ABSTRACT
Antibodies against the voltage-gated potassium channel (VGKC) were first recognised as having a potential pathogenic role in disorders of the central nervous system in 2001, with VGKC antibodies described in patients with limbic encephalitis, and the subsequent seminal paper describing the clinical phenotype and immunotherapy treatment responsiveness in 13 patients with VGKC antibodies and limbic encephalitis in 2004. These initial case descriptions were of a progressive neuropsychiatric syndrome with abnormalities of mood, sleep and cognition recognised alongside the neurological symptoms of seizures and autonomic instability. The clinical syndromes associated with VGKC complex (VGKCC) antibodies have broadened considerably over the last 15 years, with multiple cases of more restricted ‘formes frustes’ presentations associated with VGKCC antibodies being described. However, the relevance of antibodies in these cases has remained controversial. The understanding of the pathogenic nature of VGKC antibodies has further advanced since 2010 with the discovery that VGKC antibodies are not usually antibodies against the VGKC subunits themselves, but instead to proteins that are complexed with the potassium channel, in particular leucine-rich, glioma-inactivated protein 1 (LGI1) and contactin-associated protein 2 (Caspr2). Antibodies against these proteins have been associated with particular, although overlapping, clinical phenotypes, each also including neuropsychiatric features. Our aim is to critically review the association between VGKCC, LGI1 and Caspr2 antibodies with isolated psychiatric presentations—with a focus on cognitive impairment, mood disorders and psychosis. We recommend that screening for VGKCC, LGI1 and Caspr2 antibodies be considered for those with neuropsychiatric presentations.

COGNITIVE IMPAIRMENT AND VGKC COMPLEX ANTIBODIES
It has become clear since the description of the first 13 cases of voltage-gated potassium channel (VGKC) antibody-associated encephalopathy that cognitive impairment is an important, if not the predominant clinical sign.1–3 It was often the presenting symptom and was present up to a year before establishing the diagnosis. Symptoms included profound amnesia, severe and global deficits in memory, naming and frontal lobe function, often with sparing of general intellect. Immunotherapy including intravenous immunoglobulins or plasma exchange effectively reduced VGKC antibody levels and led to improved neuropsychological performance, although profound cerebral atrophy could occur, particularly of the medial temporal lobes.1–3

Indeed, from this pilot work, we already learnt three major aspects of the disease that remained characteristic in all subsequent studies:

▸ Severe impairment of memory with marked amnesia
▸ Cognitive impairment can be immunotherapy responsive
▸ Often results in hippocampal atrophy (figure 1)

A big step forward in this field was the discovery in 2010 that VGKC antibodies are principally not targeting the VGKC directly. So far, VGKC antibodies were determined using immunoprecipitation assays of radiolabelled channel complex proteins. For this, VGKC complexes were extracted from human cortex, labelled with the snake toxin 125I-o-dendrotoxin and precipitated with patient sera.4 Given the toxin specificity for the potassium channels Kv1.1, Kv1.2 and Kv1.6, it was assumed that patient antibodies target these channels. We then learnt that the antibodies rather bind to the proteins leucine-rich, glioma-inactivated protein 1 (LGI1) or contactin-associated protein 1 (LGI1) or contactin-associated protein 2 (Caspr2), which are associated with the extracted channel complex,5 6 and potentially to further associated proteins such as contactin-2,7 some of which might not represent pathogenic domains. Therefore, the term VGKC complex (VGKCC) antibodies was coined to acknowledge that they encompass a broader spectrum of antibodies. Of these, antibodies targeting the extracellular proteins LGI1 and Caspr2 are of proven relevance. More importantly, detection of one or the other predicts a differential clinical phenotype. While LGI1 antibody-positive patients commonly show severe cognitive impairment, confusion and faciobrachial dystonic seizures (FBDS), Caspr2 antibody-positive patients at high titres can suffer from Morvan’s syndrome, a spectrum including peripheral nerve hyperexcitability and neuropsychiatric features relating to limbic encephalitis.8 While all patients with LGI1 antibodies have amnesia, it is present only in 50% of patients with Caspr2 antibodies. The diverse spectrum of clinical symptoms related to specific antibodies likely relates to the differential expression of these proteins throughout the brain, the integrity of the blood–brain barrier or molecular epitope variability of the antibodies.
impaired in one or two domains despite improvement in verbal and non-verbal memory. Cognitive morbidity can be the predominant long-term symptom, as precisely described in the moving article by Dr Morrow.\textsuperscript{12}

