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Neuroimmunology of Autoimmune Encephalitis: From Antibody-Mediated Pathogenesis to Multidisciplinary Care

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Abstract:

The complex neuroinflammatory disease known as autoimmune encephalitis (AE) is typified by the generation of autoantibodies that target different central nervous system receptors, proteins, and ion channels. In this review, neuroimmunology of AE is considered, and special attention will be paid to how it is caused, presented in clinical cases, diagnosed, and treated. The most common forms of AE are anti-NMDAR, LGI1 and CASPR2 encephalitis which are all associated with the different autoantibodies and clinical presentation. In paraneoplastic AE, there is the expression of non-paraneoplastic factors, post-infectious factors and mimicry of specific molecular entities that stimulate autoantibody production. The clinical manifestations of AE include a wide variety of manifestations that can include mental disorders, cognition decline, epileptic disorders, movement, and autonomic dysfunction. The multi-disciplinary diagnosis is achieved through neuroimaging, electroencephalography, cerebro spinal fluid analysis and autoantibody testing of which the autoantibody testing is the gold standard. Also, Corticosteroids, intravenous immunoglobulins, and plasmapheresis are the first-line immunotherapies of AE; second-line agents are cyclophosphamide and rituximab, which are applied in cases of refractory disease. Immunotherapy needs to be initiated in an early manner so as to achieve better outcomes and prevent relapses. Crucial part of management is tumor removal when there is suitability. To assist patients with regard to quality of life and care, behavioral support, relapse prevention, and long-term monitoring operations are necessary. Since not

all patients can obtain complete recovery of their cognitive and motor capacities, this retraces the importance of further developing research and standardizing practices, which is necessary to enhance knowledge and improvement of AE, which cannot be completed without constant research and development of antibody panels. Patient centered care, clinical awareness, and multi-disciplinary care are important in maximizing the outcomes of affected individuals due to this complex neuroimmunological disorder.

Keywords: Neuroinflammatory diseases, Autoimmune encephalitis, Autoantibodies, Neuroimaging, Relapse prevention.

Introduction

Neuroimmunology is a dynamic field that brings together neurology, applied biology, chemistry, immunology and pathology, to explore the interactions between the nervous system and immune systems (1). Although the central nervous system (CNS) is well protected by the blood-brain barrier, it is not isolated from the immune system. There is such elaborate crosstalk between the two systems that one modifies the other to great extents. The significance is such that the term “neuroimmune unit” has been coined to refer to the complex association between the neurons/nerve fibers and their interacting immune cells (1).

“Neuroimmune unit” refers not only to the direct contact, but also to the functional interactions that are of immense importance for the CNS to recover from injuries and infection. The lymphatic and glymphatic systems of the meninges which allow the transportation of immune cells to and from the CNS, and the brain’s own composite cells; neuroglia and resident macrophages that have immune roles are also part of this complex unit. Neurotransmitters, neuropeptides and chemokines regulate this unit.

Infection, injury and autoimmunity alike can tip the fine balance between the nervous and immune systems and lead to dysregulations that disturb the immune homeostasis in the CNS. Ineffective immune regulation in CNS thus forms the pathogenesis of multifarious disease states, more so neuroinflammatory diseases. The earliest descriptions of such conditions appear in non-medical literature such as dairies, personal notes and novels, describing individuals suffering from neuroinflammatory diseases such as multiple sclerosis (MS), myasthenia gravis (MG), Encephalitis and Parkinson’s disease in detail (2). As microscopy technologies developed, nerve cells could be seen and the inflammation around them was described. At the same time, advancements in immunology have made way to the creation of rabies and polio vaccinations. As these diseases cause direct impact on CNS, this revelation also sheds understanding on how immunity is associated with CNS (2).

