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Autoimmune Encephalitis: A Literature Review

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Abstract

Autoimmune encephalitis (AIE) defines brain inflammation caused by a misdirected immune response against self-antigens expressed in the central nervous system. AIE encompasses a group of non-infectious immune-mediated inflammatory disorders of the brain parenchyma often involving the cortical or deep gray matter with or without involvement of the white matter, meninges, or the spinal cord. Suggested mechanisms that may trigger AIE include tumors (paraneoplastic), infections (para-infectious), or it may be cryptogenic. This study represents a review of the common forms of AIE, exploring their causes, diagnostic approaches, and management strategies. The previous and ongoing investigations in this field have been driven by the identification of several pathogenic autoantibodies that cause polysymptomatic neuropsychiatric and neurological diseases. AIE comprises a heterogeneous group of disorders that are at least as common as infectious causes of encephalitis. Early treatment is associated with better prognosis and is crucial for the prevention of severe complications. The underlying mechanisms for activation and autoimmune response in the CNS are still unclear. Further investigations are needed to better explain how immune mechanisms affect nervous system functions.

Introduction

Autoimmune encephalitis (AIE) refers to inflammation of the brain that occurs when the immune system mistakenly targets self-antigens found in the central nervous system. AIE comprises a group of non-infectious immune-mediated inflammatory disorders of the brain parenchyma often involving the cortical or deep gray matter with or without involvement of the white matter, meninges, or the spinal cord [1], [2]. It is estimated that 20% of all encephalitis cases in northern Europe are immune-mediated [1], [3]. It comprises a heterogeneous group of disorders that are at least as common as infectious causes of encephalitis. Suggested mechanisms that may trigger AIE include tumors (paraneoplastic), infections (para-infectious), or it may be cryptogenic [1]. The California Encephalitis Project found that anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis occurred in 47% of patients under 30 years of age [3]. The previous and ongoing investigations in this field have been driven by the identification of several pathogenic autoantibodies that underlie a range of polysymptomatic neuropsychiatric and neurological diseases. AIE is typically an acute or subacute onset that may become chronic later [1]. There are a variety of clinical manifestations including behavioral and psychiatric symptoms, movement disorders, seizures, and autonomic disturbances. Early identification and treatment can enhance patient outcomes and facilitate prompt diagnosis of an underlying associated tumor.

The original description of AIE was based on paraneoplastic conditions related to antibodies against intracellular onconeural antigens such as ANNA-1/anti-Hu [4]. These "classical" antibodies are non-pathogenic but represent markers of T-cell-mediated immunity against the neoplasm with secondary response against the nervous system. Most of the surface antibodies have been shown to

be likely pathogenic and are thought to mediate more immunotherapy-responsive forms of AIE and have less association with tumors.

In recent years, an increasing number of antibodies targeting neuronal surface or synaptic antigens has been recognized such as N-methyl D-aspartate receptor (NMDAR) antibody and leucine-rich glioma-inactivated (LGI1) antibody [1]. Specific types of encephalitis can occur in the setting of antibodies against astrocytes, (e.g., anti-aquaporin-4 [AQP4] diencephalic encephalitis) or oligodendrocytes (e.g., anti-myelin oligodendrocyte glycoprotein [MOG] brainstem encephalitis) or anti-glial fibrillary acidic protein (GFAP).

In addition, some AIE patients do not have any identifiable antibodies (seronegative) representing a disease category with novel, yet-to-be-identified antibodies or T-cell mediated disease.

This study represents a review of common forms and causes of AIE and discussion of the diagnostic approach and management.

The most useful is the practical classification concepts in AIE:

Anatomical classification

Cortical/subcortical, limbic, diencephalic, striatal, cerebellar, brainstem, encephalomyelitis, meningoencephalitis, and combined.

Etiological classification

Idiopathic, paraneoplastic, post-infectious, iatrogenic (e.g., in the setting of immune checkpoint inhibitors or other immune-modulating agents).

