

Emerging psychiatric syndromes associated with anti-voltage-gated potassium channel antibodies

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Abstract

Antibodies against the Voltage Gated Potassium Channel (VGKC) were first recognised in patients with encephalitis in 2001 (1), and the seminal paper describing the clinical phenotype and treatment responsiveness in 13 patients in 2004 (3). 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 antibodies have broadened considerably over the last 10 years, with multiple cases of more restricted presentations ‘formes frustes’ associated with VGKC antibodies being described. Our aim is to review the association between VGKC antibodies and isolated psychiatric presentations – with a focus on cognitive impairment, mood disorders and psychosis.

Cognitive impairment and VGKC antibodies

It has become clear since the **description of the first 13 cases** of 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 learned 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 [*Fig. 1*]

A big step forward in this field was the discovery in 2010 that VGKC antibodies are principally not targeting the voltage-gated potassium channel directly, but rather bind to the associated proteins **LGI1 or Caspr2** (4, 5). More importantly, detection of one or the other antibody 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 syndrome, a spectrum including peripheral nerve hyperexcitability and neuropsychiatric features relating to limbic encephalitis (6). While all subjects with LGI1

antibodies have amnesia, it is present only in 50% of patients with Caspr2 antibodies. Studies before the discovery of the antibody subgroups are now often referred to as ‘VGKC-complex’ antibodies, also taking into consideration that further epitopes such as Contactin-2 will be unravelled (6).

Although the number of VGKC-complex antibody-positive patients grew rapidly with increased awareness of the disease and availability of testing, only very few studies systematically addressed the **cognitive profile and reversibility of memory dysfunction**. In an early study of three patients, dysfunction of anterograde memory was accompanied by temporally ungraded retrograde amnesia extending more than 20 years (7). A recent study including 18 patients with VGKC antibodies (9 LGI1, 3 Caspr2, 6 negative for LGI1/Caspr2) focused on verbal learning, verbal memory and recognition, figural memory, figural learning including supra-span learning, and figural recognition, collectively analysing the function of the temporal lobes (8). During the acute disease phase, 16 of 18 patients had memory deficits in either verbal or figural memory or in both. At follow-up after 5 to 70 months, 11 of 17 patients still had impaired function of at least one memory domain. Another study evaluated cognitive function of 19 patients with VGKC antibodies (9 LGI1, 1 Caspr2, 9 not tested) using standardized neuropsychological assessment (9). Similarly, the cohort had significant impairment of memory, processing speed and executive function at the initial visit 16 to 377 days after symptom onset, while language and perceptual organisation were not affected. At visit 2 ranging from 3 to 44 months after the first assessment, processing speed and executive function had normalized while at least a third of patients was left with permanent anterograde amnesia (9). A third study addressing cognitive impairment in VGKC antibody-associated limbic encephalitis examined 15 patients and found impairments in attentional-executive functions and verbal and non-verbal memory 1 to 23 months after symptom onset, mostly in two or three domains (10). At follow-up after 1 to 68 months, 50% remained impaired in one or two domains despite improvement in verbal and non-verbal memory.

Positive **effects of immunotherapy** on clinical outcome were already observed with the very first described patients 15 years ago and confirmed in later studies (8, 11, 12). However, although more intense immunotherapy can be beneficial, most VGKC antibody-positive limbic encephalitis patients are left with significant memory impairment, with the poorest memory function in LGI1 antibody-positive patients, affecting both verbal and figural memory and suggesting permanent functional damage (8). 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-NMDA receptor encephalitis (13, 14). With the classification of FBDS (i.e. 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 (12).

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 both 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 (3, 8, 15, 16). 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-characterized patients to identify characteristic memory profiles that could facilitate early recognition of the disease and target parameters for treatment control and outcome.

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 AMPA versus NMDA receptors (17) and by supporting the maturation of NMDA receptors in the hippocampus (18). Moreover, experiments with LGI1 antibody-containing human serum could enhance the excitability at hippocampal synapses in slice experiments (19), which is believed to facilitate the process of memory encryption (20), thus supporting that VGKC-complex antibodies are directly pathogenic.

In the abovementioned 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 (21) suggest 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 (22). Subjects 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 (22). Moreover, we have seen a number of patients with cognitive impairment and low-positive VGKC RIA measures that were clearly positive for LGI1 in cell-based assays, similar findings are reported in the literature (12). Some authors refer to a cut-off at 400 pmol/l, also because lower levels were seen in up to 5% of older subjects in the community (3).

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 (23). Thus, 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.

Finally, VGKC-complex 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, but also included extrapyramidal signs and hallucinations, thus fulfilling the diagnostic 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 (24, 25). 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 (26, 27). Remarkable was also the case of a patient with rapidly progressive behavioural and cognitive decline suggestive of **frontotemporal dementia** (28). 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 (29, 30). As in other cases of VGKC antibody-associated encephalopathy, the initial diagnosis of a primary neurodegenerative disorder had to be re-classified and the deficits were responsive to immunotherapy. These data collectively suggest that the threshold for antibody testing should be low in order to not overlook treatable aetiologies.