Formal diagnostic criteria of neuroinflammatory and autoimmune conditions of the CNS ensued during the period between 1960s to1980s.In recent years there has been a bloom in the field of neuroimmunology due to the increased understanding of antigens (Ag) and antibodies (Ab), the development of immunotherapies such as Monoclonal Antibodies (Mabs) and emergence of advanced

imaging modalities like magnetic resonance imaging (MRI), positron emission spectroscopy (PET) which have improved the diagnosis and monitoring of neuroinflammatory diseases (1,2). Medical diagnosis, treatment and monitoring of neuroinflammatory and autoimmune diseases can be achieved by understanding their neuroimmunology. The disease that this literature review will be focused on is autoimmune encephalitis (AE), which is a neuroinflammatory, autoimmune encephalopathy (1,2).

In case of AE, the body produces autoantibodies due to which it attacks the antigens of its own body, causing a set of heterogeneous clinical syndromes, which occur in adults and children (3). The increase in incidence of AE is attributable to improved awareness and diagnosis of it compared to the past (4). Previously, the clinical syndromes now known to be caused by AE were thought to be exclusively associated with brain neoplasms. The autoantibodies found in classic antibody-associated paraneoplastic neurologic disorders (PNDs), typically target intracellular proteins, are always associated with neoplasms, and often lead to irreversible damage.

However, in AE, autoantibodies target extracellular or intracellular components of neuronal receptors and proteins cause reversible damage and are not necessarily associated with neoplasms (1,3). Such differentiation of receptors, proteins and ion channels in different subgroups forms the current classification of AE into the subgroups: according to targeted receptors/proteins/ion channels and physical position within neurons.

Group 1 (Ab target intracellular antigens) e.g; including anti-Hu, anti-Ma/Ta, anti-GAD, anti-Yo, anti-CV2/CRMP5 and Group 2 (Ab target cell surface antigens) e.g; anti-LGI1, anti-NMDAR, anti-CASPR2, anti-GABAAR, anti-GABABR (5).Out of them, limbic encephalitis (associated with LGI1 or CASPR2 antibodies) and NMDAR encephalitis are the two most clinically recognizable (6).

Regarding clinical manifestations, neurological features are the hallmark. Limbic system dysfunction symptoms such as behavioral changes, loss of memory or seizures are the most commonly encountered– reflecting the involvement of the medial temporal lobe. As in many patients with encephalitis, AE patients may also have cognitive issues; disorientation, confusion and amnesia are common occurrences. Under-recognized features such as autonomic dysfunctions (fluctuations in blood pressure, tachy or brady arrhythmias) and pain related to motor neuron involvement, are also noteworthy. (4)

The differential diagnosis includes infectious encephalitis, CNS vasculitis, acute dementia (e.g., Creutzfeldt-Jakob disease), malignancies such as temporal lobe glioma, lymphoma and metabolic or mitochondrial encephalopathies. The diagnosis of AE can be made based on clinical findings, cerebrospinal fluid (CSF) analysis and neuroimaging. There are several criteria that allow for the diagnosis of possible AE, such as subacute onset, exclusion of infective causes such as HSV encephalitis and MRI features of encephalitis (6,4).

In certain patients, and where facilities are available, CSF autoantibodies can also be identified, making the diagnosis more definite (4,6). Early diagnosis is of utmost importance because when the

autoimmune etiology is identified, appropriate treatment can be given. IV corticosteroids, IV immunoglobulins (IVIG) and plasma exchange are part of the first line treatment.

Second-line aggressive immunotherapy can be applied in refractory cases. The overall prognosis of the patient greatly improves when promptly and appropriately treated (3,5). The secondary complications could occur with the problem of cardiac associated complication being most common in addition to side effects associated with treatment (infections, drug toxicity). Subtle psychological symptoms may persist and need to be addressed as well (7).

This review article focuses on AE as an encephalopathy that is better understood when focusing on the underlying neuroimmunology. It explains etiology, mechanism, clinical presentation, diagnosis, and treatment of AE besides the consideration of future treatment (7).