Response to treatment with immunotherapy

Positive effects of immunotherapy on clinical outcome were already observed with the very first described patients 15 years ago and confirmed in later studies.\textsuperscript{9 9 13 14} However, although more intense immunotherapy can be beneficial, most VGKC antibody-positive patients with limbic encephalitis are left with significant memory impairment, with the poorest memory function in LGI1 antibody-positive patients, affecting verbal and figural memory and suggesting permanent functional damage.\textsuperscript{9} It is possible that delayed initiation of treatment contributes to a poor outcome, similar to the experience with a related common form of autoimmune encephalitis, anti-N-methyl-d-aspartate (NMDA) receptor encephalitis.\textsuperscript{15 16} With the classification of FBDS (ie, brief, very frequent events that often involve posturing of the hemiface and ipsilateral arm) as an LGI1 antibody-mediated syndrome, analyses suggest that early treatment can prevent the progression of the disease from this pathognomonic seizure form into the manifest limbic encephalitis with permanent hippocampal damage.\textsuperscript{15}

Already the initial studies on VGKC antibody-associated encephalopathy suggested that the hippocampus is the predominant target structure of the disease, which has later been confirmed with imaging studies. Significantly larger volumes of amygdala and hippocampus were observed in the acute phase of the disease, while hippocampal atrophy commonly develops at later follow-ups, particularly in patients with LGI1 antibodies.\textsuperscript{3 9 17 18} However, systematic studies investigating imaging abnormalities in VGKC antibody-associated limbic encephalitis and their relationship to cognitive impairment are urgently needed. These should be separately performed for the different specific antibodies (LGI1, Caspr2, others) in larger cohorts of well-characterised patients to identify characteristic memory profiles that could facilitate early recognition of the disease and target parameters for treatment control and outcome.

Hippocampal involvement in VGKC-related cognitive impairment

Given that the hippocampus represents the key structure for memory formation and cognitive function, progressive atrophy can well explain the cognitive impairment seen in these patients. The underlying mechanisms of disease might include that LGI1 can influence synaptic transmission in the hippocampus by modulating the ratio of synaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) versus NMDA receptors\textsuperscript{19} and by supporting the maturation of NMDA receptors in the hippocampus.\textsuperscript{20} Moreover, experiments with LGI1 antibody-containing human serum could enhance the excitability at hippocampal synapses in slice experiments,\textsuperscript{21} which is believed to facilitate the process of memory encryption,\textsuperscript{22} thus supporting that VGKC antibodies are directly pathogenic.

Importance of VGKC titre levels

In the above-mentioned syndrome of VGKC-related limbic encephalitis, there is usually no controversy about the role of the antibodies if high titres are present. In particular, the strong association of FBDS with LGI1 antibodies or the unusual type of seizure semiology including autonomic or pilomotor seizures in LGI1 patients\textsuperscript{23} suggests that bizarre, isolated phenotypes of movement or cognition can occur that may have led to...
consideration of a psychosomatic disease in several previous cases. However, there are difficulties in attributing cognitive impairment to VGKC antibodies in some patients. Patients with low-positive antibodies more often had neurodegenerative disorders, atypical presentations or a rather heterogeneous clinical spectrum. Nonetheless, in some patients with low-positive levels, there is no doubt about the autoimmune aetiology, and others with high-positive levels did not have the full clinical picture of limbic encephalitis.

