EPILEPSY AND AUTOIMMUNE DISEASE: ANTI-NMDA RECEPTOR, LGI1, AND OTHER SYNAPTIC AUTOIMMUNE ENCEPHALITIS

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There is increasing recognition of immune-mediated encephalitides that result in epileptic seizures. These disorders can be divided into limbic and cortical extralimbic encephalitides and may have a paraneoplastic or non-paraneoplastic etiology. When paraneoplastic, 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. Of these 4 immune responses, the anti-Hu antibodies are those most frequently described with seizures, epilepsia partialis continua, and status epilepticus. The underlying tumors are small-cell lung cancer (all antibodies), germ-cell tumors of the testis (Ma2), and thymoma (CV2/CRMP5). With the exception of the encephalitis associated with Ma2 antibodies, in which approximately 30% of patients respond to tumor removal and immunotherapy, the other disorders are rarely treatment-responsive.

In contrast, there is an expanding group of autoimmune encephalitides that are not strictly paraneoplastic given that they may occur with or without tumor association, depending on the type of antibody. A frequent feature of these immune responses (except for GAD antibodies) is that the autoantigens are extracellular and therefore accessible to circulating antibodies. These antigens include the excitatory glutamatergic receptors (NMDA, AMPA), the inhibitory GABA(B) receptor, and the recently reported true target antigens (LGI1 and CASPR2) of antibodies previously attributed to voltage-gated potassium channels (VGKC). GAD antibodies usually associate with non-paraneoplastic stiff-person syndrome and cerebellar dysfunction, but there are increasing number of reports showing that these antibodies also occur with subtypes of limbic encephalitis and refractory epilepsy. Antibodies to the NR1 subunit of the NMDAR associate with a characteristic syndrome that presents with behavioral change or psychosis and usually progresses to a decline of the level of consciousness, catatonia, seizures, dyskinesias, autonomic instability, and frequent hypoventilation. AMPA receptor and GABA(B) receptor antibodies associate with a clinical picture of limbic encephalitis, with early and prominent seizures in the case of GABA(B) receptor antibodies. Recent reports indicate that LGI1, a secreted neuronal protein, is the target antigen of limbic encephalitis previously attributed to VGKC. Interestingly, this disorder associates with frequent seizures (~80% of the patients) along with hyponatremia. Moreover, mutations of LGI1 are the cause of autosomal dominant partial epilepsy with auditory features (ADPEAF), also called autosomal dominant lateral temporal lobe epilepsy. In contrast, CASPR2, a protein that is expressed in brain and peripheral nerve, clustering the VGKC at the juxtaparanodal regions of myelinated axons is the target antigen of encephalitis and peripheral nerve hyperexcitability that may result in Morvan's syndrome. Prompt recognition of all the disorders associated with antibodies against cell surface antigens is important because they may affect children and young adults (typical of anti-NMDAR encephalitis) and are responsive to immunotherapy and/or treatment of the tumor when appropriate. As a contrast, anti-GAD associated encephalitis is less treatment-responsive.

In summary, recent studies in the field of paraneoplastic syndomes and autoimmune encephalitides provide several clues that suggest the immune etiology of some types of epileptic disorders, including the acute presentation of symptoms, the frequent detection of CSF pleocytosis and oligoclonal bands in the context of negative viral studies, and the detection of CSF antibodies reacting with the neuropil of hippocampus and the cell surface of neurons.