Methodology

Study Design and Objective

This review employs a systematic approach by analyzing the existing research to understanding the current stance on the Neuroimmunology and Autoimmune Encephalitis (AE) focusing on a qualitative, narrative synthesis methodology in order to assess existing articles and review papers to identify the different types of AE like the anti-NMDAR, LGI1, CASPR2 encephalitis, their clinical features, the core diagnostic methods- Neuroimaging, EEG, CSF studies, Autoantibody testing and also compare and evaluate immunotherapy based treatment strategies(6,8).

Literature Search Strategy

A systematic search of existing literature was conducted on databases such as Google Scholar and PubMed. The databases were queried using keywords such as “Neuroimmunology”, Autoimmune Encephalitis, Anti-NMDAR encephalitis, Autoimmune Encephalitis Classification, Brain Autoimmunity, Anti-bodies against brain tissue, Inflammation of brain, Autoimmune Encephalitis Treatment, Autoimmune Encephalitis rituximab. Use of Boolean operators was also done to refine the search (1,4).

Inclusion and Exclusion Criteria

Inclusion Criteria:

Patients are diagnosed with AE or any of its forms. Patients of all ages and genders were taken into consideration. Case reports, Cohorts, clinical trials and review papers published between 2013 and 2025 in the English language. Studies focusing on immunotherapy-based 1st and 2nd line treatments using corticosteroids like methylprednisolone and other immunosuppressants such as rituximab or cyclophosphamide.

Exclusion Criteria:

Studies that focused on animal models, non-human studies and meta-analyses were excluded.

Data Extraction and Collection

Data was collated from the studies that met the inclusion criteria followed by thematic analysis in order to: determine the causes of AE- antibodies against receptors or against intracellular antigens and neuronal surfaces. Distinguish between the forms of AE- the anti-NMDAR, LGI1, CASPR2 and IgLON5 along with the clinical features presented in each (9,10).

Discuss the investigative methods utilized to diagnose the diseases- MRI, EEG, CSF studies and Autoantibody testing. Evaluate the treatments protocols used and their efficacy - 1st line treatments using steroids or IVIg and 2nd line treatments using rituximab (11).

DISCUSSION

In this section, we will integrate the knowledge on aspects of neuroimmunology and autoimmune encephalitis, talking about the clinical spectrum, diagnostic tools, and effective treatment (11). Autoimmune encephalitis is a disorder where we can see antibodies targeting various receptors in our central nervous system, this disrupts the normal functioning causing symptoms.

Based on various studies, we understand that antibodies formed against a variety of receptors like NMDA, LGI1, CASPR2, GABABR, GABAAR, IgLON5 and more cause AE (4,8,9). The most common of them being autoantibodies against NMDA receptor and LGI1(8,9). Based on the location, we have antibodies against Intracellular antigens and Neuronal surface (e.g Anti-NMDAR). When antigens are targeted, we can see functional disruption like altered synaptic signaling or receptor internalization.

In the case of Anti-NMDAR antibodies target antigen and we can see receptor internalization resulting in hypofunction leading to psychiatric disturbances or hyperfunction leading to neuron death due to overstimulation. In the case of antibodies which affect Voltage gated Potassium Channel complex like LGI1 or CASPR2, we can see altered synaptic excitability which results in memory impairment and seizure production (8).The production of these antibodies is seen due to triggers including molecular mimicry in paraneoplastic AE (ovarian teratoma), Post infectious AE (viral prodrome seen in NMDAR encephalitis) and non-paraneoplastic AE(6).

Based on the antigen against which the antibody is made, we see a variety of clinical features, majority of which overlap but knowing characteristic signs helps differentiate them. We can see some early “red flags” as Subacute progression which is an episode of less than 3 months of memory deficits, psychiatric changes as well as altered mental state. Flu-like symptoms such as headache and fever are usually seen before NMDA receptor encephalitis. Abnormal movements, development of seizures or unexplained hyponatremia are also significant signs before the commencement of the illness (9). In Anti-NMDAR encephalitis, adults usually start with viral like illness which progresses into psychiatric or behavioral changes(hallucination) whereas it is vice versa in children. Later in the course of illness we witness dyskinesias, speech reduction, tonic-colonic seizures and decreased consciousness.