Serological classification

Antibodies to surface antigens and other antigens with high clinical relevance (e.g., GFAP, NMDAR, LGI1, AMPAR, contactin-associated protein-like 2 [CASPR2], dipeptidyl-peptidase-like protein 6 [DPPX], GABAR A/B, AQP4, glycine receptor, MOG), antibodies to surface antigens with low clinical relevance (e.g. VGCC, VGKC), antibodies to intracellular antigens (classical onconeural antibodies), seronegative AIE.

In most cases of AIE, there is a widespread immune reaction that affects the brain, spinal cord, peripheral nervous system, and meninges, leading to a poly-syndromic presentation that varies based on the location and extent of inflammation [4].

There are several clinical-anatomical syndrome categories in AIE (Table 1).

Table 1: Clinical-anatomical syndrome categories in AIE

AIE category	Related to
Cortical/subcortical encephalitis	PCA-2 (MAP1b), NMDAR, GABA A/B R, DPPX, MOG antibodies. The most common presentation is cognitive and seizure presentation
Limbic encephalitis	The Hu, CRMP5/CV2, Ma2, NMDAR, AMPAR, LGI1, CASPR2, GAD65, GABABR, DPPX, mGluR5, AK5, neurexin-3α antibodies. The most common presentation is cognitive, psychiatric, and epileptic presentation
Striatal encephalitis	CRMP5/CV2, DR2, LGI1, PD10A, NMDAR, antibodies. The most common is movement disorder presentation
Diencephalic encephalitis	Ma 1–2, AQP4, DPPX, IgLON5 antibodies. The most common is sleep disorder presentation and autonomic presentation
Brainstem encephalitis	Ri, IgLON5, Ma 1–2, DPPX, KLHL11, MOG, AQP4, and GQ1b antibodies. The most common presentation is craniobulbar presentation, movement disorder presentation, and cognitive presentation.
Cerebellitis or cerebellar degeneration	Hu, VGCC, CASPR2, Ri, KLHL11, Yo, NIF, Tr, mGluR1, GAD65 antibodies. The most common presentation is ataxic presentation.
Meningoencephalitis	It can be seronegative AIE or linked to GFAP antibody. The most common presentation is meningeal presentation, seizure presentation, cognitive presentation
Encephalomyelitis	Amphyphysin, GAD65, PCA-2 (MAP1B), glycine receptor, GABA A/B R, MOG, CRMP5/CV2, DPPX, AQP4, antibodies. The most common presentation is spinal presentation, movement disorder presentation including PERM and SPS, opticospinal presentation
Autonomic neuropathy/ ganglionopathy	Hu, anti-ganglionic AchR, CRMP5 antibodies. The most common is autonomic presentation.
Neuropathy/ neuronopathy	NIF155, Hu, amphiphysin, PCA-2 (MAP1B), CONTACTIN1, CRMP5, CASPR1, CASPR2 antibodies. The most common is sensorimotor and ataxic presentation.
Neuromuscular junction dysfunction	AchR, VGCC antibodies. The most common is myasthenic presentation
Myopathy	Striational antibodies. The most common is motor presentation

NMDAR: N-Methyl D-aspartate receptor, LGI1: Leucine-rich glioma inactivated, AQP4: Anti-aquaporin-4, MOG: Myelin oligodendrocyte glycoprotein, GFAP: Glial fibrillary acidic protein, CASPR2: Contactin-associated protein-like 2, DPPX: Dipeptidyl-peptidase-like protein 6, GAD65: Glutamic acid decarboxylase 65.

Diagnostic Approach

The first and most important step in AIE diagnosis is taking a detailed history and clinical examination. AIE is usually with acute or subacute onset [1]. Chronic presentations are usually seen in CASPR2, LGI1, DPPX, glutamic acid decarboxylase 65-antibody encephalitis [5]. A recurrent course may point toward an autoimmune etiology. Insufficient treatment or rapid interruption of the immunotherapy often results with AIE relapses. In hyperacute presentations, vascular etiology should be considered. Neurodegenerative disease or other etiologies should be considered in chronic presentations. Idiopathic AIE is usually with monophasic course, while paraneoplastic AIE is usually with progressive course.

