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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.

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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.