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Review

From VGKC to LGI1 and Caspr2 encephalitis: The evolution of a disease entity over time

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ABSTRACT

A wide variety of clinical syndromes has been associated with antibodies to voltage-gated potassium channels (VGKCs). Six years ago, it was discovered that patients do not truly have antibodies to potassium channels, but to associated proteins. This enabled the distinction of three VGKC-positive subgroups: anti-LGI1 patients, anti-Caspr2 patients and VGKC-positive patients lacking both antibodies. Patients with LGI1-antibodies have a limbic encephalitis, often with hyponatremia, and about half of the patients have typical faciobrachial dystonic seizures. Caspr2-antibodies cause a more variable syndrome of peripheral or central nervous system symptoms, almost exclusively affecting older males. Immunotherapy seems to be beneficial in patients with antibodies to LGI1 or Caspr2, stressing the need for early diagnosis. Half of the VGKC-positive patients lack antibodies to both LGI1 and Caspr2. This is a heterogeneous group of patients with a wide variety of clinical syndromes, raising the question whether VGKC-positivity is truly a marker of disease in these patients. Data regarding this issue are limited, but a recent study did not show any clinical relevance of VGKC-positivity in the absence of antibodies to LGI1 and Caspr2. The three VGKC-positive subgroups are essentially different, therefore, the lumping term 'VGKC-complex antibodies' should be abolished.

Contents

1. Introduction

In the last ten years several antibodies to neuronal surface antigens have been identified. Most of these antibodies are proven or strongly believed to be pathogenic and cause a well-defined syndrome, such as anti-NMDA-receptor encephalitis [1]. However, controversy exists regarding antibodies to the voltage-gated potassium channel complex (VGKC). VGKCs are present on the membrane of neurons in both the central and peripheral nervous system. They play a crucial role

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in returning the cell to the resting state after an action potential. Antibody-mediated disturbance of this process was initially suspected in patients with neuromyotonia, Morvan's syndrome and limbic encephalitis [2–4]. Sera of these patients tested positive in the VGKC-radioimmunoassay (RIA), a test measuring the amount of antibody bound to solubilized complexes of VGKCs. However, all attempts to show reactivity of these samples to cells transfected with intact VGKCs failed. Subsequent investigations demonstrated that the antibodies were not directed to the VGKC itself, but to associated proteins, which are included in the VGKC-test. Two of these proteins were identified in 2010: leucine-rich glioma-inactivated1 (LGI1) and contactin-associated protein-like 2 (Caspr2) [5,6]. This major step forward enabled the distinction of three VGKC-positive subgroups: anti-LGI1 patients, anti-Caspr2 patients and VGKC-positive patients lacking both antibodies. This review is structured accordingly, first describing the clinical syndrome caused by LGI1-antibodies. These patients have a limbic encephalitis, often with hyponatremia, and about half of the patients have typical faciobrachial dystonic seizures (FBDS). Caspr2-antibodies cause a more variable syndrome of peripheral or central nervous system symptoms, almost exclusively affecting older males. The third section reviews the group of VGKC-positive patients lacking antibodies to LGI1 and Caspr2. About half of the VGKC-positive patients belong to this group (varying between 16% and 77% in the respective studies) [5,7–11]. The group encompasses children and adults with a wide variety of clinical syndromes, raising the question whether VGKC-positivity is truly a marker for disease in these patients. A recent study focused on this issue did not detect clinical relevance of VGKC-positivity in the absence of LGI1 and Caspr2 antibodies [10]. (See Table 1.)

2. VGKC-positive subgroups

2.1. LGI1-antibodies

LGI1 is a secreted protein, mainly present in the hippocampus and the temporal cortex. It is capable of binding to proteins of the ADAM (a disintegrin and metalloproteinase) family. LGI1 connects presynaptic ADAM23 to postsynaptic ADAM22, which is essential for inhibitory signal transmission from the presynaptic potassium channel to the postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic-acid (AMPA)-receptor. Antibodies to LGI1 reduce LGI1-ADAM interaction and reversibly reduce postsynaptic AMPA-receptor clusters [12]. A genetic disruption of the LGI1 protein in humans causes autosomal-dominant lateral temporal lobe epilepsy [13,14]. LGI1 knock-out mice die of lethal epilepsy in the postnatal third week, confirming the essential role of LGI1 in synaptic transmission [15].

