Chapter 10: Autoimmune encephalitis

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1 Introduction

Autoimmune encephalitis (AIE) is an encephalopathy syndrome that may be associated with the presence of antibodies. These antibodies can be directed against intracellular proteins (classic paraneoplastic encephalitis syndromes) or extracellular neuronal proteins (classic AIE) (Figure 1).

Figure 1 Classification of encephalitides

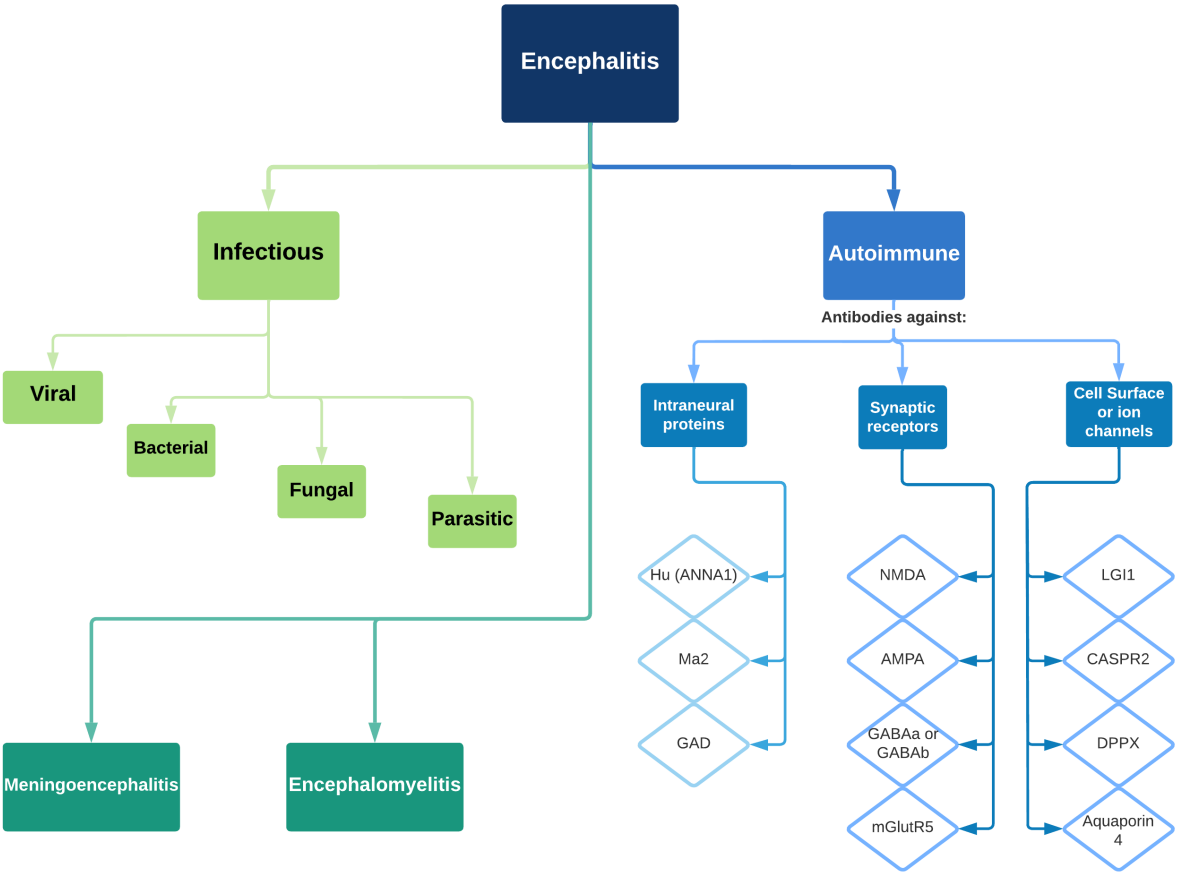


Fig 1. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CASPR2, contactin-associated protein-like 2; DPPX, dipeptidyl-peptidase-like protein-6; GABA, gamma-aminobutyric acid; GAD, glutamic acid decarboxylase; DR2, dopamine 2 receptor; LGI1, leucine-rich, glioma-inactivated 1; mGluR5, metabotropic glutamate receptor 5; NMDA, N-methyl-D-aspartic.