Mood and psychotic disorders and VGKC antibodies

As the clinical phenotype for the limbic encephalitides associated with LGI1 and CASPR2 antibodies have been delineated over the last 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 (31). More general behavioural change 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, with a mean age of 9 (range 4-15) with autoimmune encephalitis and VGKC antibodies behaviour change was reported by psychiatric problems were identified in 45% (32), 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(33). 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 complex antibodies. Sleep disorders (hypersomnolence, insomnia, or dream enactment) were also present in 33% (33)

The prevalence of VGKC antibodies in purely psychiatric populations has not been fully explored. There are several case reports of patients with predominantly psychiatric presentations with VGKC antibodies, most of whom respond positively to treatment with immunotherapy when treated (table 1).

Table 1. Published case descriptions of VGKC antibodies with predominantly psychiatric presentations. IVIG= intravenous immunoglobulins PLEX=plasma exchange. * a further 2 cases of VGKC antibodies with a psychiatric presentation are referred to, but details not given.

Authors	age gender	Antibody and highest titre (pMol/l)	Psychiatric presentation	Encephalopathic symptoms	Immunotherapy treatment and response
Parthasarathy et al 2009 ⁴²	1, 58M	>2000 n/k	3 months thought disorder, paranoid delusions, auditory, visual hallucinations	Seizures, hyponatraemia,	IVIG, steroids, limited improvement, PLEX substantial improvement
Zandi et al 2010 ⁴³	1, 22F	1435 n/k	10 months paranoid delusions, insomnia,	no	Not treated
Ganguli et al 2011 ⁴⁴	1, 56M	506 n/k	2 years Depression, self harm, paranoid delusions, auditory visual hallucinations	Amnesia, epilepsy, hyponatraemia	PLEX, IVIG Steroids Limited cognitive improvement
Gotkine et al 2011 ⁴⁵	21F	444 LGI1	10 weeks anxiety, panic,	Seizure, low sodium	PLEX, steroids, complete improvement

			restlessness		
Iyer et al 2012 ⁴⁶	1, 13F	344 Negative to CASPR2/LGI1	8 weeks Agitated depression, neuroleptic malignant syndrome	no	3 days methylprednisolone, Complete improvement
Kruse et al 2015* ³¹	63F	170 LGI1	Depression, insomnia, agitation	Cognitive decline	Not treated
	77F	80 negative to LGI1/CASPR2	Depression, anxiety, hallucinations, agitation, insomnia	Confusion, cognitive decline	Not treated
	60M	640 LGI1	Thought disorder, psychosis, agitation	Confusion, dyskinesia	5 days methylprednisolone, marked improvement
	77M	90 negative to LGI1/CASPR2	Agitation, aggression, disinhibition	Subacute worsening of chronic cognitive disorder	5 days methylprednisolone more agitated,
	57M	150 negative to LGI1/CASPR2	Depression, anxiety	Cognitive decline	5 days methylprednisolone, improved

In one study of 213 of psychiatric inpatients at the Mayo Clinic tested over a 10 year period, 7 had positive VGKC antibodies (34). However the reasons for antibody testing in this group of psychiatric patients, who represented only 1.7% of all hospitalised patients, were usually because of the presence of other neurological symptoms, such as confusion, or movement disorder. Furthermore the reasons for offering immunotherapy were in the cases where the patients had other features suggestive of an encephalitis (34).

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. 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. There have been no studies investigating the prevalence of VGKC antibodies in wholly psychiatric patient populations, to our knowledge.

A further difficulty in deciding the likely clinical relevance of the VGKC antibody in an atypical clinical presentation is the lack of specificity of a positive VGKC result. Low levels of VGKC antibodies are seen in healthy control populations, ranging between 3- 6.9% (3, 34). The presence of a VGKC antibody in itself is therefore not sufficient to indicate a pathogenic process.

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 voltage-gated potassium channel have been associated with an increased risk of schizophrenia (35). Furthermore these SNPs are related to lower IQ score, slower cognitive processing speed, decreased hippocampus gray matter volume, altered memory task fMRI signals, as well as a positive response to olanzapine in patients with schizophrenia (36)

Mutations of the CNTNAP2 gene that codes for the CASPR2 protein have been identified in patients with treatment refractory seizures, schizophrenia, autism and intellectual disability (37,38).

Hyponatraemia is a common association in VGKC antibody encephalitis, affecting the majority of cases (3, 31). Hyponatraemia has also been long associated with psychiatric illness, and schizophrenia in particular, with reports predating the use of antipsychotic drugs (39), and estimated to be present in up to 20% patients with chronic schizophrenia (40). In one case series 18% of deaths of people with schizophrenia under the age of 53 was associated with hyponatraemia (41). The cause of the 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 VGKC antibodies that may be causally related to their illness, and that may therefore be treatment responsive to immunotherapy in the same way that other presentations with these antibodies. To date no distinctive pattern of psychiatric presentation has been identified.

It is therefore a priority that the prevalence of VGKC antibodies in purely psychiatric populations is further explored, and the clinical relevance of antibodies detected is assessed. A particular priority might be on those psychiatric presentations with a strong signal of a possible autoimmune component. This would include post partum illnesses, those with subacute onset and those with other suggestive symptoms, such as hyponatraemia or movement disorder.

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