Approximately 250 anti-LGI1-encephalitis patients have been reported so far. Major underdiagnosis of this relatively 'new' disease entity is suspected, as we have seen a serious increase in incidence over the last few years (own observation). Median age of onset is around 60 years with a 2:1 male predominance [5,6,16]. The vast majority of the patients have a limbic encephalitis, characterized by subacute disturbance of memory, behavior and spatial orientation. Seizures are common, and include both subtle partial seizures and (secondary) generalized tonic clonic seizures. Very specific for LGI1-encephalitis, but only present in half of the patients, are faciobrachial dystonic seizures (FBDS), also referred to as tonic seizures [17,18]. FBDS are very brief (<3 s) unilateral contractions of the arm, often involving the ipsilateral face (or leg), and occurring up to 100 times a day. Patients drop items and falls are reported [18,19]. FBDS are often unrecognized by physicians, and only the minority of the EEG recordings show ictal changes [17,18]. FBDS often precede the onset of cognitive decline, and prompt start of immunotherapy could possibly prevent progression to limbic encephalitis [20]. Hyponatremia is present in 60% of the anti-LGI1 patients. Brain MRI shows T2 high signal of the medial temporal lobe in two-thirds of the patients [5,6,16]. Basal ganglia abnormalities are seen in some patients with FBDS [21]. CSF is usually unremarkable, or cell count or protein are minimally raised. Tumor screening is positive in 0–11% of the patients [5,6,16,22]. Various tumors seem to be associated, but thymoma and lung cancer are probably most common. LGI1-antibodies can be detected by a (commercially available) cell-based assay, or by the typical staining pattern seen on immunohistochemistry (Fig. 1). Antibodies can be found in both serum and CSF, but to our experience, serum testing is more sensitive. The result (pM) of the VGKC-RIA is usually increased to a plurality of the cut-off value for positivity [22]. The effect of immunotherapy has not been studied in randomized trials, but is favorable in smaller patient series. Most patients are treated with intravenous or oral corticosteroids, intravenous immunoglobulin (IVIg) or a combination of both, and show substantial improvement [5,6,16]. Seizures, especially FBDS, often disappear instantly, while cognitive improvement is slow (own data). Data regarding second line therapy are limited. In a series of five patients treated with rituximab marked improvement was seen in only one patient. This disappointing outcome might be due to the long delay until start of rituximab (median 414 days) [23]. Relapse rate of anti-LGI1 encephalitis ranges between 0–20%, but will probably increase with extended follow up [6,16,22]. To our experience, relapses can occur more than seven years after the initial disease episode. Long term outcome is currently studied more extensively.

2.2. Caspr2-antibodies

Caspr2 is a membrane protein expressed in the central and peripheral nervous system. Its cytoplasmic domain is essential for potassium channel clustering at the juxtaparanodes of myelinated axons [24]. Mutations in the gene encoding for Caspr2 (CNTNAP2) are associated with focal epilepsy, schizophrenia and other disorders [25,26]. Antibodies target multiple epitopes of the Caspr2 protein [27], and react to both brain and peripheral nerve [28].

Less than hundred anti-Caspr2 patients have been reported so far, with age of onset around sixty years. For unknown reasons, 80–90% of the patients are male [5,28]. Common central nervous system

Table 1
Subgroups of VGKC-positive patients.

	LGI1 positive	Caspr2 positive	LGI1 and Caspr2 negative
Patient characteristics	60–70% male Age ~ 60	80–90% male Age ~ 70	50% male All ages
Clinical syndrome	Limbic encephalitis (~50% FBDS)	Peripheral nervous hyperexcitability Limbic encephalitis Morvan's syndrome	Variable, including cognitive decline, psychiatric symptoms, epilepsy, pain syndrome, CFS
Hyponatremia	60%	Rare	Rare
VGKC RIA result* (range)	>400 pM (200–1500 pM)	>200 pM (50–1000 pM)	<300 pM (100–300 pM)
Response to immunotherapy	Good	Good	Limited data; most likely equal to matched VGKC-negative patients

CFS = cramp fasciculation syndrome. RIA = radioimmunoassay.
* Cut-off value for positivity 100 pM.