2 Paraneoplastic encephalitis

As indicated by the name, these syndromes are usually related to cancer. The antibodies target intracellular proteins in paraneoplastic encephalitis and aren't pathogenic but useful biomarkers of a cytotoxic T-cell mediated process. That is, these antibodies likely arise due to the T-cell-driven damage directed at the intracellular molecules, but the exact pathogenic pathways for the development of these antibodies and the associated immune response are

not yet clearly understood. In addition, the response to immunosuppressive therapy is limited.

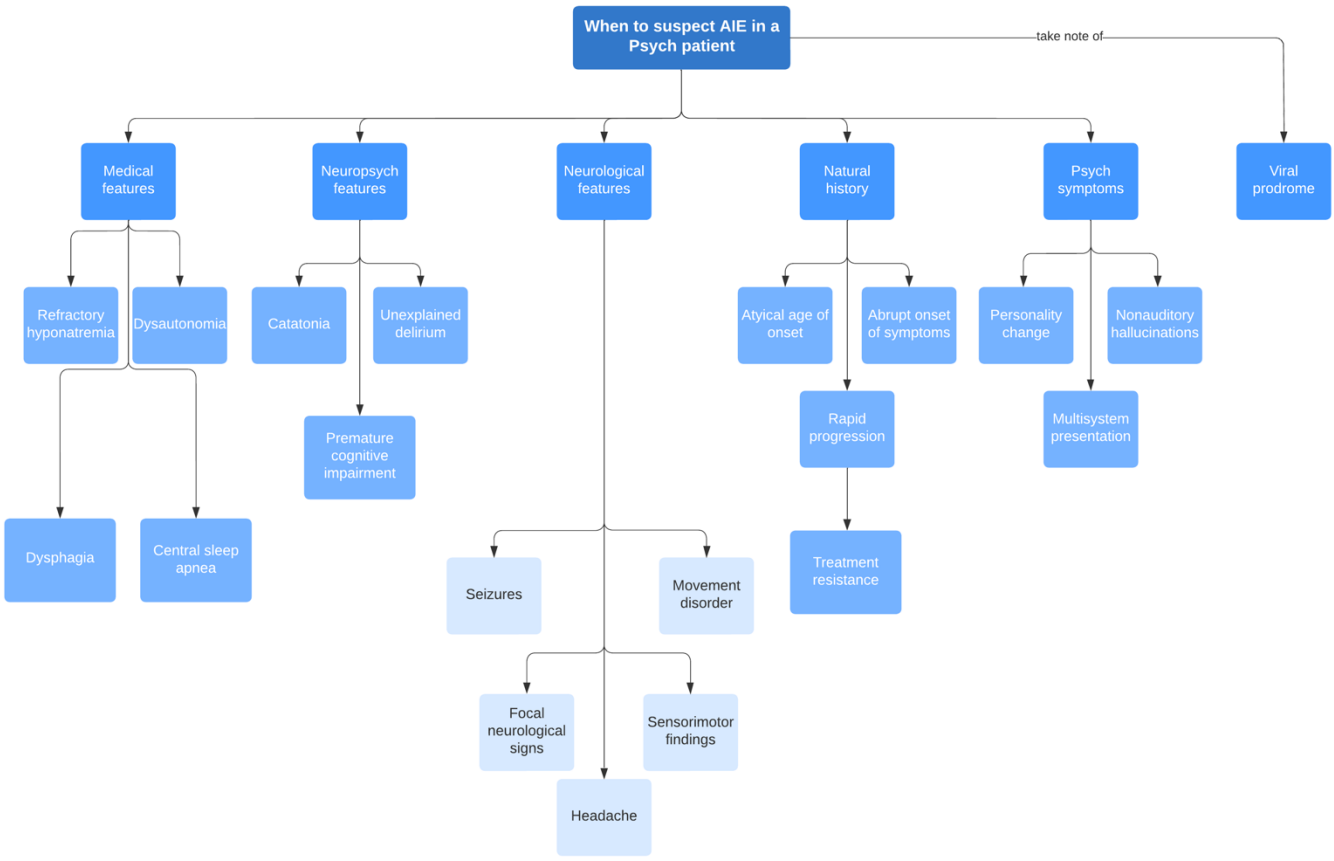
3 Autoimmune encephalitis (AIE)

