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Case Report

Anti N-Methyl-D-Aspartate Receptor (NMDAR) Encephalitis in Paediatric Age Group - A Short Review

Shubhankar Mishra*

Department of Neurology, S.C.B Medical College, Cuttack, India

***Corresponding Author:** Shubhankar Mishra, Department of Neurology, S.C.B Medical College, Cuttack, India.

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Abstract

Autoimmune encephalitis (AE) is rapidly growing topic in paediatric neurology. Novel antibodies associated with the disease, clinical experience and outcomes with diverse immunotherapeutic agents make it the game changer. Anti NMDAR encephalitis is one of the commonest AE, seen in children. Patients present with impaired memory, cognition, seizures and movement disorder over a period of days or weeks (acute or subacute presentation). The syndrome is frequently associated with malignancy like ovarian teratomas. But association with other tumours are also seen. Immune response to first-line immunotherapeutic agents (corticosteroids, intravenous immunoglobulin, plasma exchange, and immunoadsorption) is good, but most patients are administered second-line prophylactic immunotherapy (rituximab and cyclophosphamide). This review will outline the diagnostic criteria and treatment modalities of Anti NMDAR Encephalitis.

Keywords: *NMDAR; Childhood Dementia; Steroids*

Introduction

Autoimmune encephalitis (AE) is a difficult clinical diagnosis due to the similarities in the clinical, imaging and laboratory findings of many forms of autoimmune and infectious encephalitis. The knowledge of AE is also limited in developing countries. Patients present with cognition decline and loss of memory over a short period (acute or sub-acute presentation). Testing for infectious diseases for exclusion along with analysis of neuronal autoantibodies can lead to the correct diagnosis. If a clear autoimmune etiology is established, treatment usually involves in immunotherapy. N-methyl-d-aspartate receptor (NMDAR) antibody encephalitis is a potentially fatal autoimmune syndrome in which there is antibody production against the NMDAR causing profound dysregulation of neurotransmission [1]. It's more commonly seen in paediatric population and adolescents.

Clinical Presentation

The manifestations of anti-NDMAR encephalitis syndrome is preceded by a prodromal stage including headaches, fevers, diarrhoea, or upper respiratory infection symptoms [2,4]. Acute or sub acute onset psychiatric manifestations along with forgetfulness in pediatric age group is most common presentation. Many psychiatric changes like anxiety, paranoia, mania, hyper-religiosity, delusions, illusions and hallucinations are seen within 2 weeks. Acute memory loss is also one of the commonest presentation [3,4]. Neurological deficits with movement disorders like ataxia, dystonia and choreoathetosis and autonomic instability may also occur as the disease progresses. Seizures present relatively early but overlap between epileptiform movements and orofacial or faciobrachial dyskinesias may create confusion for clinicians. Sometimes overlap of the syndromic symptoms with that of psychosis often leads to misdiagnosis in early phase of disease [3]. Anti NMDAR encephalitis must be suspected when child or teenager presents with abnormal behaviour, change in personality

with irritability and insomnia, followed by speech dysfunction, dyskinesias, memory deficits, autonomic instability, and a change in level of consciousness.

Discussion and Conclusion

Pathophysiology

NMDARs play a central role in synaptic transmission for human memory, cognition, and learning [5]. Activity of the NMDAR is affected by several exogenous factors, including PCP (Phencyclidine), ketamine, and ethanol, along with endogenous brain-immune interactions. The NMDAR is composed of NR1 and NR2 subunits [5]. The autoantibodies in anti-NMDAR encephalitis are directed against NR1 subunit in the frontotemporal and hippocampal regions of brain where the receptor density is high [2,6]. This pattern of involvement helps explain common psychiatric signs and symptoms seen in this disease, which localize to frontal and temporal lobe of brain resulting cognitive decline and personality changes. Commonly, anti-NMDAR antibody is associated with malignancies like ovarian teratoma [3].

Diagnosis

Neuroimaging by MRI has been negative in up to 50 - 70% of patients [2,4]. T2 or FLAIR sequence hyperintensities in the hippocampal, frontobasal, insular, or basal ganglia regions are commonest features seen in MRI [4] (Figure 1). EEG reveals encephalopathic pattern with abnormal slowing [7]. Drug resistant seizures are very common in anti-NMDAR encephalitis, which may occur at any point during the disease course [8]. The extreme delta brush pattern is a frequent finding in anti-NMDAR encephalitis [9]. This distinctive EEG pattern with clinical scenario must be followed by testing for NMDAR antibodies (Figure 2).

