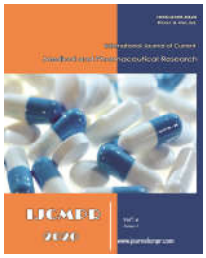
INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH
ISSN: 2395-6429, Impact Factor: 4.656
Available Online at www.journalcmpr.com
Volume 6; Issue 01(A); January 2020; Page No.4859-4863
DOI: http://dx.doi.org/10.24327/23956429.ijcmpr202001819



Research Article

ANTI-NMDA RECEPTOR ASSOCIATED LIMBIC ENCEPHALITIS; A CASE REPORT OF A YOUNG LADY WITH NO PREVIOUS NEUROPSYCHIATRIC HISTORY WITH SUB-ACUTE PSYCHOSIS AND CATATONIA

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ARTICLE INFO

Article History:
Received 10th October, 2019
Received in revised form 2nd November, 2019
Accepted 26th December, 2019
Published online 28th January, 2020

Key words:
autoimmune encephalitis, psychosis, catatonia, seizure.

ABSTRACT

Autoimmune encephalitisis a cluster of closely associated diseases that share overlapping clinical symptoms, however, are ultimately distinguished by the precise antibody subtypes driving the main immune-mediated attack on different brain structures. Anti-N-methyl-D-aspartate (NMDA) receptor antibody-associated limbic encephalitis is the most common form of autoimmune encephalitis, primarily affecting young women under the age of 50. Patients affected present with a range of neuropsychiatric symptoms, including anxiety, hostility, psychosis as well as abnormal movements, speech dysfunction, memory deficits, seizures and altered levels of consciousness. We aim to discussa case of young lady with anti-NMDA-receptor-associated encephalitis presenting with subacute onset of polymorphic psychosis that within two months progressed into catatonia, seizures and coma. The patient had no previous psychiatric history and was initially treated with antipsychotics and electroconvulsive therapy. Our experience emphasises the definite diagnosis of anti-NMDA receptor associated encephalitis is not easy, especially in its early phases. This is because most patients initially present with psychiatric symptoms than neurological manifestation. Furthermore, immunological and laboratory testing are not easily accessible and where available, take a rather long time to determine the diagnosis. What is more, few psychiatrists consider the autoimmune nature of this neuropsychiatric syndrome. Therefore, psychiatrists should consider the possibility of anti-NMDA receptor associated encephalitis in young women under the age of 50 who present with characteristic neuropsychiatric symptoms.

INTRODUCTION

The term "autoimmune encephalitis" generally refers to a group of closely connected conditions that share overlapping clinical symptoms, however, are eventually differentiated by the specific antibody subtypes driving the underlying immune-mediated attack on different brain structures [48]. The exact aetiology of autoimmune encephalitis is not known, however, Dropcho[8] was one of the first researchers who suggested the autoimmune aetiology of these conditions. Earlier cases of autoimmune encephalitis were associated with malignancy and it was thought that the antibodies were generated as a response to tumour antigens. The antibodies later develop molecular imitation against auto antigens, thereby causing neurological syndrome [36].

We present a case of a young lady in her early twenties, with positive anti-NMDA antibodies presenting with subacute polymorphic psychiatric symptoms including anxiety, agitation, disorganised behaviour and catatonia with subsequent neurological symptoms including dysarthria, seizure and comatose state. Moreover, we aim to review the pathophysiology, clinical symptomatology and diagnosis of autoimmune encephalitis, in particular the anti-NMDA receptor associated encephalitis, which quite often presents with psychiatric symptoms that may be easily overlooked or misdiagnosed within psychiatric settings.