In AIE, antibodies are directed against neuronal cell surface receptors or synaptic proteins. These antibodies are pathogenic, the presence of a tumour is variable, and most patients respond to immunotherapy and make good recoveries. However, in AIE, the neuronal damage is propagated by the antibodies. For instance, the antibodies can bind to the receptor leading to internalization of this receptor, reducing its functionality (e.g., NMDA-R, AMPA-R), or antibodies can directly inhibit the receptor (e.g., GABA-R), or these antibodies can displace the receptor from its complex (e.g., LGI1).

4 Clinical manifestations

AIE commonly presents with psychiatric symptoms with or without neurological features (see Figure 2 for red flags). The psychiatric features are often acute and severe, obscuring the accompanying physical symptoms and leading to patients presenting to psychiatric services initially. Consequently, this may delay the diagnosis of autoimmune encephalitis, and there is often a poor response to psychotropic medication alone.

Figure 2: Red flags in a psychiatric patient



Autoimmune encephalitis (AIE) diagnosis

The definite diagnosis of AIE requires the detection of an antibody directed against extracellular neuronal proteins. It can take up to two weeks or more to get the antibody results in clinical practice. However, evidence shows that early treatment leads to better outcomes. Therefore, treatment should be initiated with a diagnosis of a probable AIE while awaiting confirmatory results (see Figure 3). A patient with new-onset encephalitis is regarded to have probable AIE if they have a subacute onset of short-term or working memory deficits or altered mental status or psychiatric symptoms with at least a focal central nervous system (CNS) finding or unexplained seizures, or pleocytosis on cerebrospinal fluid (CSF), or magnetic resonance imaging (MRI) findings suggestive of encephalitis, and a reasonable exclusion of alternate causes (see Figure 4 and Figure 5).

2.1. N-methyl d-aspartate receptor (NMDA-R) encephalitis

NMDA-R encephalitis is most common in young and female patients. The symptoms typically present in stages:

- Initially, patients have a virus-like prodrome (headache, fever, and lethargy).
- Within 2-weeks, patients develop progressive behavioural problems, short-term memory deficits (anterograde amnesia), confusion, and psychosis.
- Subsequently, increasing severity of language deficits, seizures, and abnormal movements. Eventually, global encephalopathy and autonomic dysfunction (hyperthermia, unstable BP, or cardiac arrhythmias demonstrating brainstem involvement) develop.

A tumour is usually found in a third of patients, and ovarian teratoma is the most common. CSF often shows pleocytosis (lymphocytic), increased protein, oligoclonal bands, and detection of NMDA-R antibodies. MRI brain is usually normal but can show hyperintensities in the temporal lobes and less in the cerebral cortex or brainstem. Immunotherapy (intravenous immunoglobulin, immunosuppressive therapy, or plasmapheresis) and tumour resection is highly effective in most cases. Full recovery with treatment is expected but may take up to 18 months, with language and memory deficits the last to recover.