Moreover, we have seen a number of patients with cognitive impairment and low-positive VGKC radioimmunoassay (RIA) measures that were clearly positive for LGI1 in cell-based assays—similar findings are reported in the literature. Some authors refer to a cut-off at 400 pmol/L, also because lower levels were seen in up to 5% of older patients in the community. However, a large series suggested that 61% of patients with LGI1 or Caspr2 antibodies would have been overlooked when VGKC antibody levels below this cut-off were excluded. Given that LGI1/Caspr2 antibodies can be detectable in the absence of positive VGKC RIAs, and that the specific antibodies much better associate with a certain clinical phenotype, we strongly recommend to always test for LGI1 and Caspr2 in cell-based assays. Some authors go even further and suggest that testing of VGKC antibodies might be dispensable and the RIAs could be replaced by specific testing for LGI1 and Caspr2 (future studies with larger patient cohorts will have to elucidate whether this comes at risk of overlooking treatable autoimmune aetiologies in some patients). Until then, low VGKC antibody titres should not be neglected but always be interpreted in the clinical context, depending on the type of cognitive impairment and kinetic of progression.

**VGKC antibodies in dementia**

Finally, VGKC antibodies are increasingly detected in patients with the initial diagnosis of dementia, in particular if onset of dementia is subacute and the course progresses rapidly. There are a number of cases of VGKC antibody-associated encephalopathy in which the symptoms were dominated by severe cognitive impairment and included rapidly progressing extrapyramidal signs, hallucinations and MRI changes in diffusion-weighted images, thus fulfilling the diagnostic clinical criteria for Creutzfeldt-Jakob disease (CJD). Based on these studies, VGKC antibody-associated limbic encephalitis has become an important early differential diagnosis for CJD and vice versa. VGKC antibodies were rarely seen in pathologically confirmed CJD and occurred mainly at low levels, suggesting that they are a secondary phenomenon rather than driving the disease. Remarkable was also the case of a patient with rapidly progressive behavioural and cognitive decline suggestive of frontotemporal dementia. An unexplained ‘repetitive facial grimacing’ makes it likely that the patient had LGI1 antibodies, and steroid therapy resulted in sustained improvement. Similarly, there is an increasing number of case reports describing reversible dementia with predominant short-term memory deficits associated with VGKC antibodies. As in other cases of VGKC antibody-associated encephalopathy, the initial diagnosis of a primary neurodegenerative disorder had to be reclassified and the deficits were responsive to immunotherapy. These data collectively suggest that the threshold for antibody testing should be low in order not to overlook treatable aetiologies.

**MOOD AND PSYCHOTIC DISORDERS AND VGKC ANTIBODIES**

**Psychiatric symptoms in those with VGKC antibodies**

As the clinical phenotype for the limbic encephalitis associated with LGI1 and Caspr2 antibodies has been delineated over the past decade, it has been recognised that psychiatric symptoms of mood disturbance, in particular depression and anxiety, have been a part of the presentation in a substantial minority of cases (16.5% in one large case series of 316 patients with VGKC antibodies). Changes in behaviour or agitation are also seen in a further proportion of cases, and this may be particularly the case in children. In an analysis of 20 children (ages 4–15, mean 9) with autoimmune encephalitis and VGKC antibodies behaviour change was reported by psychiatric problems were identified in 45% which includes a combination of hallucinations, agitation, mood disorders as reported by the treating neurologist. 0/7 had positive LGI1, Caspr2 or contactin antibodies.

Furthermore, when case reviews of all those testing positive for VGKC antibodies are made, a significant proportion of cases have a predominantly neuropsychiatric presentation, which is particularly characterised by a depressed mood state. In a case series of 67 consecutive patients with VGKC antibodies, 24 had a particularly florid neuropsychiatric presentation, of whom 62% had either anxiety or depression. In all cases, this was in the context of other symptoms, usually confusion, memory loss and seizures in 13/24. The patients with a neuropsychiatric presentation were more likely to have a medium or high titre of VGKC antibodies. Sleep disorders (hypersonomnolence, insomnia or dream enactment) were also present in 33%.

**VGKC antibodies in psychiatric presentations**

The prevalence of VGKC antibodies in purely psychiatric populations has not been fully explored. One study found a prevalence of Caspr2 antibodies in 0.9% of 2333 patients with a variety of neurological and psychiatric diagnoses, as well as healthy controls. There are several case reports of patients with predominantly psychiatric presentations with VGKC antibodies, most of whom respond positively to treatment with immunotherapy (table 1).