LGI1 is characterized by faciobrachial dystonic seizures which is a hallmark feature for it along with memory impairment, seizures, REM sleep disturbance (8). CASPR2 is known for showcasing Morvan Syndrome-a triad of encephalitis, dysautonomia, neuromyotonic as well as frequent relapses (8). IgLON5 causes progressive neurodegenerative sleep-movement disorder along with dysphagia and chorea whereas GABABR and GABAAR lead to refractory seizures (4). A multi-disciplinary approach for diagnosis of AE depends on 4 core investigations: Neuroimaging, EEG, CSF studies and Autoantibody testing (1,5,6,12). Although autoantibody is the gold standard, the results take time and therefore the decision for treatment is taken before the arrival of results (1,11). The presence of CSF pleocytosis and elevated protein concentration is a sign of neuroinflammation therefore to distinguish and confirm AE we need to do autoantibody testing, making it the gold standard (1,12).

Before the diagnosis, checking of diagnostic criteria is done: Subacute onset of memory deficits, altered mental state or psychiatric symptoms ≥ 1 of the supportive signs (new or unexplained seizures, FLAIR hyperintensities (temporal lobe), pleocytosis. Ruling out any other disease or disorder (6,15). Neuroimaging findings are usually nonspecific even in the case of Anti-NMDAR abnormalities are seen only in approximately 1/3 of cases (5). EEG which is supportive yet non-specific can be distinctive in cases like Anti-NMDAR where we see “extreme delta brush” due to prolonged illness or LGI1 having temporal seizures shows “DC shift” (5,8). CSF analysis helps in revealing lymphocytic pleocytosis and elevated protein and in case if NMDAR shows pleocytosis, LGI1 is often normal whereas GABA leads to pleocytosis with mesiotemporal involvement (4,8,12). Autoantibody testing with CSF is more specific and sensitive than serum and is important as it helps in confirmation and distinguishes AE from other diseases like viral encephalitis or psychiatric disorders (1,12). This can be comprehended by the fact that early detection and initiation in the case of AE is important because any delay in action would result in poor outcomes. In the field of treatment of AE, we see that immunosuppression and tumor removal are the major steps of management along with this long-term relapse prevention and symptomatic therapy also play a key role (11,13).

The detection of autoantibodies and patient improvement with immunotherapy shows the clear involvement of a faulty immune reaction (11, 14, 15).Depending on the agents, the treatment may consist of first-line and second-line immunotherapy(11,14,15).In cases of Neuronal Surface Antibodies like Anti-NMDAR, LGI1 or CASPR2, we see a positive response to immunotherapies as well as favorable prognosis to early treatment. On the contrary, in case of antibodies targeting nuclear and cytoplasmic proteins, it shows poor response to immunotherapy alone but on cancer treatment it shows better results (8,11). First-line therapy initiated based on clinical suspicion of AE, before the arrival of antibody testing results to prevent poor outcomes and are aimed to reduce levels of antibodies without any delay.

Corticosteroids either alone or in combination with IVIg/Plasmapheresis. Corticosteroids like methylprednisolone bind to intracellular glucocorticoid receptors and suppress pro-inflammatory gene transcription along with extra benefits like restoration of BBB and prevention of brain edema. Along with the benefits, we should not forget the limitations which can be seen as the use of corticosteroids

can lead to transient worsening of symptoms, especially hallucinations. We need to keep in mind that due to these limitations, the risk of long-term use of corticosteroids might overpower the benefits (8,15).In cases where presence of tumor is detected, removal should be done as part of initial therapy as based on studies, patients who did not undergo tumor removal in cases of Anti-NMDAR encephalitis showed worse outcomes and relapses were seen.