AIE may be triggered by certain immune-modulating therapies such as TNFα inhibitors and immune-checkpoint inhibitors (ICIs) or by herpes simplex virus encephalitis [1].

In most cases, the initially taken patient history and clinical examination are followed by brain imaging and cerebrospinal fluid (CSF) analysis.

The first diagnostic step is to confirm multifocal or focal brain pathology. Magnetic resonance imaging (MRI) is the most common diagnostic tool for that. Electroencephalogram is used as a diagnostic tool in MRI-negative cases or if the patient is encephalopathic or having seizures. In cases with uncertain diagnosis

and MRI-negative cases, PET, positron emission tomography is used as a diagnostic tool. The second step in diagnosis involves conducting blood tests to detect serum neuronal antibodies, as well as a lumbar puncture. Cerebrospinal fluid should be tested for infections, inflammatory markers (IgG index and oligoclonal bands), and in some cases cytology. The second diagnostic step tools are used to rule out competing possibilities and to confirm inflammatory etiology: If the diagnosis remains uncertain after the initial two diagnostic steps, a brain biopsy may be utilized as a diagnostic tool in select cases to confirm the underlying cause and guide therapeutic decision-making. The third diagnostic step is to perform a screening for potentially associated neoplasm. In general, computed tomography is often the first tool used for neoplasm screening, followed by additional screening modalities if necessary until a neoplasm is detected. A targeted screening approach could be implemented (e.g., if the clinical picture is suggestive of anti-NMDAR encephalitis pelvic ultrasound and further diagnostic steps are used), if the clinical picture is highly suggestive of a specific neoplasm.

Treatment and Prognosis

The 2016 AIE clinical criteria and several retrospective studies emphasize the importance of starting immunotherapy once infectious etiologies are excluded based on CSF results (cell count, viral PCR, glucose, Gram stain) and when AIE is highly suspected. The results of those studies have shown that early and aggressive immunotherapy is associated with better outcomes in AIE patients and that the delay of immunotherapy until AIE is confirmed by a positive antibody is potentially hazardous and impractical [1], [6]. Titulaer *et al*. have investigated the long-term outcome in patients with anti-NMDA receptor encephalitis by analyzing the treatment and prognostic factors. Between January 01, 2007, and January 01, 2012, Titulaer *et al*., in a multi-institutional observational cohort study, analyzed the presence of NMDAR antibodies in CSF or in serum samples of patients with encephalitis. 577 subjects who tested positive for NMDAR antibodies have been included; median age of the study subjects was 21 years, and overall age range was from 8 months to 85 years. 211 of the patients were children, younger than 18 years. Study subjects were assessed by use of the modified Rankin scale at 6 time points: Symptom onset and at months 4, 8, 12, 18, and 24. Treatment included first-line immunotherapy (steroids, intravenous immunoglobulin, and plasmapheresis), second-line immunotherapy (rituximab and cyclophosphamide), and tumor removal. Most patients with anti-NMDAR encephalitis respond to immunotherapy. Second-line immunotherapy is usually effective when first-line treatments fail. In this cohort, the recovery of some patients took up to 18 months [6].

There are no robust clinical trials comparing the acute treatment of AIE with different modalities of immunotherapy; therefore, the choice of the initial therapy may be based on the clinical presentation, comorbidities, and anecdotal evidence. Various treatment approaches including corticosteroids, intravenous immunoglobulin, plasma exchange, rituximab, and cyclophosphamide are currently used [6]. Data on treatment response and prognosis are mostly available for anti-NMDAR encephalitis [7].

A common reasonable approach to achieve initial immunosuppressive and anti-inflammatory effect in AIE patients is empiric treatment with intravenous methylprednisolone at a dose of 1 g/day for 3–7 days [1]. Specifically, corticosteroid-responsive are patients with FBDS suggestive of LGI1-antibody encephalitis, and presentations with demyelinating pattern on MRI [8], or radial enhancement suggestive of autoimmune GFAP astrocytopathy or dotted enhancement suggestive of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids [9].