In one study of 213 psychiatric inpatients at the Mayo Clinic tested over a 10-year period, 7 had positive VGKC antibodies. However, the reason for antibody testing in this group of psychiatric patients, who represented only 1.7% of all hospitalised patients, was the presence of other neurological symptoms, such as confusion, or movement disorder. Furthermore, the immunotherapy was only offered in the cases where the patients had other features suggestive of encephalitis.

It therefore remains unknown whether other patients with a wholly psychiatric presentation also have levels of VGKC antibodies that may be clinically significant, and then whether removal of the antibodies leads to an improvement in their psychiatric symptoms. Of the case studies listed in table 1, two of three of those with an identified antibody (LGI1) were treated with immunotherapy, and both improved. Five out of seven of those without an identified antibody were also treated and four of those improved, three substantially so. Case series to date have been subject to selection bias, in that only patients where the clinician suspects limbic encephalitis have had their VGKC antibodies tested. To the best of our knowledge, there have been no studies investigating the prevalence of the range of VGKC antibodies in wholly psychiatric patient populations, using appropriately matched control samples.

**Relevance of non-LGI1/Caspr2 VGKC antibodies**

A particular difficulty in deciding the likely clinical relevance of the VGKC antibodies in an atypical clinical presentation is the uncertainty of the relevance of a positive VGKC result in the
absence of a specific antibody. Low levels of VGKCC antibodies are seen in healthy control populations, ranging between 3% and 6.9%. A recent study reported a lack of response to treatment with immunotherapy in patients with low levels of VGKCC antibodies with the suggestion that VGKCC antibodies in the absence of a particular target are likely to be irrelevant. The conclusion from this study is that the presence of a VGKCC antibody in itself is not sufficient to indicate a pathogenic process.

However, studies to identify the antigenic target in those with VGKCC antibodies have found a proportion of patients with high levels of VGKCC antibodies and an immunotherapy responsive-encephalopathy do not have antibodies against Caspr2 or LGI1. The assumption is that they have an, as yet unidentified, antigenic target. This is estimated at 19% of patients with VGKCC antibodies.5

There are also studies to suggest that VGKCC antibodies in children, even at relatively low titres, are associated with an inflammatory neurological presentation. Further cases have been described with LGI1 antibodies and a treatment-responsive illness, in the absence of significant levels of VGKCC antibodies. The suggestion therefore is that while the VGKCC antibodies are not themselves pathogenic, they may indicate a non-specific biomarker for neuronal inflammation. Supporting evidence for this would come from the coexistence of VGKCC with other antibodies or with other autoimmune disorders.

Relevance of VGKC in psychiatric disorders

There are supporting areas of research to suggest that the VGKC is mechanistically relevant for psychiatric disorders. Single nucleotide polymorphisms (SNPs) in the second intron of the KCNH2 gene, which codes for the one component of the VGKC, have been associated with an increased risk of schizophrenia. Furthermore, these SNPs are related to lower IQ score, slower cognitive processing speed, decreased hippocampal grey matter volume, altered memory task functional MRI (fMRI) signals, as well as a positive response to olanzapine in patients with schizophrenia.

Mutations of CNTNAP2 gene that codes for Caspr2 protein have been identified in patients with treatment-refractory seizures, schizophrenia, autism and intellectual disability. Hyponatraemia is a common association in VGKC antibody encephalitis, affecting the majority of cases. Hyponatraemia has also been long associated with psychiatric illness, and schizophrenia in particular, with reports predating the use of antipsychotic drugs and estimated to be present in up to 20% patients with chronic schizophrenia. In one case series, 18% of deaths of people with schizophrenia under the age of 53 were associated with hyponatraemia. The cause of hyponatraemia in people with schizophrenia has historically been assumed to be as a result of a psychogenic polydipsia, with patients drinking excessive water as a result of delusional beliefs. It is an intriguing possibility that there may be an alternative biological underpinning to this phenomenon.