Pathophysiology

Glutamate is the most widely utilised excitatory neurotransmitter in the nervous system. The brain glutamate/glutamine cycle is the metabolic pathway that involves the synaptic release of glutamate from neurons, rapid and efficient glutamate uptake by astroglia, conversion of glutamate to glutamine by astrocytic glutamine synthetase, followed by release of glutamine to the interstitium, and uptake by the neurons for conversion back to glutamate [39, 49]. This process efficiently prevents excessive accumulation of glutamate in the interstitium that would induce excitotoxic neurodegeneration [19]. The intrasynaptic glutamate level must be kept low to maximize the signal-to-noise ratio upon the release of glutamate from nerve terminals and to minimize the risk of excitotoxicity consequent to excessive glutamatergic stimulation of susceptible neurons [49]. Likewise, glutamate receptors expressed in various types of benign and malignant

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neoplasms, play a role as growth factors and are important for cancer development and progression[43]. Expression of glutamate receptors in tumour cells triggers an anti-tumour immune response, which can suppress tumour growth and symptoms [1]. This tumour immune response can break the immune tolerance and different glutamate receptor autoantibodies can attack the neuronal tissue. The antibody-mediated attack on neuronal structures results in a localised inflammatory response[38].

The vast majority of the excitatory neurotransmission in the central nervous system is mediated by glutamate, which activates both pre and postsynaptic glutamate receptors and ionotropic glutamate receptors (iGluRs). iGluRs are ligand-gated cation channels that are divided into three structurally distinct functional classes: the α-amino-3-hydroxy-5-methyl-4-isoxasolepropionic acid (AMPA) receptors, kainate receptors, and N-methyl-D-aspartate (NMDA) receptors [47].

The NMDA-type glutamate receptors mediate a major component of excitatory neurotransmission in the CNS. Seven NMDA receptor subunits exist that have distinct regional and developmental expression and possess a wide range of functional and pharmacological properties. They are widely distributed at all stages of development and are critically involved in normal brain functions, including neuronal development and synaptic plasticity. NMDA receptors are also implicated in the pathophysiology of numerous neurological and psychiatric disorders, such as ischemic stroke, traumatic brain injury, Alzheimer's disease, epilepsy, mood disorders, and schizophrenia [14, 15]. Furthermore, evidence indicates that synaptic and extra-synaptic NMDA receptors have distinct compositions and couple with different signalling pathways: while synaptic NMDA receptors promote cell survival, extra-synaptic NMDA receptors promote cell death [28]. It is considered that excessive glutamate release from presynaptic sites activates an excessive number of postsynaptic NMDA receptors, thus triggering excitotoxic neuronal death (apoptosis) by allowing excessive Ca2+ influx[30, 31,35,42]. NMDA receptors over activity is the proposed underlying mechanism of epilepsy, dementia and stroke, whereas decreased NMDA receptors activity results in symptoms of schizophrenia[3, 20].

Clinical presentation

Anti-NMDA receptor antibody-associated encephalitis is the most common form of all autoimmune encephalitis. Moreover, it is most common in women under the age of 50, with the female to male ratio of 4 to 1 [45]. The disorder can start with "flu-like" symptoms, followed by psychiatric symptoms [36]. Patients affected present with a range of symptoms, including anxiety and panic attacks, hostility and aggression, inappropriate sexual behaviours or psychotic symptoms. Psychiatric symptomatology often fluctuates. Neurological symptoms such as abnormal movements, speech dysfunction, memory deficits, seizures and altered levels of consciousness emerge later during the course of the illness [5, 6]. Writhing movements of the face and limbs may be most prominent in the comatose phases of the illness [18], while seizures may occur in any stage of the illness [24]. Patients with anti-NMDA receptor encephalitis commonly recover from a totally unresponsive state to eventually resume a good quality of life [26].

Anti-AMPA antibody-associated limbic encephalitis is an uncommon subtype of autoimmune encephalitis with subacute onset of psychiatric symptoms, often seen in women with lung, breast and thymic cancer [4, 22].

