

Hot topics of autoimmune encephalitis

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INTRODUCTION

Within the last few years, a new group of diseases featured with cognitive impairment, seizures and behavior disorders was reported. And these diseases were commonly diagnosed as “viral encephalitis” and “sporadic encephalitis” than autoimmune encephalitis (AE) before AE had confirmed etiological. With the development of autoantibody serological tests, many patients who had been previously considered as patients with “viral encephalitis” can now be definitively diagnosed with AE. Currently, AE has become one of the hotspots in neuroimmunology. A retrospective review suggests that earlier treatment of N-methyl-D-aspartate receptor (NMDAR) antibody encephalitis in children results in better outcomes.^[1] Also, there is another study that showed that people who received immunotherapy within 40 days from onset had a better recovery than those who received immunotherapy after 40 days from onset.^[2] Therefore, early immunotherapy could improve the prognosis of AE. Also, treatment regimens vary from different types of AE. For example, anti-NMDAR (detected) encephalitis usually requires intensive immunosuppression, whereas encephalitis associated with LGI1 antibodies usually responds well to steroids alone.^[3] The lower frequency of neurological relapses is likely due to better recognition

of the disorder, earlier treatment, and increasing use of second-line immunotherapy.^[4] Early diagnosis of these disorders is, therefore, required.

DISCUSSIONS ON “A CLINICAL APPROACH TO DIAGNOSIS OF AUTOIMMUNE ENCEPHALITIS”

In a paper published in *The Lancet Neurology*, Graus et al.^[5] propose new guidelines for the diagnosis of AE. This guideline includes five diseases involving limbic encephalitis (LE), anti-NMDAR encephalitis, Bickerstaff brain stem encephalitis, acute disseminated encephalomyelitis (ADEM) and hashimoto encephalopathy. These diseases show some similar characteristics of onset and clinical features. When AE is suspected, a stepwise diagnosis should be made according to the recommended diagnostic path. This guideline classifies the diagnosis of AE into three levels: possible, probable and definite. The two former levels do not rely on the tests of auto-antibodies, while the definite diagnosis of AE generally need positive antibody result. Each level needs some supportive and exclusive points to diagnosis.



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Diagnosis of possible AE should exclude other probable diseases reasonably. Increased signal on T2-weighted fluid-attenuated inversion recovery (FLAIR) imaging in the medial aspect of the temporal lobes is an important differential diagnosis essential. Cerebrospinal fluid (CSF) analysis and characteristic clinical manifestations also count. However, some diseases are difficult to preclude due to atypical clinical manifestations or due to the lack of relevant detection methods, such as viral encephalitis.^[6-8] Whether to continue in accordance with the recommendations of diagnostic path remains to be further verified. Concerned to the imaging features of LE, the guideline emphasizes that bilateral temporal lobes involvement is one of the necessary factors for the definite diagnosis of autoimmune LE. However, it does not imply to deny the existence of LE which is just unilateral temporal lobe involved or with normal imaging.^[9,10] When the autoantibody test results are unknown, the diagnostic criteria of autoimmune LE can exclude the disease involving the limbic system as well, such as viral encephalitis, glioma, epilepsy, *etc.*, to avoid over-diagnosis.

The guideline lists anti-NMDA receptor encephalitis separately,^[11] and for the first time presents detailed probable and definite diagnostic criteria. The diagnosis is based on the specific symptoms, auxiliary examination, autoantibody detection and tumor evidence. Anti-NMDAR encephalitis is singled as an independent diagnosis may be due to the following reasons: (1) anti-NMDAR encephalitis has a characteristic manifestation other than typical LE, such as the involuntary movement of the face, speech disorders, autonomic dysfunction and central hypoventilation; (2) although the exact incidence of various types of AE cannot be calculated, anti-NMDAR is much higher than other types of AE based on current data;^[5,12] (3) there was a clear correlation between NMDAR encephalitis and teratoma; (4) the most common magnetic resonance imaging manifestations of anti-NMDAR encephalitis are abnormal non-specific signals in cortical or subcortical, and the positive rate is low. Moreover, Imaging evidence of bilateral limbic system involvement is the necessary condition of the clinical diagnosis of autoimmune LE.^[5,12] To sum up, anti-NMDAR encephalitis is currently diagnosed independently of autoimmune limbic encephalitis disease. It is noteworthy that the diagnostic criteria for anti-NMDAR encephalitis do not include near-term memory impairment in the clinical manifestations. Because it is difficult to assess memory impairment in those patients with psychiatric symptoms or in child patients.^[5] As the more common symptom of the disease,^[4] memory disorders can often be obtained by

asking history. So, near-term memory disorder could be included into the diagnostic criteria, but still needs further clinical validation.