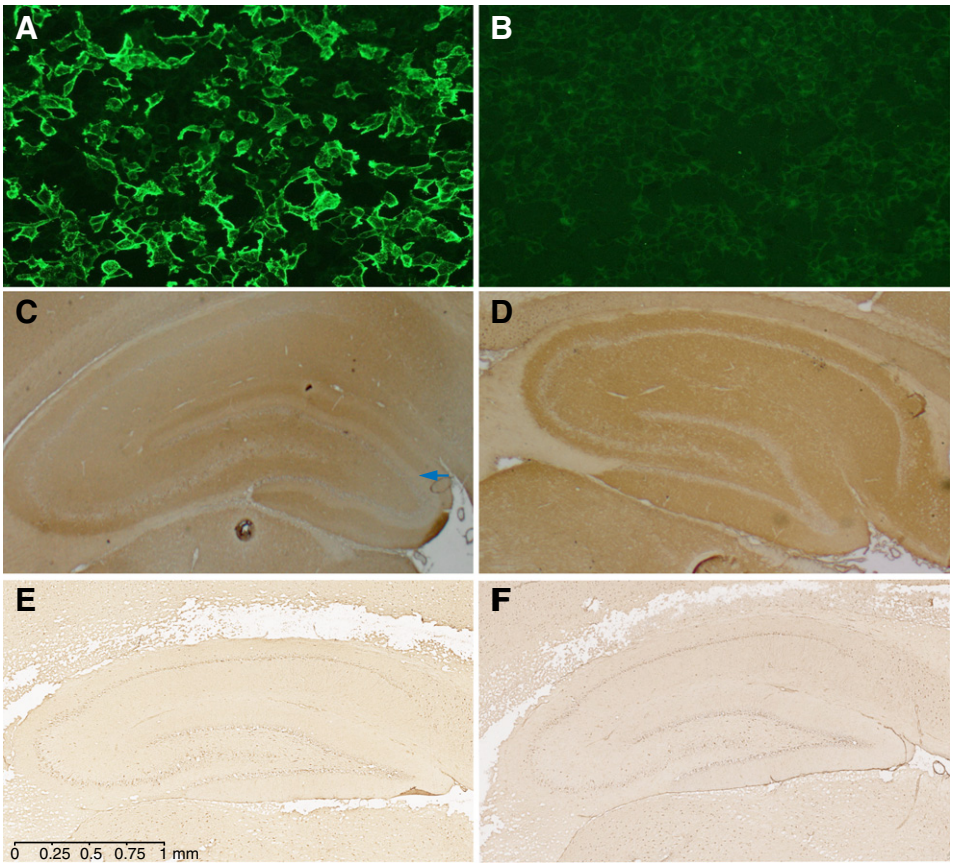

Fig. 1. Cell-based assay (A–B) and immunohistochemistry (on rat brain, C–F). (A) Caspr2-antibody positive sample. (B) Caspr2-antibody negative control. (C) LGI1-antibody positive sample, showing staining of the hippocampus, except for the inner 1/3rd of the dentate gyrus (blue arrow). (D) Caspr2-antibody positive sample, showing diffuse staining of the hippocampus. (E) Negative control sample. (F) VGKC-radioimmunoassay positive sample (titer 118 pM) without antibodies to LGI1 and Caspr2. The hippocampus shows no staining.

symptoms are cognitive decline and seizures. Cerebellar symptoms are reported as well [5,28,29]. Peripheral nervous hyperexcitability causes fasciculations and cramps. A combination of these central and peripheral nervous system symptoms, accompanied by autonomic dysfunction and insomnia, is known as Morvan's syndrome. Morvan's syndrome is strongly associated with Caspr2-antibodies, but seronegative patients are reported as well [30]. Other symptoms associated with Caspr2 antibodies are pain and weight loss [5,28,31]. Caspr2-encephalitis potentially mimics Creutzfeldt-Jakob disease (CJD) and some patients with a positive Caspr2-antibody test ultimately appeared to have CJD [32,33]. It is unknown whether the anti-Caspr2 tests in these patients were false positive, or that the antibodies were actually present but clinically irrelevant. To our experience, a positive anti-Caspr2 cell-based assay requires further laboratory confirmation and physicians should be especially wary if the VGKC-RIA titer is not clearly raised (own observation). Tumor incidence in anti-Caspr2 patients ranges from 0 to 32% [5,28,31]. Thymomas are most common and some of these patients suffer from myasthenia gravis as well [30]. Several other tumors, such as lung tumor and endometrial carcinoma have been reported [5,34,35]. Tumor treatment is essential for neurological improvement. In addition, and in non-tumor patients, immunotherapy seems to be beneficial [5,28]. First line treatment consists of corticosteroids, IVIg or plasma exchange, but no trials have compared different treatment approaches. Prompt start of treatment is recommended, as early treatment was associated with better outcome in NDMA-receptor encephalitis [36]. To our experience, Caspr2-antibody mediated disease can relapse, similar to syndromes caused by antibodies to LGI1 or NMDA-receptors.

