Topic: Autoimmune neurological diseases associated with autoantibodies specific for synaptic antigens

Diagnostic algorithms in autoimmune encephalitis

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ABSTRACT

Over the past decade the discovery of novel forms of encephalitis associated with neuronal surface antibodies had changed the paradigms for diagnosing and treating disorders that were previously mischaracterized. Recognition of clinical syndromes, consistent methods of diagnosis, and early targeted immunotherapy can lead to a favorable outcome in diseases that may be associated with significant disability or death if left untreated. Here the conditions associated with neuronal surface antibodies are briefly reviewed, some general aspects of these syndromes are considered and guidelines that could help in the recognition of these disorders are suggested. Furthermore, a diagnostic algorithm to detect and characterize neuronal cell surface autoantibodies is suggested and some of the caveats of serum testing are outlined. Future directions will involve the identification of novel autoantibodies, the standardization of methods to detect and characterize them, as well as evaluation of the most efficacious therapeutic strategies in patients with established diagnosis of autoimmune encephalitis.

Key words: Autoimmune encephalitis; neuronal surface autoantibodies; paraneoplastic syndromes

INTRODUCTION

Anti-neuronal autoimmune encephalitis (AIE) is a complex syndrome resulting from a self-directed response to neuronal antigens. These disorders can be associated with immunoglobulinG (IgG) autoantibodies specific to intracellular neuronal antigens (e.g. Hu, Yo, Ri) and to neuronal surface or synaptic antigens [e.g. N-methyl-d-aspartate receptor (NMDAR), amino-3-hydroxy-5-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), gamma-aminobutyric acid B GABA(B)R]. The first group of AIE typically occurs in the setting of cancer, resulting from an autoimmune reaction against intracellular antigens co-expressed by the cancer and the central nervous system (CNS). The autoantibodies are thought to be not pathogenic but an epiphenomenon, and patients show limited or no response to immunotherapy. Compelling evidence suggests that in the second group of AIE, the binding of the autoantibodies to extracellular antigens directly causes neuronal dysfunction, which can be reversed by antibody-depleting therapies,[1] such as plasmapheresis and intravenous immunoglobulins. In contrast to classical paraneoplastic syndromes, AIE associated with synaptic autoantibodies is often not paraneoplastic and can affect patients of all ages, including children and young adults.[2]

Over the past ten years, the characterization of encephalitis associated with neuronal surface autoantibodies has changed our perspective on their diagnosis and treatment. In these disorders, the autoantibodies are associated with a characteristic phenotype and their detection contributes to the neurological diagnosis. As early treatment speeds recovery, reduces disability and decreases relapses, it is important that the immune pathogenesis of these disorders is promptly recognized.

In this paper a diagnostical gorithm is proposed for a clinical approach to AIE and screening of the associated autoantibodies.

DIAGNOSTIC APPROACH

The diagnosis of AIE should be suspected in patients developing subacute cognitive impairment, psychiatric disturbances, movement disorders or seizures. The diagnosis will be further support by the evidence of CNS inflammation from cerebrospinal fluid (CSF) analysis or magnetic resonance imaging (MRI). Autoantibody testing has a critical role in confirming the diagnosis and in leading

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the search for the presence of an underlying neoplasm [Figure 1].

Clinical presentation

AIE is usually a multistage process. Most of these disorders have a rapid course, developing over a few days or weeks, with behavioral and memory alteration, decreased level of consciousness and seizures. This clinical picture is typical of limbic encephalitis (LE). However, the severity and predominance of some symptoms over others may help the clinician in the diagnosis of different AIE subtypes and may lead the search for specific antibodies [Table 1]. For example, both GABA(B)R and gamma-aminobutyric acid A [GABA(A) R] antibodies are typically associated with refractory seizures,[4,5] patients with leucine-rich glioma-inactivated 1 (LGI1) autoantibodies can present with facio-brachial dystonic seizuresand hyponatremia caused by syndrome of inappropriate antidiuresis (SIAD),[6] while AMPAR-antibodies are frequently found in patients with LE or psychosis.[7] In anti-NMDAR encephalitis, psychiatric disturbances are the most frequent symptoms of onset in women,[8] while seizures are prominent in men.[9]

The detection and characterization of IgLON family member 5 antibodies represents an interesting link between autoimmunity and neurodegeneration. These autoantibodies were found to be associated with sleep disturbances, cognitive impairment, the movement disorder and brainstem symptoms with a chronic progressive course.[10]

In some cases, symptoms may extend beyond CNS: AIE associated with autoantibodies to dipeptidyl-peptidase-like protein-6 may present with diarrhea poorly responsive to symptomatic treatment and significant weight loss that can precede neurological symptoms including brainstem and