Paraneoplastic AIE associated with classical onconeuronal antibodies tends to respond best to cancer therapy and is often resistant to immunosuppression. Theoretically, corticosteroids are preferred option for immunosuppression over plasma exchange (PLEX) or intravenous IG (IVIg) in cases with highly suspected or known paraneoplastic AIE associated with classical onconeuronal antibodies. They are thought to have a primarily T-cell-mediated inflammation and corticosteroids have inhibitory effect on T-cell overactivity which is the pathogenic hallmark of ICI-associated immune adverse events; in some cases, second-line therapies may also be needed [10].

In cases with known relation to antibody-mediated disease (e.g., NMDAR-antibody encephalitis) and when corticosteroids are contraindicated, IVIg at a dose of 2 g/kg over 2–5 days is an option for fast immunomodulation [6]. A recent randomized blinded study showed IVIg efficacy over placebo in controlling seizures in a small number of patients with CASPR2 antibody and LGI1 antibody AIE [11]. In addition, the use of IVIg is potentially ineffective in cases of paraneoplastic AIE associated with antibodies against intracellular antigens because they are cell mediated rather than antibody mediated. IVIg is associated with increased thromboembolic risk and due to volume expansion may also worsen coexisting hyponatremia, which may potentially predispose to brain edema and worsening mental status [12].

Another effective option for acute immunomodulation when corticosteroids are contraindicated or ineffective is the use of plasma exchange PLEX (5–10 sessions every other day). In patients with fulminant or severe presentations, it provides a potentially faster immunomodulation. Abboud *et al*. in their retrospective review showed similar results in other antibody-mediated conditions like NMOSD [13].

In a small retrospective study, DeSena *et al*. evaluated 14 patients with NMDAR-antibody encephalitis. Results of this study showed better improvement in the modified Rankin score in patients treated with both PLEX and corticosteroids than those treated with corticosteroids alone [14]. In AIE cases with coexisting NMOSD or associated central demyelination, PLEX may be particularly effective.

Despite the lack of high-quality evidence, combined first-line therapies can be used from the beginning in cases with severe initial clinical picture (e.g., NMDAR-antibody encephalitis, NORSE, and severe dysautonomia).

Second-line agents are used if there is no meaningful clinical or radiological response to optimized first-line therapy after 2–4 weeks. Both rituximab and cyclophosphamide have been used as second-line agents for rescue therapy in AIE with good results [8]. Specialized centers usually prescribe rituximab (375 mg/m^2) weekly for 4 weeks and cyclophosphamide (750 mg/m^2) for 6 months in patients older than 16 years. Younger patients should receive rituximab alone [1].

Early treatment is associated with better prognosis [15]. The treatment response and relapse rate vary among patients with AIE. Half of the patients with anti-NMDAR encephalitis fail initial immunotherapy and may require second-line treatment options, with relapses occurring in 12%. Relapses, sometimes years after the first episode, may occur in 10% of patients with anti-CASPR2 encephalitis and 31% of patients with anti-LGI1 encephalitis. In cases with anti-LGI1 encephalitis, 33% of the patients are left disabled, mostly due to memory problems.

Conclusion

AIE may present with either acute or subacute onset of wide variety of symptoms. It is extremely important to consider underlying autoimmune pathogenesis as early as possible in cases with a sudden altered mental state or clinical picture of encephalitis. For AIE diagnosis of extreme importance are physical examination and clinical presentation.

Early treatment is associated with better prognosis and is crucial for the prevention of severe complications.

The underlying mechanisms for activation and autoimmune response in the CNS are still unclear. Further investigations are needed to better explain how immune mechanisms affect nervous system functions. The diagnosis should not rely solely on antibody testing as patients with AIE may be seronegative. The treatment can be adapted and re-evaluated by the antibody results.

In addition, randomized, controlled trials could help to establish more specific therapies for the different subtypes of AIE.

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