Figure 3: Clinical approach to possible encephalitis

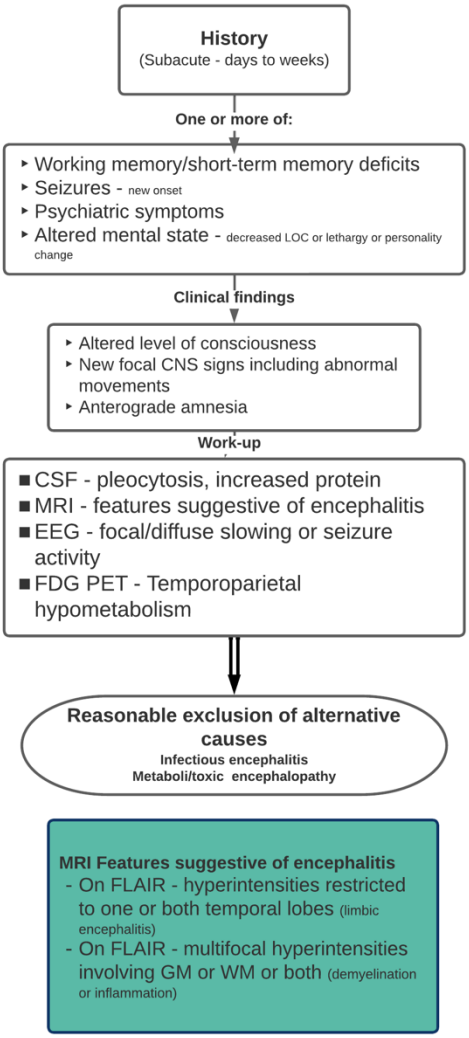


Fig 3: CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalogram; FDG PET, fluorodeoxyglucose positron emission tomography; FLAIR, fluid-attenuated inversion recovery; GM, grey matter; LOC, level of consciousness; MRI, magnetic resonance imaging; WM, white matter

Figure 4: Diagnostic pearls in autoimmune encephalitis (AIE)