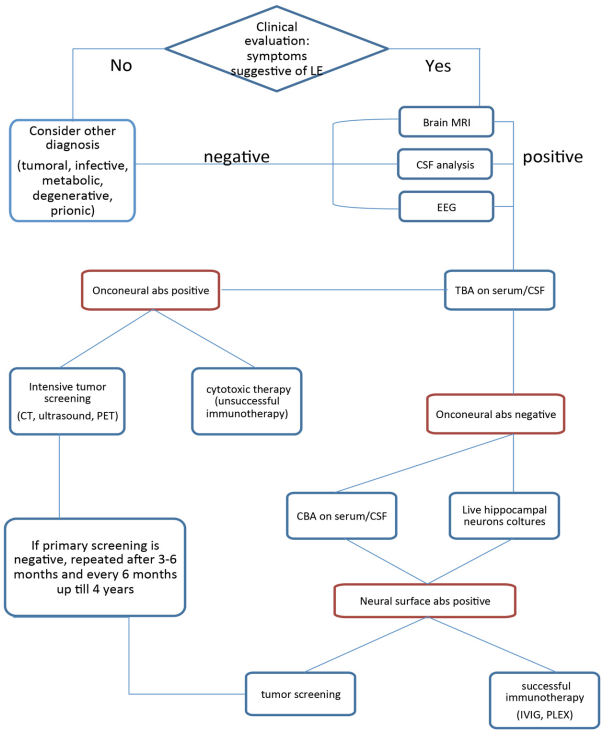

Figure 1: Flowchart summarizing a preferred diagnostic approach to AIE. AIE: Anti-neuronal autoimmune encephalitis; CSF: cerebrospinal fluid; CBA: cell-based assay; EEG: electroencephalogram; TBA: tissue-based assays; CT: computed tomography; PET: positron emission tomography; MRI: magnetic resonance imaging; IVIG: intravenous immunoglobulin; PLEX: plasmapheresis

psychiatric dysfunction.[11]

Ancillary tests

At presentation, about 80% of patients with AIE have a mild-to-moderate CSF lymphocytic pleocytosis (usually < 100 white blood cells/L), 30% have a mild-to-moderate increase inprotein concentration, and 50-60% have oligoclonal bands.[12] In contrast to most autoimmune encephalitides, encephalitis with LGI1-IgGusually occurs with normal or

Table 1: Neuronal surface autoantibodies, associated tumors and clinical syndromes

Antigen	Tumor	Clinical symptoms	Clinical clues
NMDAR	Ovarian teratoma (58%) < 18 years old	Memory impairment, psychosis (mainly in women), seizures (mainly in men), central hypoventilation	Orobuccal dyskinesia; dysautonomia
LGI1	Thymoma (< 10%)	LE	Hyponatremia; faciobrachial dystonic seizures
CASPR2	Thymoma (38%)	Encephalitis/Morvansynd/ neuromyotonia	Peripheral nerve hyperexcitability; neuropathic pain
AMPAR	SCLC, breast, thymoma (60-70%)	LE, psychosis	
GABA(B) R	SCLC (50%)	LE, ataxia	Refractory seizures
GABA(A) R	-	Status epilepticus, seizures, LE	Refractory seizures
mGluR1	Hodgkin and non Hodgkin lymphoma (e.g. cutaneus lymphoma); prostate adenocarcinoma[3]	Cerebell arataxia	
mGluR5	M. Hodgkin	Ophelia syndrome	Memory impairment
DPPX (Kv4.1)	Follicular B cell, lymphoma, CLL	Hallucinations, agitation, myoclonus, tremor, SPS	Diarrhea
IgLON5	-	Brain stem dysfunction, LE	Non-REM and REM-sleep disorder
GlyR	Thymoma	SPS, progressive encephalitis	
Dopamine 2R	-	Basal ganglia encephalitis, Sydenham Chorea	

NMDAR: N-methyl-d-aspartate receptor; LGI1: leucine-rich glioma-inactivated 1; CASPR2:contactin-associated protein-like 2; AMPAR: amino-3-hydroxy-5-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; GABA A/B R: gamma-aminobutyric acid A/B receptor; mGluR1/5: metabotropic glutamate receptor type 1/5; DPPX: dipeptidyl-peptidase-like protein-6; GlyR: Glycine receptor; CLL: chronic lymphatic leukemia; SCLC: small cell lung cancer; LE: limbic encephalitis; SPS: stiff-person syndrome; IgLON5: IgLON family member 5

minimal CSF findings.[13]

The electroencephalogram (EEG) is almost always abnormal in all types of AIE, showing focal or diffuse slow activity that can be associated with focal or multifocal epileptic discharges. Except for a pattern referred to as extreme delta brush, that may occur in patients with anti-NMDAR encephalitis,[14] there are no pathognomonic EEG abnormalities for any AIE subtypes.

