affecting mainly men with a male:female ratio of 2:1. This form of limbic encephalitis is characterised by subacute onset of psychiatric symptoms such as short-term memory impairment, affective symptoms and psychosis. Myoclonus, hyponatraemia and faciobrachial dystonic seizures as well as headache are common. Moreover, most patients develop faciobrachial dystonic seizures before the onset of amnesic syndrome. Respiratory failure and critical illnesses are less common in anti-LGI1-limbic encephalitis than in anti-N-methyl-D-aspartate (NMDA) antibody-associated encephalitis. Furthermore, the anti-LGI1-limbic encephalitis has better response to immunotherapy and better prognosis compared with anti-NMDA antibody-associated encephalitis. In addition, patients suffering from anti-LGI1-limbic encephalitis tend to be older men with a median age of 60.<sup>6</sup> Anti-NMDA antibody-associated encephalitis predominantly affects young women under the age of 50.<sup>7</sup>

Contactins are a group of cell adhesion molecules that are mainly expressed in the brain. They play pivotal roles in neurogenesis, neuronal development, synapse formation and plasticity, axo-glia interactions and neural regeneration. Contactin-associated protein-like 2 (CASPR2) is found in the central and peripheral nervous system, where it is highly expressed throughout the brain and spinal cord, particularly in the frontal and temporal lobes, striatum, dorsal thalamus and the cortex. In humans, alterations in the CASPR2 gene are associated with a variety of neurological disorders, including epilepsy, schizophrenia, autism spectrum disorders, intellectual disability and language delay, but also obesity.<sup>8</sup> In addition, in humans, autoantibodies that target the extracellular domain of CASPR2 are linked to autoimmune epilepsies, cerebellar ataxia and autoimmune encephalitis.<sup>4</sup>

Anti-CASPR2 antibody-associated limbic encephalitis is characterised with three main syndromes: Morvan's syndrome, Isaac's syndrome and encephalitis.<sup>3,4</sup> The most common phenotype is Morvan's syndrome, a condition that was first described by Augustine Marie Morvan, a French physician, politician and writer, in 1890. Morvan's 'la choree fibrillaire' is characterised by neuromyotonia, pain, hyperhidrosis, weight loss, severe insomnia and hallucinations. Neuromyotonia is a rare neurological condition, which is characterised by peripheral nerve hyperexcitability. Likewise, patients with Morvan's syndrome quite often present with confusion, memory problems, fluctuations in blood pressure, painful cramps and myoclonus.<sup>9</sup>

The Isaac's syndrome was a peripheral nerve hyperexcitability syndrome that presents as continuous motor activity. Clinical findings include cramps, fasciculations and myokymia. Some of these patients also present with symptoms such as hyperhidrosis and/or CNS symptoms similar to those from Morvan's syndrome.<sup>10</sup>

### Antibody testing

Antibody status is not needed to consider limbic encephalitis as having a definite autoimmune origin because immune-mediated limbic encephalitis can occur without detectable autoantibodies. Measurements of autoantibodies, however, remain important because the diagnosis of autoimmune limbic encephalitis could be confirmed by their presence in cerebrospinal fluid (CSF) and/or serum. Moreover, their presence clarifies the immunological subgroup of autoimmune encephalitis, with comorbidities, tumour association and prognosis that might differ.<sup>7</sup>

### CSF testing

Analysis of CSF plays a central part in diagnosis of all cases of encephalitis. Most patients with autoimmune encephalitis have CSF antibodies and relevant antibodies are found in their CSF. Moreover, the types of antibodies in the CSF can determine the clinical picture as well as correlate with the progress of the illness. CSF analysis of patients suffering from autoimmune limbic encephalitis shows mild-to-moderate lymphocytic pleocytosis (usually less than 100 white blood cells/mm<sup>3</sup>) in 60% to 80% of patients, and elevated IgG index or oligoclonal bands in approximately 50% of cases. However, patients with LGII antibodies present with much lower frequency (about 40%) of CSF pleocytosis.<sup>7</sup>

### Imaging

Brain MRI in patients with autoimmune encephalitis may be normal or bilateral abnormalities in the medial temporal lobes on T2 signal.<sup>6,7</sup> On other hand, similar MRI findings are found in almost 95% of patients with herpes simplex virus encephalitis, as well as in individuals suffering from tuberculosis and syphilis.<sup>6</sup>

### Electroencephalogram

EEG findings in limbic encephalitis can be normal or non-specific<sup>6</sup> or showing slow-wave activities involving the temporal lobes.<sup>7</sup> EEG is in particular useful for excluding subclinical seizures, as well as for prognosis and differential diagnosis. It has been suggested that normal EEG correlates with good prognosis, independent of other prognostic factors. Conversely, periodic or rhythmic patterns, seizures and new-onset refractory status epilepticus are associated with poor prognosis. Anti-LGII receptor-mediated limbic encephalitis is associated with faciobrachial dystonic seizures, with characteristic rapid jerking of one side of the face and/or upper extremity. EEG may show multifocal onset seizures or other abnormalities.<sup>6</sup> The delta brush pattern is observed typically in patients with anti-NMDA-receptor-mediated encephalitis.<sup>6,7</sup>

### Treatment

There are no established guidelines for treatment of autoimmune encephalitis, and diverse regimens are currently being used based on the patient's clinical status and the clinicians' opinion. Corticosteroids, intravenous immunoglobulin and plasma exchange are the first-line treatments. Corticosteroids are frequently the first choice, followed by intravenous immunoglobulin and plasma exchange. Corticosteroids with either intravenous immunoglobulin or plasma exchange represent the usual choice when a combination of first-line agents is administered. When first-line immunotherapy is insufficient, secondary immunomodulatory agents such as rituximab and cyclophosphamide are the most common medications.<sup>6,7</sup>

### CONCLUSION

Limbic encephalitis represents a cluster of autoimmune disorders, with inflammation in the medial temporal lobe and surrounding areas. Anti-LGII antibody-associated limbic encephalitis accounts for most cases of anti-VGKC complex-associated encephalitis, which is characterised by subacute onset of psychiatric symptoms such as short-term memory impairment, affective symptoms and psychosis. Myoclonus, hyponatraemia and faciobrachial dystonic seizures are common. Limbic encephalitis and in general autoimmune encephalitis are not easy to diagnose as most patients initially present with psychiatric symptomatology than neurological symptomatology. Furthermore, immunological and laboratory testing are not easily accessible and where available take a rather long time to determine the diagnosis. What is more, few psychiatrists consider autoimmune nature of the neuropsychiatric presentation. It is important to consider limbic encephalitis in all patients with new-onset psychosis or mania. Characteristic indicators of autoimmune encephalitis include neurological symptoms such as facial twitching, seizures, confusion and cognitive decline.

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