First line immunotherapies show significant improvement, but more than half of the patients still required second line immunotherapies for better and stronger results. Agents like Rituximab and Cyclophosphamide are used as second-line immunotherapies (11). When the symptoms persist or worsen for ≥4 weeks we turn to them for better and long-term results. Rituximab is best used for antibody mediated AE targeting B cells and plasma blast precursors while Cyclophosphamide targeting hematopoietic cells shows better results in cell-mediated AE (11). Based on retrospective data, use of rituximab has been shown to reduce relapse risk by approximately 90% (11,13,15).

It is often seen that due to the difficulty in distinguishing between Autoimmune encephalitis and infectious encephalitis in the acute period causes a delay in therapy initiation. When good response to treatment is witnessed, supportive treatment and tumor surveillance are initiated (11). In Anti-NMDAR encephalitis, it is noted that early initiation of immunotherapy gives good results but if delayed for more than 4 weeks, we will witness poor prognosis. For the treatment of dyskinesis in this syndrome, use of Benzodiazepines (sometimes at higher doses) is preferred (11). Behavioral symptoms are treated with, Olanzapine, an antipsychotic, at 10mg daily is given but with caution due to the risk of neuroleptic malignant syndrome.

LGI1 encephalitis shows positive response to corticosteroids. The use anti-seizure alone rarely control faciobrachial seizure but sodium channel blockers have shown to more effective but again are supposed to be used with caution due to the risk of developing Steven Johnson Syndrome or cutaneous reactions (8).CASPR2 encephalitis enhances positive results on the use of second-line immunotherapy agents , if not used, frequent relapses are seen (8,14). IgLON5 and GABA show responses variable (4,15). Recovery usually takes up to 2 years and longer and patients mostly may not return to former motor and cognitive functions. It should be taken into consideration that early initiation of therapy, to be precise use of rituximab for reduces relapses, shows improved outcomes (11).

Conclusion

Autoimmune encephalitis is very complex system and also it emerges very fast, and it is a treatable condition despite presenting with psychiatric symptoms and seizure and other conditions like cognitive changes. There are several advancements which made autoimmune encephalitis transform into a treatable disease, these include antibody detection and neuro imaging, and multidisciplinary care is important because of the Comorbidities like psychological disorders which can trigger recovery. In few cases like paraneoplastic autoimmune encephalitis, it strengthened the cancer screening because of tumor removal and to improve the patient quality of life we must emphasize on continuous research

and learning and also we need to evaluate and standardized the treatments and follow ups.for the best outcomes we need clinical awareness and patient centered approach which is essential for quality of life for those who are affected

Some patients are not fully recovered from months to years and also, they did not regain cognitive and motor ability despite therapeutic advancements, so because of these there are few essential components of care which are important like long term monitoring, relapse prevention and behavioral support. For positive prognosis we need improved antibody panels, continued research work and standardized treatment algorithms which play a vital role. Treatment is determined or decided on rapid initiation of immunotherapy prior to antibodies confirmation using first like agents such as intravenous immunoglobulin, plasmapheresis and corticosteroids. For initial treatment there is a resistance and delayed recovery in few cases for that we use second line immunosuppressants such as cyclophosphamide and rituximab to improve long term outcomes and reduce the risk of relapse .Autoantibody detection(particularly via CSF rather than serum) and cerebrospinal fluid analysis they are the key aspect of diagnostic purpose because brain MRI and EEG findings are non-specific and normal in early stages. These tools help to distinguish the conditions which mimic the autoimmune encephalitis (mimicking conditions such as viral encephalitis, primary psychiatric disorders). Absence of structural abnormalities on neuro imaging and indicators of risk like new onset seizures, subacute psychiatric changes, unexplained hyponatremia and flue like prodromes encourage vigilance or suggest need to broaden the differential diagnosis.

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