MRI of the brain is often diagnostic in patients with LE, usually showing increased Fluid Attenuated Inversion Recovery/T2-weighted (FLAIR/T2) signal involving one or both temporal lobes, without contrast enhancement. Similar findings can, however, occur in patients with herpes simplex encephalitis or medial temporal lobe seizures. In NMDAR encephalitis brain MRI is normal in up to 66% of cases, while the remaining patients may have unspecific cortical or subcortical FLAIR/T2 abnormalities, sometimes involving the posterior fossa or medial temporal regions, often with small areas of demyelination, and more rarely with extensive demyelinating abnormalities.[15]

In patients with GABA(A)R antibodies, brain MRI often shows multifocal cortical-subcortical FLAIR abnormalities.[16]

Detection of autoantibodies

Several techniques are available for intracellular and synaptic antibody detection, for example, tissue-based assays (TBA; in-house or commercially available), cell-based assay (CBA; in-house or commercially available), indirect immunofluorescence on live hippocampal or cortical neurons (in-house) and immunoprecipitation (IP; in-house). In TBA, antibodies in patient serum or CSF are detected by indirect immunofluorescence on a substrate of mouse or rat brain sections. TBA is an excellent screening method, as the antibody target antigen can be suspected from the staining pattern (e.g. neuropil), although it must be confirmed by more specific techniques [Figure 2A]. As regards the detection of onconeural antibodies (e.g. Hu, Ma2, Ri, amphiphysin), commercial immunoblots with recombinant proteins for the most common autoantibodies are widely available. On the other hand, the gold standard for neuronal surface autoantibody detection is CBA, in which cells (e.g. human embryonic kidney 293 cells) expressing the appropriate antigens are incubated with patients' serum/CSF, and antibodies are identified by indirect immunofluorescence [Figure 2C]. This is a highly sensitive technique, but it is time consuming and requires specific facilities and expertise.

Indirect immunofluorescence on live hippocampal or cortical murine neurons is used as a screening method, in some laboratories, for the detection of antibodies binding neuronal plasma membrane proteins [Figure 2B].

The most reliable method of detecting antibodies specific for neuronal plasma membrane antigens involves using a combination of TBA and indirect immunofluorescence on live neuronal cultures as screening following by confirmatory CBA.

Caveats in the diagnosis

Standardized methods of antibody testing are critical to ensure the correct diagnosis of AIE. However there are few studies, mainly in anti-NMDAR encephalitis,[17-19] comparing the sensitivity and specificity of different techniques in serum and CSF samples from patients with AIE. For example, Gresa-Arribas *et al.*[20] examined paired serum

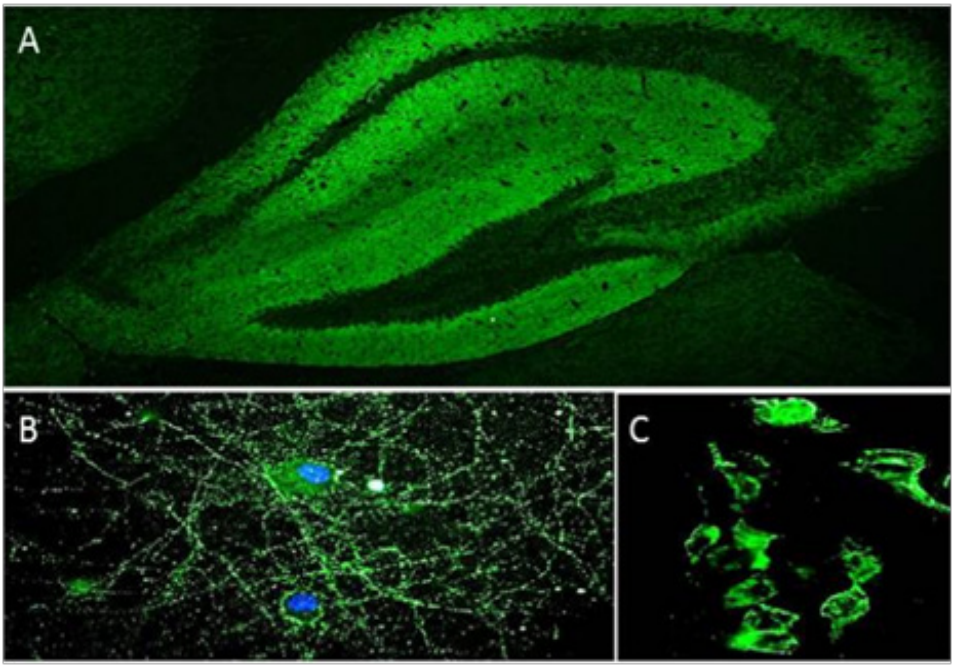

Figure 2: IgG in the CSF from a patient with anti-NMDAR encephalitis bind to the neuropil of the mouse hippocampus (A), to the cell-surface of live, non-permeabilized mouse hippocampal neurons (B) and to the plasma membrane of HEK293 cells expressing NMDAR (C). anti-NMDAR: anti-N-methyl-d-aspartate receptor