

Anti-CASPR2 and Epilepsy: don't forget to think about it

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Summary

Autoimmune encephalitis (AE) is an important cause of seizures. With the discovery of highly specific neuronal-antibodies the recognition of the clinical syndrome associated with each marker is crucial to the right diagnosis and treatment regime. In this short review we summarize the importance of CASPR2 antibodies in unknown etiology seizures and its epileptogenesis.

Keywords: CASPR2; epilepsy; autoimmune encephalitis; autoimmune epilepsy

Introduction

Autoimmune encephalitis (AE) is a growing field in neurology. The discovery of highly specific neuronal-antibodies [1] makes a typical syndrome recognition important to reach the correct antibody diagnosis and correct treatment regimen important. Thus, it is possible to achieve the correct diagnosis of these antibodies and the eligible treatment regimen.

Seizures are a common presentation among those with AEs, with 20% of them being diagnosed with epilepsy on admission [2]. It is interesting to note that the cluster of evidence involving neuronal antibodies and epilepsy is still growing. In a study evaluating the prevalence of these antibodies in patients with new and/or established epilepsy, it was found that 11% of those had positive antibodies with antibodies against Voltage-Gated potassium channel (VGKC) complex, representing almost half of them [3]. A similar result occurs in a study that evaluated children with new-onset seizures, of which 9.7% had positive antineuronal antibodies with CASPR2 (the second more frequently found) [4]. In the pediatric cohort of Wright *et al.* (2016) the results were very similar [5].

Contactin-associated protein-like 2 (CASPR2) is a cell adhesion molecule with an important function in clustering VGKC in the juxtaparanodal region of the Node of Ranvier [6]. Together with Leucine-Rich Glioma-Inactivated 1 (LGI-1) protein, CASPR2 (anti-CASPR2) antibodies form among patients who have VGKC antibodies [7]. Although seizures appear more frequently in anti-LGI-1 (80%) patients than in patients positive for anti-CASPR2 (49%) [8,9] other studies have actually shown that seizure is also a common symptom in CASPR2 antibodies disease in children [10] and in adults^{8,10,11} The incidence of positive antibody patients can reach up to half of the patients [8].

Curiously, the prevalence of neuronal antibodies appears to be higher in some subtypes of epileptic syndromes [4,12,13]. Ekizoglu and colleagues evaluated the prevalence of neuronal antibodies in patients with focal-epilepsy of unknown cause and mesial temporal lobe epilepsy with hippocampal sclerosis: 16% of patients were positive for neuronal antibodies, with 4.9% of patients positive for CASPR2 specifically [12]. In temporal lobe epilepsy, the prevalence found was 5%, with antibodies. Of these, 4 patients were positive for CASPR2 [14]. Afterward, in a cohort study that included patients with late-onset epilepsy, CASPR2 was the only specific neuronal antibody found (3%) [15].

Therefore, temporal lobe epilepsy with or without hippocampus atrophy, focal epilepsy of unknown origin, epilepsy with peri-ictal autonomic disturbance and late-onset epilepsy may place anti-CASPR2 encephalitis on the differential diagnosis table [12-15]. Epileptic activity on the initial electroencephalogram (EEG) appeared only in 30% of patients with CASPR2 [8]. Consequently, it is extremely important to pay attention to clinical details that can help clarify the diagnosis.

Among those details, we highlight: patients with advanced age, presenting with a sub-acute progressive cognitive decline, or sleep disorders, as well as psychiatric complaints of recent onset, autonomic dysfunction (especially hyperhidrosis and heart rhythm abnormalities). Other red flags may be cerebellar symptoms and impairment of the peripheral nervous system, especially neuropathic pain and neuromyotonia (Table 1) [8,10,11,16]. These data advise in favor of disease with positive CASPR2 antibodies.

Clinical characteristics of CASPR2 positive patients	
Epilepsy Presentation	Neuronal antibodies seems more likely in patients presenting with focal epilepsy of unknown etiology, epilepsy with peri-ictal autonomic dysfunction and late onset epilepsy, in these scenarios CASPR2 antibodies disease should be taken in consideration of the clinical picture support it. Complex partial syndromes are the most common form of seizures in CASPR2 patients ⁸ .
Sleep Disturbances	Insomnia is the most common sleep disturbances reaching half the patients in some studies ¹¹ .
Autonomic Symptoms	Hyperhydrosis and tachycardia are the main autonomic dysfunction ¹¹ .
Cognitive Disturbances	Amnesia and behavioral occur in more than half of the patients ¹¹ .
Peripheral Nervous Systems	Peripheral nerve excitability and neuropathic pain (with burning sensation) are the core peripheral manifestations.
Cerebellar Symptoms	Not a common presentation (12%) ¹¹ but a report of episodic ataxia triggered by orthostatism and anger should be taken under consideration ¹⁶ .
Weight loss	58% of the patients have weight loss on the progression of the disease ¹¹ .
Diagnosis	77% of the patient's present with 3 or more of these core symptoms presented above against just 17% for patients positive for LGI-1 and 3% in NMDA receptor patients ¹¹ . So these combination of symptoms in a encephalitic patient should put CASPR2 antibodies testing on mind.

Table 1: The table discuss the epilepsy sub-types that appeared to have a more strong association with neuronal antibodies and core clinical features that should make CASPR2 antibodies diagnosis present on the differential.

In addition, a worrying fact in anti-CASPR2 encephalitis is that a great amount of the patients do not present changes in the magnetic resonance image; the image is normal, without registering T2 hyper-intensities [8,10,11] especially in the initial presentation [8]. That is why normal imaging does not exclude AE, including anti-CASPR2 encephalitis.

These findings are probably related to the fact that CASPR2 antibodies are of the IgG4 subclass and do not activate complement, nor do they induce internalization (common features in other AE syndromes). On the other hand, disrupt the interaction between CASPR2 and transient axonal glycoprotein-1 (TAG-1) where they make the clustering of the juxtapanode VGKC [17-19]

However, the distribution of VGKC along the axon relies on this interaction (CASPR2 and TAG-1) especially in the juxtapanodal region, which are important for the control of neural excitability [20].

The epileptogenesis activity linked to anti-CASPR2 antibodies is not completely defined, although there is evidence that these antibodies target the inhibitory neurons in the hippocampus [21] causing an increase in the VGKC and reducing the activity of these neuronal cells [19]. It is believed that this cascade of phenomena results in an increase in the triggering activity of the CA3 neurons in the hippocampus, giving rise to the seizure crisis [22]. Also, functional neuroimaging studies have already reported abnormalities in the hippocampus associated with anti-CASPR2 patients [23], whilst this has been correlated with amnesia and not with epileptic activity itself.

In conclusion, CASPR2 antibodies often present with seizures, and the primary diagnosis for these patients may be epilepsy. Therefore, a carefully clinical evaluation can help guide the screening of antibodies and the establishment of the correct treatment. Finally, further studies are needed to elucidate the pathogenesis of epilepsy associated with anti-CASPR2, and thus complement the puzzle of Unknown Etiology Seizures

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Disclosure of conflict of interest

None of the authors has any conflict of interest to disclose.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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