2.3. VGKC-positivity in the absence of antibodies to LGI1 and Caspr2

The clinical spectrum of VGKC-positive patients has emerged, including epilepsy, pain syndromes, cognitive decline, polyneuropathy and cramp fasciculation syndromes [8,11,37]. This clinical heterogeneity mostly concerns VGKC-positive patients lacking LGI1 and Caspr2 antibodies. This raises the question whether these patients actually have a common disease entity [8,22]. Data answering this question are limited, partly because these patients can only be separated from patients with LGI1 or Caspr2 antibodies since six years. Recent studies do include antibody subtyping, but unfortunately many studies subsequently lump the three groups for analysis, or classify patients according to VGKC-RIA results instead of specific antibody results [7,8,38,39]. Higher VGKC-RIA results are linked to neuroinflammatory conditions, and to the detection of LGI1-antibodies [7–9,31,40]. These associations are broadly supported, but do not contribute to clinical reasoning in VGKC-positive patients lacking LGI1 and Caspr2 antibodies. The majority of VGKC-positive patients, but especially those with LGI1 or Capsr2 antibodies, respond to immunotherapy [11,37], suggesting an inflammatory condition in all. However, therapeutic response is not compared to VGKC-negative controls and could also be a reflection of the natural course of any disease. A recent retrospective study analyzed the clinical relevance of VGKC-positivity in the absence of LGI1 and Caspr2 antibodies. Twenty-five VGKC-positive patients (LGI1/Caspr2 antibody negative) were compared to fifty VGKC-negative patients, matched for age, gender and clinical syndrome. The two groups were not different in evidence for autoimmune inflammation ($p = 0.38$), according to predefined criteria blindly assessed by independent researchers. Patients with limbic encephalitis

were more likely to have an autoimmune inflammation than patients with other syndromes, irrespective of VGKC-RIA results. VGKC-positive patients lacking antibodies to LGI1 and Caspr2 did not show better response to immunotherapy than matched VGKC-negative patients. In conclusion, VGKC-positivity in the absence of antibodies to LGI1 and Caspr2 did not show to be a marker for autoimmune inflammation [10]. However, novel antibodies might be detected in small subgroups of VGKC-positive patients in the future, especially in those with limbic encephalitis. More studies will hopefully add to this clinically relevant topic, finally providing clarity after years of considerable misinterpretation of VGKC-results.

3. Conclusion

Three groups of VGKC-positive patients should be distinguished. Patients with LGI1-antibodies suffer from limbic encephalitis with different seizure types and hyponatremia. Patients with Caspr2-antibodies can have both central and peripheral nervous system symptoms, accompanied by insomnia, weight loss and pain. Case series show sufficient evidence for benefit of immunotherapy in both LGI1 and Caspr2 antibody mediated disease. Prompt diagnosis is essential, tumor screening is indicated, and both syndromes can relapse. A third group of VGKC-positive patients lack antibodies to LGI1 and Caspr2. Data regarding this group are limited. A recent study did not detect clinical relevance of VGKC-positivity in the absence of LGI1 and Caspr2 antibodies. Lumping the three VGKC-positive groups using the term 'VGKC-complex antibodies' should be discouraged and abolished.

Take-home messages

- VGKC-positive patients should be classified according to the presence (or absence) of antibodies to LGI1 and Caspr2
- LGI1-antibodies cause a limbic encephalitis, often with hyponatremia.
- Caspr2-antibodies are mainly present in older male patients with a limbic encephalitis, peripheral nervous hyperexcitability or a combination of both.
- Antibodies to LGI1 or Caspr2 are assumed to be pathogenic and the associated syndromes respond well to immunotherapy. A minority of the patients have a tumor.
- A substantial part of the VGKC-positive patients lack antibodies to LGI1 and Caspr2. A recent study did not show any clinical relevance of VGKC-positivity in these patients.

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