Vignette

A young lady in her early twenties with no previous neuropsychiatric history was admitted to psychiatric services in October 2017. She reported initial symptoms of headache, insomnia, and anxiety as well as diarrhoea and nausea that started two months prior to presentation. Prior to admission, the patient's symptoms had escalated; she was anxious, agitated, tearful and very distressed. She developed speech problems and was unable to coherently communicate. She was repeating single words or yelling "she can't stop, sorry, boobs, fat, fatty". The patient was found exposed in the lounge, singing incoherently, incontinent of urine, rolling on floor, pulling her hair, shouting and thrashing her legs. The patient was found walking into walls, lying on the floor, and sometimes standing under the shower without running water, making washing movements. Following two episodes of loss of consciousness, the patient was taken to a medical unit where she was diagnosed with a urinary tract infection and commenced antibiotics before returning to psychiatric unit. Within four weeks, post admission the patient became mute, assumed fixed uncomfortable postures (waxy flexibility), deteriorated in terms of mobility and became wheelchair bound. As she refused food and fluid intake, she was treated with electroconvulsive therapy. No progress was made; therefore, the patient was transferred to a medical unit. The patient was treated for urosepsis with intravenous antibiotics. Following four episodes of tonic-clonic seizures; she was commenced on levetiracetam and lamotrigine. Examinations: no significant changes of full blood count, liver enzymes, or minerals. C-reactive protein raised to 20mg/L. EEG: "Intermittent runs of diffuse slow waves with a temporal dominance. CT head was normal. Lumbar puncture was unsuccessful; MRI head: Minor low signal change in left temporal lobe. Anti-VGKC antibodies: negative. Anti-NMDA-receptor antibodies: positive. Patient was diagnosed with anti-NMDA-receptor encephalitis and successfully treated with anticonvulsants (lamotrigine and levetiracetam). On outpatient review in March 2019 the patient reported foot drop/numbness, but no other neuropsychiatric symptoms.

Antibody testing

Presence of antibodies is not necessary for clinicians to consider a potential diagnosis of limbic encephalitis. This is because immune-mediated autoimmune encephalitis can occur without detectable autoantibodies[11]. Measurements of autoantibodies, however, remains important because the diagnosis of autoimmune limbic encephalitis could be confirmed by their presence in cerebrospinal fluid (CSF) and/or serum. Moreover, their presence clarifies the immunological subgroup of autoimmune encephalitis, with co-morbidities, tumour association and prognosis that might differ[7].

The antibodies associated with autoimmune encephalitis are IgG antibodies. Detection of IgA or IgM antibodies against any of the antigens has unclear significance[11]. The NMDA receptor is a hetero-tetramer comprised of two GluN1 subunits and two GluN2/3 subunits. Detection of IgG antibodies against the GluN1 subunit is a signature of the anti-NMDA receptor

encephalitis[10].However, NMDA receptor IgM and IgA responses have been reported in patients with schizophrenia and other psychiatric disease but also in up to 10% of normal controls[25]. Conversely, the types of IgG responses associated with anti-NMDA receptor encephalitis are not found in patients with schizophrenia [29].

Despite the importance of antibody testing in autoimmune encephalitis, it is not realistic to include antibody status as part of early diagnostic criteria. Antibody testingis not readily available and where accessible, results can take several weeks to obtain. Additionally, over the course of the disease, levels of antibodies decline, but even after recovery most patients still had antibodies in both serum and CSF [7].

Cerebrospinal fluid testing

Analysis of cerebrospinal fluid playsa central part in diagnosis of all cases of encephalitis. Most patients with autoimmune encephalitis have CSF antibodies and relevant antibodies are found in their CSF[17, 27]. For example, in patients with anti-NMDA receptor encephalitis up to 14% have antibodies in the CSF, but not in the serum [12]. Crucially, the types of antibodies in the CSF can determine the clinical picture[34]as well as correlate with the progress of the illness [12]. Furthermore, antibody testing using serum could lead to false-positive or false-negative results. Nonetheless, this problem rarely occurs with CSF analysis [11]. CSF analysis of patients suffering from autoimmune limbic encephalitis shows mild-to-moderate lymphocytic pleocytosis (usually less than 100 white blood cells per mm^3) in 60% to 80% of patients, and elevated IgG index or oligoclonal bands in approximately 50% of cases [13, 17, 21].