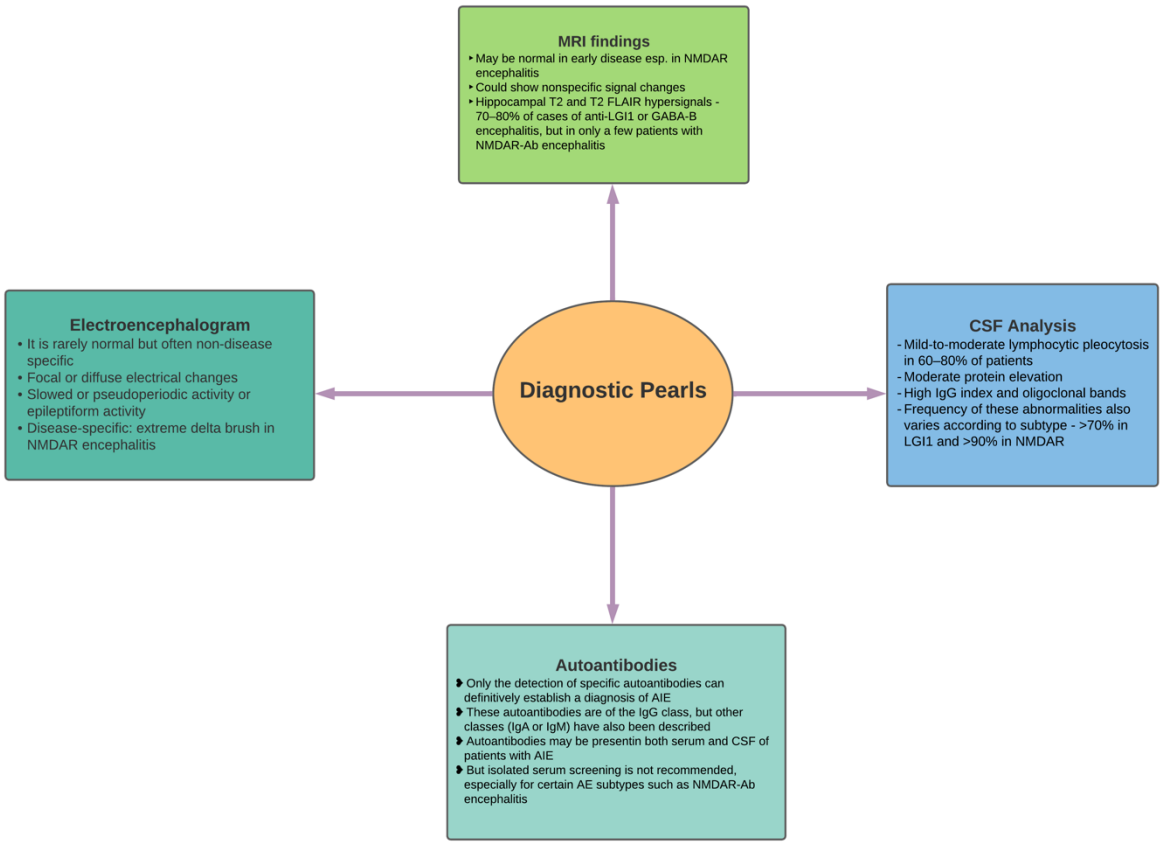


Fig 4. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery; GABA, gamma-aminobutyric acid; LGI1, leucine-rich, glioma-inactivated 1; MRI, magnetic resonance imaging; NMDA, N-methyl-D-aspartic

2.2. Voltage-gated potassium channel (VGKC) antibodies

VGKC-antibody encephalitis comprises antibodies targeting at least three antigens: leucine-rich glioma-inactivated protein 1 (LGI1), contactin-associated protein-like 2 (CASPR2), and contactin-2 (the clinical significance of this antibody remains uncertain).

2.2.1 Leucine-rich glioma-inactivated protein 1 (LGI1) antibody encephalitis

LGI1 is much more common in adult males in their 4-5th decade and is less associated with a tumour. It has a much slower and more insidious onset. Features of limbic encephalitis are common, such as cognitive impairment, seizures, and psychiatric disorders. In addition, this disease is also typically associated with faciobrachial dystonic seizures (FBDS) and refractory hyponatremia. The CSF is often normal or shows a minimally inflammatory picture and detection of LGI1 antibodies. The MRI can be unremarkable, but T2/FLAIR high signals in the temporal lobes may be present. The EEG usually shows focal or diffuse slowing and

may also show epileptiform activity. The response to immunotherapy is much greater than in other AIEs.

2.2.2 Anti- contactin-associated protein-like 2 (CASPR2) encephalitis

CASPR2 antibody encephalitis is commoner in adult males in their 5-6th decade and is less associated with cancer. Anti-CASPR2 antibodies may cause limbic encephalitis, though less commonly than anti-LGI1 antibodies. They typically cause neuromyotonia that presents as muscle hyperexcitability, with fasciculations appearing as a “bag of worms” rippling under the skin. Also, they can cause the broader Morvan syndrome (neuromyotonia, insomnia, dysautonomia, and delirium).

5 Hashimoto encephalopathy

Hashimoto encephalopathy (HE), also known as steroid-responsive encephalopathy, is associated with autoimmune thyroiditis and presents with encephalopathy and elevation in antithyroid antibodies. HE is much more common in women in their 5-6th decade. The exact underlying pathogenesis of HE remains unknown. Clinical features include psychiatric symptoms, memory difficulties, stroke-like episodes, and neurological symptoms such as seizures, ataxia, and myoclonus. There are two recognizable clinical subtypes: episodic with stroke-like symptoms that are relapsing and remitting, and progressive subtype with insidious onset and prominent cognitive deficits. Antithyroid antibodies, including anti-peroxidase antibodies (most detected) and antithyroglobulin antibodies, are detected both in the serum and CSF in most cases. However, the titre of the antibodies does not correlate with clinical severity, and levels may remain elevated after recovery. Laboratory results could also reveal hypothyroidism, euthyroid, or hyperthyroidism. Most patients have a normal MRI brain, and a common finding on EEG is mild to severe generalized slowing. Most patients show complete recovery with high-dose steroid therapy, and early intervention leads to better outcomes.

6 Treatment and outcomes of Autoimmune encephalitis (AIE)

The treatment involves using immunotherapies to reduce antibody production and treating associated tumours if present.

