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Autoimmunity, Seizures, and Status Epilepticus

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Summary

The recent discovery of a category of autoimmune encephalitis associated with antibodies against neuronal cell-surface and synaptic proteins has renewed interest for autoimmune causes of epilepsy. The identification of autoimmune encephalitis has changed paradigms in the diagnosis and management of several novel and treatable syndromes that occur with seizures and status epilepticus previously attributed to viral or idiopathic etiologies. This review focuses on the novel group of autoimmune encephalitis and also discusses some classical paraneoplastic syndromes that constitute another group of autoimmune disorders that may result in seizures.

Keywords

autoimmune; encephalitis; epilepsy; seizures; status epilepticus

The autoimmune encephalitides that occur with seizures and status epilepticus can be divided into limbic and diffuse encephalitis, and may have a paraneoplastic or non-paraneoplastic etiology. Table 1 shows the most frequent autoantigens of these disorders grouped according their clinical relevance, likelihood of being paraneoplastic, location of the antigen, and response to immunotherapy (Lancaster & Dalmau, 2012).

Encephalitis and antibodies against intracellular paraneoplastic antigens

Although most of the immune responses shown in Table 1 can associate with an underlying tumor, there are some that almost always are paraneoplastic (e.g., >90% of patients have cancer). Any paraneoplastic encephalitis involving the limbic system or cerebral cortex may result in seizures and status epilepticus. The associated antibodies include, Hu, Ma2, CV2/CRMP5, and amphiphysin. While there is strong evidence that the first three immune responses are mediated by cytotoxic T-cells responses, there are studies indicating that amphiphysin antibodies may be directly pathogenic (Geis et al., 2010). Of these 4 immune responses, anti-Hu antibodies are those most frequently described with seizures, epilepsy partialis continua, and status epilepticus. The underlying tumors are small-cell lung cancer

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(all antibodies), germ-cell tumors of the testis (Ma2), and thymoma (CRMP5). Most of these disorders show limited response to immunotherapy.

Encephalitis and antibodies against cell-surface or synaptic antigens

A frequent feature of these immune responses (except for GAD antibodies) is that the autoantigens are extracellular and therefore accessible to circulating antibodies. In some patients the presence of an underlying tumor that expresses synaptic proteins, or a previous viral infection appear to be involved in triggering the immune response, but in many instances no trigger is identified. The spectrum of symptoms, frequency of associated tumors, mechanisms of disease, treatment, and outcome varies according to the target antigen. Using in vitro or in vivo models, the antibodies of all the disorders studied to date (NMDAR, AMPAR, mGluR5, LGI1) have direct structural or functional effects on the target antigen. On the other hand, it is unclear whether antibodies against GAD are able to penetrate the cell and result in neuronal dysfunction as shown in some experimental models. The poor response of anti-GAD associated seizures or encephalitis to immunotherapies directed at depleting the antibodies or antibody-producing cells, compared with the more favorable response of disorders related to cell-surface antigens, suggest that anti-GAD cytotoxic T-cell mechanisms are also pathogenically involved (Lancaster & Dalmau, 2012).

Antibodies to the NR1 subunit of the NMDAR associate with a syndrome different from limbic encephalitis, that characteristically occurs with behavioral change or psychosis and usually progresses to a decline of the level of consciousness, catatonia, dyskinesias, autonomic instability, and frequent hypoventilation (Titulaer et al., 2013). Seventy percent of the patients develop seizures and/or status epilepticus. About 40% of the patients are younger than 18 years; their clinical picture does not differ significantly from that of adults, but approximately 30% of children and teenagers present initially with seizures or status epilepticus. The combination of epileptic seizures and complex, elaborate orofacial and limb movements without EEG correlates complicates the clinical recognition of the seizures. About 50% of women older than 12 years have an underlying ovarian teratoma. Younger patients and men rarely have tumors. Despite the severity and duration of the disorder, patients often respond to immunotherapy and when appropriate tumor removal; some patients improve spontaneously. The recovery is slow and may take many months. After recovery, most patients remain free of seizures.