There are therefore reasons to suspect that a proportion of patients with a purely psychiatric phenotype may have VGKCC antibodies that may be causally related to their illness, and that may therefore be treatment responsive to immunotherapy in the same way as other presentations with these antibodies. To date, no distinctive pattern of psychiatric presentation has been identified.

Table 1 Published case descriptions of VGKCC antibodies with predominantly psychiatric presentations

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age, gender</th>
<th>VGKCC antibodies, highest titre (pmol/L), LGI1/Caspr2 antibody</th>
<th>Psychiatric presentation</th>
<th>Encephalopathic symptoms</th>
<th>Immunotherapy treatment and response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parthasarathy et al</td>
<td>1, 58 M</td>
<td>&gt;2000, n/k</td>
<td>3 months</td>
<td>Thought disorder, paranoid delusions, auditory, visual hallucinations</td>
<td>Seizures, hyponatraemia</td>
</tr>
<tr>
<td>Zandi et al</td>
<td>1, 22 F</td>
<td>1435, n/k</td>
<td>10 months</td>
<td>Paranoid delusions, insomnia</td>
<td>No</td>
</tr>
<tr>
<td>Ganguli et al</td>
<td>1, 56 M</td>
<td>506, n/k</td>
<td>2 years</td>
<td>Depression, self-harm, paranoid delusions, auditory, visual hallucinations</td>
<td>Amnesia, epilepsy, hyponatraemia</td>
</tr>
<tr>
<td>Gotkine et al</td>
<td>21 F</td>
<td>444, LGI1</td>
<td>10 weeks</td>
<td>Anxiety, panic, restlessness</td>
<td>Seizure, low sodium</td>
</tr>
<tr>
<td>Iyer et al</td>
<td>1, 13 F</td>
<td>344, Negative to Caspr2/LGI1</td>
<td>8 weeks</td>
<td>Agitated depression, neuroleptic malignant syndrome</td>
<td>No</td>
</tr>
<tr>
<td>Kruse et al</td>
<td>63 F</td>
<td>170, LGI1</td>
<td>77 F</td>
<td>80, Negative to LGI1/Caspr2</td>
<td>Depression, anxiety, hallucinations, agitation, insomnia</td>
</tr>
<tr>
<td></td>
<td>60 M</td>
<td>640, LGI1</td>
<td>Thought disorder, psychosis, agitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>77 M</td>
<td>90, Negative to LGI1/Caspr2</td>
<td>Agitation, aggression, disinhibition</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>57 M</td>
<td>150, Negative to LGI1/Caspr2</td>
<td>Depression, anxiety</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*A further two cases of VGKC antibodies with a psychiatric presentation are referred to, but details are not given.

Caspr2, contactin-associated protein 2; IVIG, intravenous immunoglobulin; LGI1, leucine-rich, glioma-inactivated protein 1; n/k, not known, usually when study predates 2010 and availability of LGI1 and Caspr2 testing; PLEX, plasma exchange; VGKCC, voltage-gated potassium channel complex.
CONCLUSIONS
It is a priority that the prevalence of VGKCC, LGI1 and Caspr2 antibodies in purely psychiatric populations is further explored, and the clinical relevance of antibodies detected is assessed. A particular focus might be on those psychiatric presentations with a strong indication of a possible autoimmune component. This would include postpartum illnesses, those with subacute onset and those with other suggestive symptoms, such as hypnotherapy or movement disorder. It is important that screening studies use appropriately matched control samples.

It is important that neurologists are aware of the psychiatric phenomenology that is commonly associated with these antibodies and actively assess and manage these symptoms where present, and equally that psychiatrists keep VGKCC antibodies in mind as a possible differential diagnosis for patients with atypical features. Furthermore, it is a research priority to identify the antigenic targets for the non-LGI1, Caspr2 and VGKCC antibodies that may be particularly relevant for those with neuropsychiatric presentations.

Finally, given the uncertainty and scepticism among many clinicians regarding the relevance of these antibodies in atypical presentations, we suggest that treatment with immunotherapy should ideally be undertaken in the context of a randomised controlled clinical trial so that the evidence base regarding the effectiveness of immunotherapy can be established.

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REFERENCES