First-line therapies (either of the following):

- High dose steroids
- Immunoglobulins
- Intravenous plasmapheresis

Second-line therapies

- Cyclophosphamide
- Rituximab

- Mycophenolate mofetil

Early initiation of therapy is crucial and is associated with reduced mortality and improved functional outcomes. Symptomatic psychiatric treatment is often necessary. However, patients with AIE might have increased sensitivity to neuroleptic treatment. Recovery from AIE is often remarkable, such that even comatose patients can return to their premorbid baseline level of functioning. However, cognitive dysfunction can persist for years after the acute illness, even in those who reported good recovery.

Figure 5: Encephalitis work-up mind map

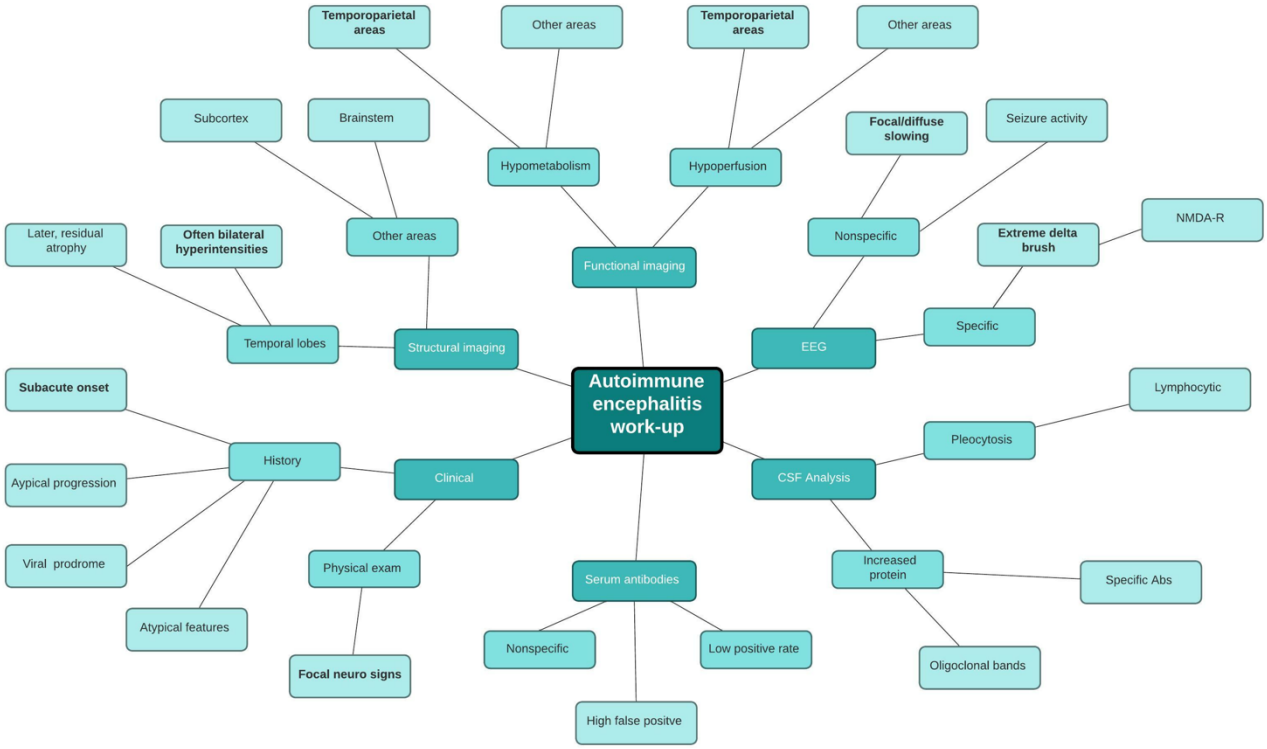


Fig 5: Abs, antibodies; CSF, cerebrospinal fluid; EEG, electroencephalogram; NMDA, N-methyl-D-aspartic

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