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Oral Presentation

Challenge in Diagnosis and Management of Autoimmune Encephalitis

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Abstract

The first description of an autoimmune encephalitis dates back to 1888, when Hermann Oppenheim described a patient with neurological symptoms but no underlying brain pathology (Oppenheim, 1888). The field of autoimmune encephalitides associated with antibodies targeting cell-surface antigens is rapidly expanding and new antibodies are discovered frequently. Epidemiological studies suggest that anti-NMDA receptor encephalitis may be the most common cause of autoimmune encephalitis after acute demyelinating encephalitis. Autoimmune encephalitis is a difficult clinical diagnosis due to the similarities in the clinical, imaging and laboratory findings of many forms of autoimmune and infectious encephalitis. Patients generally have impaired memory and cognition over a period of days or weeks. There may be clues to specific causes on history of physical examination, but often these specific signs are absent.

Clinical clues in the recognition of particular types of autoimmune encephalitis	
Clinical finding	Associated autoantibody disorders
Psychosis	NMDAR, AMPAR, GABA-B-R
Dystonia, chorea	NMDAR, Sydenham chorea, D2R
Hyperekplexia	GlyR
Status epilepticus	Most characteristic of GABA-B-R and GABA-A-R but NMDAR is much more common; may occur in other types as well
New onset type 1 diabetes	GAD65
Fasciobrachial dystonic seizures	LGI1
Neuromyotonia, muscle spasms, fasciculations	Caspr2
Stiff-person syndrome and/or exaggerated startle	GAD65, GlyR, Amphiphysin (with GAD65 being most common in stiff person/stiff limb and GlyR in PERM, and Amphiphysin in women with breast cancer)
CNS (myoclonus, startle, delirium) and gastrointestinal hyper-excitability	DPPX
Cranial neuropathies	Ma2, Hu, Miller-Fisher, Bickerstaff (but also infections like Sarcoidosis, Lyme, TB)
Cerebellitis	GAD65, PCA-1 (Yo), ANNA-1 (Hu), DNER (Tr), mGluR1, VGCC

Autoimmune Encephalitis Involves Several Types

The first group includes the classic paraneoplastic disorders associated with antibodies to intracellular antigens, such as anti-Hu. of diseases with different pathophysiology. The second group involves autoantibodies to extracellular epitopes of ion channels, receptors and other associated proteins, such as the NMDA receptor. Occupying an

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intermediate position are diseases with autoantibodies to intracellular synaptic proteins such as GAD65. It is unclear whether this group involves T-cell responses and/or functional effects of antibodies. final group includes other forms of autoimmune encephalitis in which precise antigens are less clearly established, such as lupus cerebritis or ADEM. The classical presentation of encephalitis consists of subacute (days to a few weeks) progressive decrease in the level of consciousness, often with fluctuations, and altered cognition. Memory, especially retention of new information, may be impaired early in the clinical course. Patients may progress to coma. Psychiatric manifestations are common early in the course of autoimmune encephalitis. Although this presentation is well known for anti-NMDAR encephalitis, anti-AMPAR and anti-GABA-B-R both may have prominent early psychiatric manifestations (Overall, anti-NMDAR encephalitis is more common and should be suspected first, especially in young adults and children, but they could each cause this presentation across a wide range of ages. Abnormal movements may be the presenting symptom in several types of autoimmune encephalitis. These may resemble dystonia or chorea, with writhing and fixed abnormal postures of the limbs. In adults with anti-NMDAR encephalitis, writhing movements of the face and limbs may be most prominent in the comatose phases of the illness. GAD65 and GlyR autoimmunity may present with stiff person syndrome (SPS) or progressive encephalomyelitis with rigidity and myoclonus A striking feature of PERM with GlyR antibodies is a pathologically exaggerated startle response Seizures are common in autoimmune encephalitis and may be a presenting symptom. Fasciobrachial dystonic seizures (FBDS) are brief seizures consisting of rapid jerks of the face and/or ipsilateral arm and shoulder.10 Seizures may be partial or associated with temporary disruptions in consciousness and may be multifocal and variable on EEG. FBDS are characteristic of LGI1 autoimmunity and may precede other symptoms of the disease by weeks or months. Patients may have hundreds of these seizures per day. These seizures may have only limited response to seizure medications but respond well to immune therapies. Cerebellitis is a distinct syndrome of ataxia of gait, limb movements, eye movements, voice, and/or swallowing. The precise mixture of symptoms varies from patient to patient. Vertigo and nystagmus are common. Cerebellitis may occur with infectious causes, but the presentation of a subacute cerebellar syndrome portends a good probability a specific autoimmune etiology and also a significant risk of tumors. Certain types of autoimmune encephalitis may precede or follow neuromuscular manifestations, particularly acquired neuromyotonia (Isaacs syndrome). Isaacs syndrome presents with muscle spasms, cramps and fasciculations due to peripheral nerve hyper-excitability. Morvan syndrome (Morvan's fibrilllary chorea) consists of peripheral nerve hyper-excitability with encephalitis and severe insomnia.

Diagnostic Approaches

Antibody Testing

Autoantibody testing is extremely important for the proper diagnosis of autoimmune encephalitis. However, the tests have complexities that require consideration, and taking certain test results as conclusive evidence of autoimmune encephalitis can be a mistake.

Imaging

Brain MRI in patients with NMDAR, AMPAR, LGI1, Caspr2, and GABA-B antibodies may be normal or show increased T2 signal, especially in the medial temporal lobes. As mentioned above, imaging abnormalities in routine MRI and FDG PET are not specific and clinical MR imaging can also return completely normal results, e.g. in NMDAR,

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DPPX or GlyR encephalitis. Advanced imaging techniques, e.g. automated volumetric analyses, quantification of signal alterations, or the application of new sequences or imaging methods, e.g. resting-state functional MRI will help to bridge the gap between clinical and radiological findings.

EEG

EEG is useful in patients with autoimmune or infectious encephalitis for excluding subclinical seizures, for prognosis, and sometimes for suggesting particular diagnoses. In patients with HSV encephalitis, EEG may predict prognosis in addition to helping exclude non-convulsive seizures; normal EEG correlates with good outcomes independent of other prognostic factors.48

Biopsy

Brain biopsy generally is not used in the diagnosis of encephalitis for several reasons.

Cancer Screening

Paraneoplastic disorders are, in general, autoimmune disorders that are triggered by tumors.

Treatment Approaches

Treatment for suspected autoimmune encephalitis is often given empirically prior to specific antibody test results. This may include steroids and/or IVIG. If a cell-surface/synaptic antibody disorder is diagnosed, initial treatments may include IVIG, plasmapheresis, and/or steroids. Steroids may be beneficial in a range of autoimmune disorders but could potentially create problems with the diagnosis of certain disorders such as CNS lymphoma. IVIG offers an important advantage of being unlikely to make infectious encephalitis worse. Plasmapheresis is also unlikely to significantly worsen infectious encephalitis. The proper diagnosis and management of autoimmune encephalitis requires an organized approach. Evaluation should begin with a detailed history and physical examination to detect clues to specific causes. A diverse range of infections should be considered, and appropriate testing should be done to exclude relevant pathogens.

Keywords: Antibody, Autoimmune, Patient

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