AUTOIMMUNE ENCEPHALITIS AND OTHER NERVOUS SYSTEM DISEASE OVERLAP SYNDROME

Demyelinating disease

A recent case study of a large number of patients showed that a group of patients with anti-NMDAR antibody encephalitis have an overlap in clinical/MR manifestations with optic neuromyelitis and myelitis.^[13] In this group of patients, MR usually shows multifocal, subscapular or extensive T2/FLAIR phase abnormalities which suggests an overlap with demyelinating disease such as optic neuromyelitis. More than half of these patients suffered demyelinating disease before or after the onset of anti-NMDAR antibody encephalitis. In some patients in this group, anti-NMDAR antibody encephalitis and demyelinating disease occurred at the same time, which greatly challenges the diagnosis. Some patients with early diagnosis of ADEM, neuromyelitis optica or multiple sclerosis could appear psychiatric symptoms, faciobrachial dystonic seizures and/or autonomic dysfunction which strongly suggests a diagnosis of anti-NMDAR encephalitis.

Herpes simplex virus encephalitis (HSE)

It is reported that HSE has a recurrence rate of 25%.^[14] Some of the recurrent patients would recover after antiviral treatment. But some recurrent patients presented with new symptoms such as choreoathetosis and so on. As for them, virological examination was negative and antiviral therapy was not effective. This part of patients' serum and CSF anti-NMDAR antibody was positive.^[15] Their conditions improved after immunotherapy. Some studies have reported anti-NMDAR antibody encephalitis could occur after HSE.^[16,17] Since then, HSE recurrent patients were found other non-specific neuronal surface-mediated antibody positive in serum or CSF, suggesting that HSE infection may be one of the causes of AE.

AE combined with other antibodies

Overlap anti-neuronal antibodies in AE is rare. Anti-NMDAR encephalitis is the most common type of AE. This disease combined with other neuronal antibodies, such as anti-Aquaporin antibody, anti-myelin oligodendrocyte glycoprotein antibody is rarely reported. The proportion of anti-GABABR encephalitis with multiple antibodies appears to be higher. Höftberger *et al.*^[18] reported 20 patients with GABABR antibodies, seven of them had

overlap antibodies. Five patients with small-cell lung cancer had additional onconeural antibodies (Ri, amphiphysin, or SOX1), and 2 without tumor had GAD65 and NMDAR antibodies. In addition, AE can also overlap with other immune mediated non-nervous system autoantibodies, such as antibodies to thyroid peroxidase or GAD65.^[19]

DETECTION METHODS OF AUTOIMMUNE ENCEPHALITIS ANTIBODY

Even though the launched diagnostic criteria of AE do not depend on the detection of autoantibody, it still needs to emphasize the importance of autoantibody detection. Commonly used methods for autoantibody detection include cell-based assay (CBA), immunohistochemical staining of brain tissue, immunocytochemical staining of cultured single hippocampal neurons in rodents (only for animal experiments).^[5] CBA method is the more recognized detection method in domestic laboratory. The sensitivity and specificity of the CSF detection of CBA is 98.5% and 100%, respectively. The sensitivity and specificity of serum antibody detection of CBA were 85.5% and 98.2%.^[20,21] In clinical practice, there are also many patients that meet the autoantibody-negative AE diagnostic criteria, which may be due to the limited types of antibody that can be detected or the false negative test results can be recorded. The guidelines also recommend that patients who meet the criteria of probable AE, but do not have well characterized autoantibodies, investigation of CSF and serum for new antibodies in reference laboratories is important. And if the immunohistochemical staining was positive, even if not sure what kind of antibody, it still highly suggested of AE.

TREATMENT OF AUTOIMMUNE ENCEPHALITIS

Selecting the appropriate therapeutic time window and the appropriate drugs and drug doses of early standardized treatment of AE are particularly important. Currently, the treatment of AE is divided into first-line immunotherapy, second-line immunotherapy and tumor resection (with tumor patients). First-line immunotherapy including steroids, intravenous immunoglobulin and/or plasma exchange, combined with tumour removal, second-line immunotherapy is mainly immune inhibitors such as rituximab and/or cyclophosphamide. Currently, there is no research to compare which treatment regimen is better, but generally it is accepted to take the first-line treatment of a program or a combination of two options. If the first-line treatment is invalid, then switch to the second-

line treatment. For patients with AE associated with tumor, tumor resection should be carried out as soon as possible.^[15]

CONCLUSION

With the introduction of new diagnostic criteria for AE, the diagnosis of AE can be standardized. Early diagnosis of AE, starting immunotherapy or resection of the tumor is conducive to improving the prognosis of the disease. However, the sensitivity and specificity of the diagnostic criteria remain to be further clinical validated. For antibody-negative AE, the existence of new antibodies still needs further exploration.

Authors' contributions

Drafting/revising the manuscript, study concept or design: Y. Peng, J.W. Wang

Study supervision, intellectual contribution: J.W. Wang

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Conflicts of interest

There are no conflicts of interest.

Patient consent

There is no patient data involved.

Ethics approval

Not applicable.

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