Imaging

Brain magnetic resonance imaging (MRI) in patients with autoimmune encephalitis may be normalor non-specific[26]. Nevertheless, bilateral abnormalities in the medial temporal lobes on T2 signal are quite characteristic MRI findings of autoimmune limbic encephalitis [6, 11, 24, 27]. Similar MRI findings are found in almost 95% of patients with herpes simplex virus encephalitis[41], as well as in individuals suffering from tuberculosis and syphilis [46]. MRI findings of patients with anti-dipeptidyl-peptidase-like protein 6 (DPPX) or anti-$GABA_A$ antibody-associated encephalitis have fewer distinctive findings [16, 46].

Electroencephalography (EEG)

EEG is useful for excluding subclinical seizures, as well as for prognosis and differential diagnosis [26]. Not all patients with autoimmune encephalitis present with EEG abnormalities. It has also been suggested that normal EEG correlates with good prognosis, independent of other prognostic factors [44]. Most studies, however, report EEG abnormalities in patients with autoimmune encephalitis. Lawn *et al*. (2003)[27] in the EEG of a group of 22 patients with autoimmune encephalitis, found focal or generalized slowing and/ or epileptic form activity, maximal in the temporal regions, in all 22 patients tested. Schmitt *et al*., (2012)[37] reported delta brush EEG pattern in patients with anti-NMDA receptor encephalitis. In a most recent study, Moise *et al*. (2019) [32]confirmed a signature EEG pattern in anti-NMDA receptor autoimmune encephalitis, termed extreme delta brush, identified as generalized rhythmic delta activity plus fast activity. In a systematic literature review of 446 cases of anti-NMDA receptor encephalitis; 373 EEGs were abnormal, and this strongly correlated with admission to the intensive care unit and the recovery time. Admission to intensive care unit and recovery were also correlated with delta range abnormalities including extreme delta brush[9]. What is more, it has been reported that periodic or rhythmic patterns, seizures, and new-onset refractory status epilepticus conferred an increased risk of poor outcome regardless of autoimmune encephalitis subtype [32].

Treatment of autoimmune encephalitis

Patients with autoimmune encephalitis present with variable clinical manifestations, severity, comorbidities, and immunotherapy responsiveness and thus treatment should be individualized. There are no established guidelines for treatment, and diverse regimens are currently being used based on the patient's clinical status and the clinicians' opinion[40].Common first-line immunotherapeutic agents include corticosteroids (methylprednisolone 1g daily, for 3 – 5 days) intravenous immunoglobulin (intravenous immunoglobulin 2g/kg over 5 days) and plasma exchange (1 session every other day for 5-7 days). Corticosteroids are frequently the first choice, followed by intravenous immunoglobulin and plasma exchange [33]. Corticosteroids with either intravenous immunoglobulin or plasma exchange represent the usual choice when a combination of first-line agents is administered. When first-line immunotherapy is insufficient secondary immunomodulatory agents such as rituximab and cyclophosphamide are the most commonly used medications[40]. Rituximab is widely used to treat various autoimmune disorders and appears to be effective [2, 23].

CONCLUSION

Autoimmune encephalitides are caused by humoral or cellular reactions against certain neuronal antigens. Anti-NMDA receptor antibody-associated encephalitis is the most common form of autoimmune encephalitis, especially affecting women under the age of 50. Patients present with a wide range of neuropsychiatric symptoms, including anxiety, hostility, inappropriate sexual behaviours or psychotic symptoms. Neurological symptoms such as abnormal movements, speech dysfunction, memory deficits, seizures and altered levels of consciousness emerge later during the course of the illness.

The definite diagnosis of autoimmune encephalitis is not easy, especially in the early phases of the illness. This is because most patients initially present with psychiatric symptoms rather than neurological manifestation. Furthermore, immunological and laboratory testing are not easily accessible and where available take a rather long time to determine the diagnosis. What is more, few psychiatrists consider the autoimmune nature of this neuropsychiatric syndrome. Therefore, psychiatrists should consider the possibility of anti-NMDA receptor associated encephalitis in the group of young women under the age of 50 who present with rather characteristic neuropsychiatric symptoms.

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