NEUROPSYCHIATRY AND ENCEPHALITIS

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The term autoimmune encephalitis refers to an inflammatory disorder of the brain mediated by T-cell or B-cell immune mechanisms, involving any type of cell (neuron, astrocyte, oligodendrocyte) and triggered by tumors, viruses or unknown mechanisms. For this presentation, I will restrict the term autoimmune encephalitis to a group of antibody-associated disorders in which the targets are on the neuronal cell surface or at the synapse. There are currently 15 disorders associated with these types of antibodies (see Syllabus *"Autoimmune encephalitis - The cell surface and synaptic antibodies"*).[1] Although many of these disorders occasionally associate with psychosis and other psychiatric manifestations only a few consistently occur with these symptoms, almost always in association with other neurological manifestations.

Psychosis

Acute change of behavior, personality and frank psychosis are common presentations of any type of encephalitis, including herpes simplex encephalitis (HSE). Among the antibody-associated encephalitis the most common disease associated with psychosis is anti-NMDA receptor encephalitis. The median age of patients with this disorder is 21 years, with a wide age range (<1 year-93 years) and approximately 40% of the patients are younger than 18 years.[2] In young adults, the acute development of anxiety, agitation, insomnia, hallucinations and delusional thoughts is a common presentation.[3] In view of the fact that many patients seem to have psychosis, initial admission to psychiatric wards is common. At this stage of the disease the differential diagnosis with a primary psychiatric disorder can be difficult; the MRI is normal in about 60% of the patients and the routine CSF studies is normal in 10% (unless antibodies are investigated). In the next days or weeks after presenting with psychosis, most patients develop additional symptoms (abnormal movements, discussed below), decrease of the level of consciousness, seizures, or autonomic disturbances. The EEG is usually abnormal at disease onset, and it can be an important clue along with the study of CSF (which in ~90% of the patients show pleocytosis) to suggest an autoimmune basis of the disorder. A small number of patients with anti-NMDAR encephalitis (~4%) develop isolated or predominant psychosis or psychiatric manifestations during the initial episode of encephalitis.[2]

Psychosis as the main presentation of encephalitis has been reported in a few patients with any of the other antibodies to neuronal cell surface or synaptic proteins, such as AMPA receptor, DPPX, LGI1, or Caspr2 (see Table 1 of Syllabus *"Autoimmune encephalitis - The cell surface and synaptic antibodies"*). In these disorders the accompanying symptoms and demographic features are often different from those associated with anti-NMDAR encephalitis. For example, patients with AMPAR antibodies usually develop limbic encephalitis and 70% have a systemic cancer;[4] patients with DPPX antibodies may show psychosis usually preceded by diarrhea or gastrointestinal symptoms and followed by non-specific symptoms of CNS hyperexcitability (seizures, tremor, hyperekplexia, myoclonus);[5, 6] patients with LGI1 antibodies often develop faciobrachial dystonic seizures or hyponatremia and rarely have an underlying tumor (thymoma);[7, 8] patients with Caspr2 may present with psychosis in the context of limbic encephalitis and Morvan syndrome.[9]

Viral encephalitis such HSE may trigger autoimmune synaptic disorders (e.g., NMDAR antibodies) which in adults predominantly manifest with acute psychiatric symptoms and psychosis,[10] and in children with choreoathetosis.[11]

In very rare instances NMDAR antibodies have been identified in patients who only developed psychosis.[3, 12, 13] A substantial limitation of some of these studies is that the antibodies were identified at low titers (similar to those identified in patients without autoimmune conditions), were not investigated in the CSF, and were not confirmed with additional studies.[13]

In summary, the acute development of psychosis in patient without a past history of psychiatric disorders or without any systemic cause of the symptoms should be investigated for an infectious or autoimmune cause. Considering that many patients undergo CSF analysis to rule out an infectious process (e.g., HSE), an aliquot of CSF should also be sent for autoantibody analysis.

Schizophrenia

The association of VGKC-complex antibodies and NMDAR antibodies to schizophrenia was initially suggested in a few patients.[14] However, the characterization of the antibodies has been controversial, and the possibility of false positive serum results cannot be ruled out.[15] For example, several recent studies and the experience of the past 5 years indicate that VGKC-complex antibodies (different from LGI1 and Caspr2) have limited, if any, clinical utility.[16, 17] These antibodies can be identified in many different disorders (including disorders that are considered not autoimmune)[18] and normal subjects. Therefore, the detection of VGKC-complex antibodies in a few patients with schizophrenia is not unexpected, and the significance uncertain. It is important to keep in mind that VGKC-complex antibodies (again, different from LGI1 or Caspr2) are not visible with techniques such as tissue immunohistochemistry or cultured neurons, and therefore the targets are unknown and unlikely to reside on the neuronal cell surface.

The studies that have attempted to associate NMDAR antibodies with schizophrenia have another set of limitations. There has been little effort to clarify the type of antibodies and epitope targets in these patients. Investigators that suggested the association, indicated the presence of NMDAR antibodies in serum of 10% of the population (healthy subjects and patients with many types of disorders including schizophrenia, Parkinson, dementia, stroke, among others).[19] The CSF of schizophrenic patients has not been investigated. Given that 10% of all subjects (including normal subjects) have these antibodies, the question is why antibody-related symptoms are not more frequent if these antibodies are clinically relevant. To answer this question investigators have attributed symptoms as occurring in people who have had opening of the blood-brain-barrier (BBB) caused by trauma, even remotely at birth, or any other process that may have potentially, at some time point, disrupted the BBB.[20] However, disruption of the BBB and presence of CSF antibodies has not been shown by any of these studies. More importantly, the antibody class is usually IgA or IgM and the targets can be the GluN1 or GluN2 subunits of the NMDAR. There are no studies showing that these antibodies reach the brain and have pathogenic effects on NMDAR. Moreover, these antibodies are different from those associated with NMDAR encephalitis, which are IgG, are always present in the CSF, are directed against a well-defined extracellular epitope of GluN1 (amino acids N368/G369), and have pathogenic effects in cultured neurons and in vivo, in an animal model.[21]

Recent reviews on the theory of hypofunction of NMDAR in schizophrenia,[22, 23] and the significance of autoantibodies in psychosis and schizophrenia have recently been published.[24,25]

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