Antibodies to LGI1 associate with a form of limbic encephalitis that usually affects older individuals causing memory deficits and several types of seizures, including myoclonic-like or tonic seizures (Lai et al., 2010). The recognition of the seizures (named by some as facio-brachial-dystonic seizures) as an autoimmune disorder should lead to prompt immunotherapy that may prevent symptom progression to severe limbic encephalitis (Andrade et al., 2011; Irani et al., 2011). Interestingly, LGI1 is a secreted protein that forms a trans-synaptic complex that interacts with the pre-synaptic VGKC through ADAM23. LGI1 null-mice die within the first 2 weeks of life due to tonic seizures. Mutations of LGI1 result in autosomal dominant temporal lobe epilepsy, a benign condition in humans. About 60% of patients with antibodies against LGI1 have hyponatremia.

Antibodies to Caspr2 may occur in patients with Morvan's syndrome, diffuse encephalitis, and less frequently in cases of classical limbic encephalitis or neuromyotonia (Irani et al., 2010; Lancaster et al., 2011b). In patients with Morvan's syndrome the association with thymoma, seems to be more frequent than in patients with other symptoms, who rarely have tumors.

Antibodies to GABA(B) receptor associate with limbic encephalitis with early and prominent seizures (Lancaster et al., 2010). These antibodies occur in most patients with

limbic encephalitis and SCLC who are Hu antibody negative. While patients with Hu antibodies rarely have substantial responses to immunotherapy, those with GABA(B) receptor antibodies usually respond to steroids, IVIg and other immunotherapies.

Antibodies to AMPAR also associate with classical limbic encephalitis that is responsive to immunotherapy (Lai et al., 2009). As with the other cell-surface autoantigens, this disorder can occur with or without a tumor association. The tumors more frequently involved are cancer of the breast, lung and thymus. Patients with this disorder often have clinical relapses and may harbor other autoantibodies (TPO, N-type VGCC), suggesting a tendency to autoimmunity.

Antibodies to mGluR5 have been reported in a few patients with limbic encephalitis and Hodgkin's lymphoma (Ophelia syndrome) (Lancaster et al., 2011a). Although the disorder is rare, the consistency of the presence of these antibodies suggests they are the dominant etiology of this syndrome. Patients respond dramatically to treatment of the tumor and immunotherapy, such as steroids and IVIg.

Antibodies to DPPX have recently been described in a few patients with encephalitis characterized by symptoms of CNS hyperexcitability, including agitation, myoclonus, tremor and seizures (Boronat et al., 2013). At symptom presentation patients often have diarrhea or gastrointestinal dysfunction, which may be accompanied by substantial weight loss leading to suspect Whipple's disease or a paraneoplastic disorder. The disorder usually responds to steroids and other immunosuppressants with a tendency to relapse when steroids are discontinued.

Antibodies to GAD usually associate with non-paraneoplastic stiff-person syndrome and cerebellar dysfunction, but there are an increasing number of reports showing that these antibodies also associate with subtypes of limbic encephalitis and refractory epilepsy (Malter et al., 2010). The response to immunotherapy is usually poor.

Encephalitis and antibodies against antigens of unclear clinical significance

While antibodies to well-defined antigens, such as the NR1 subunit of the NMDAR, LGI1, Caspr2, AMPAR, GABA(B) receptor, mGluR5, or GAD specifically associate with a limited set of syndromes and thus are useful in diagnostic testing, the clinical significance of other antibodies is unclear. For example, most patients with Rasmussen's encephalitis do not have antibodies against GluR3 and therefore the utility of these antibodies as a diagnostic test and their potential role in the pathogenesis of the disorder are unclear. Similarly, the significance of "VGKC-complex antibodies different from LGI1 or Caspr2" is at this time uncertain; the identity and location of the antigens are unknown, these antibodies occur in association with symptoms that vary widely from patient to patient, and responses to immunotherapy are variable. A substantial number of patients with disorders currently known to be associated with relevant cell surface or synaptic proteins are misdiagnosed with Hashimoto's encephalitis due to the limited diagnostic criteria of this disorder (e.g., encephalopathy associated with TPO antibodies that respond to steroids). However, TPO antibodies are encountered in 10% of normal individuals, including children and, as shown in this review, many other disorders associated to well-defined cell surface antigens or inflammatory disorders of unknown etiology can also respond to steroids.

Common features of autoimmune encephalitis with cell-surface or synaptic antigens

Patients of any age who develop rapidly progressing symptoms presenting or accompanied by seizures or status epilepticus, usually including behavioral change and memory deficits, with CSF lymphocytic pleocytosis and/or oligoclonal bands of unclear etiology, EEG findings of encephalopathy and/or epileptic activity, should have serum and CSF studied for antibodies. About 30% of patients with anti-NMDAR encephalitis develop a characteristic EEG pattern named extreme delta brush. In some forms of encephalitis [LGI1, AMPAR, GABA(B) receptor] the MRI often shows increased T2-FLAIR signal in medial temporal lobes, but in other disorders the MRI is often normal or with mild transient cortical-subcortical changes. The diagnosis is established by demonstrating antibodies in serum and CSF, keeping in mind that sometimes antibodies are only detectable in CSF. Detection of antibodies should prompt treatment with immunotherapy, such as steroids, IVIg or plasma exchange. If these fail, the use of second line therapies, such as rituximab and cyclophosphamide are often effective. The process of recovery can be very slow, resulting in admission to hospitals and rehabilitation centers for many months. The reasons for this remain unclear, but many patients have high levels of CSF antibodies for long time, the effects of antibodies on neuronal circuitry are likely prominent, and there is evidence that for some of these disorders the antibodies are produced in the CNS by plasma cells that are long-lived and difficult to eliminate.

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Table 1

Autoantigens of encephalitis associated with seizures and status epilepticus

Syndrome	Clinical significance	Location of epitopes	Frequency of systemic tumor	Response to immunotherapy
INTRACELLULAR PARANEOPLASTIC ANTIGENS				
Hu	High	Intracellular	>90%	Infrequent
CV2/CRMP5	High	Intracellular	>90%	Infrequent
Ma2	High	Intracellular	>90%	Moderate
Amphiphysin	High	Intracellular	>90%	Poor
CELL-SURFACE OR SYNAPTIC ANTIGENS				
NMDAR (NR1)	High	Extracellular	Varies with age, gender and ethnicity	Frequent
LGII	High	Extracellular	<10%	Frequent
Caspr2	High	Extracellular	~40%	Frequent
GABA(B) receptor	High	Extracellular	70%	Frequent
AMPAR (GluR1/2)	High	Extracellular	70%	Frequent
mGluR5	High	Extracellular	>90%	Frequent
DPPX(subunit of Kv4.2 K ⁺ channel)	N/A	Extracellular	N/A	Frequent
GAD	High (may occur with cell-surface antibodies)	Intracellular	<5%	Moderate
ANTIGENS OF UNCLEAR CLINICAL SIGNIFICANCE				
AMPAR (GluR3)	Unclear	Extracellular ?	No tumor association	Infrequent
VGKC-protein complex antibodies different from LGII/Caspr2	Low	?	?	Variable
Thyroid peroxidase	Low	Intracellular	No tumor association	Frequent

CRMP5: Collapsin response mediator protein-5; GAD: glutamic acid decarboxylase; NMDAR: N-methyl-D-Aspartate receptor; LGII: leucine rich glioma inactivated protein 1; Caspr2: Contactin-associated protein-like 2; GABA(B) receptor: -Aminobutyric acid-B receptor; AMPAR: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; mGluR5: metabotropic glutamate receptor 5; DPPX: dipeptidyl-peptidase-like protein-6

N/A: not available, too early to assess significance.