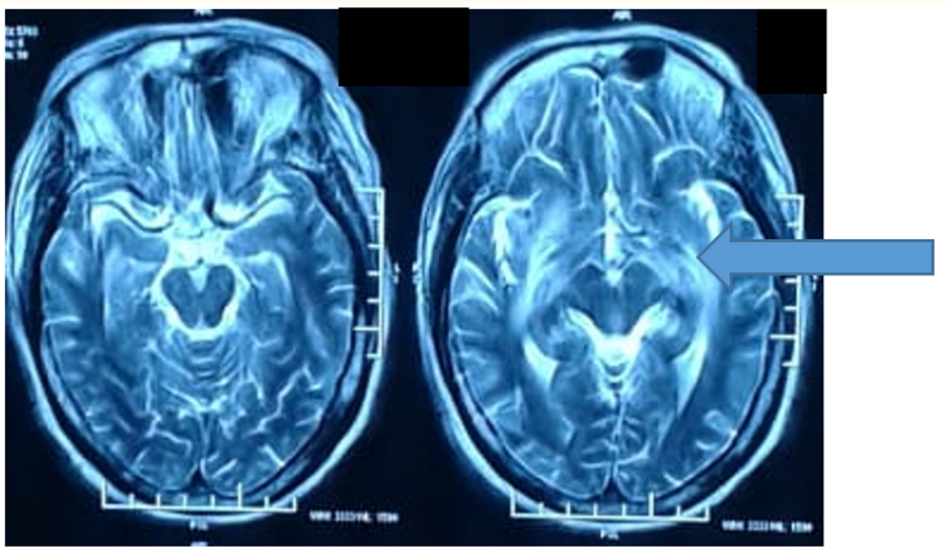

Figure 1: *Temporal lobe hyperintensity.*

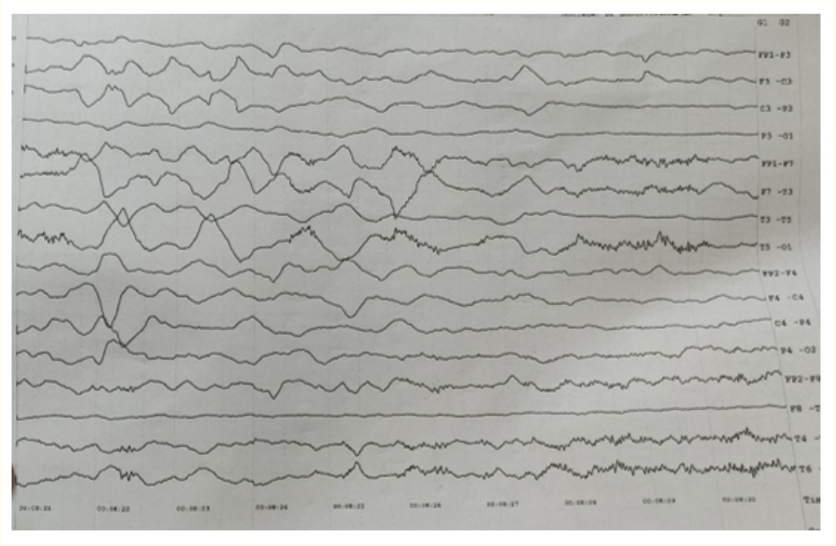

Figure 2: *Delta brush appearance in EEG.*

Definitive diagnosis is based upon finding anti-NMDAR antibodies in the CSF or serum (Table 1). CSF studies show lymphocytic pleocytosis along with normal to mild elevation of protein. Oligoclonal bands are very common, which may be present in 60% of patients [4]. CSF titres correlate with disease activity [2,3]. NMDAR antibody tests are most sensitive and specific with CSF rather than serum. Serum test has low false positive rate and a higher false negative rate. Pathogenic autoantibodies are IgG in nature [10]. IgM and IgA tests are not recommended. IgG responses associated with anti-NMDAR encephalitis are not found in patients with other psychiatric diseases like schizophrenia [11].

Probable anti-NMDA receptor encephalitis
Diagnosis can be made when all three of the following criteria have been met: 1. Rapid onset (less than 3 months) of at least four of the six following major groups of symptoms: • Abnormal (psychiatric) behaviour or cognitive dysfunction • Speech dysfunction (pressured speech, verbal reduction, mutism) • Seizures • Movement disorder, dyskinesias, or rigidity/abnormal postures • Decreased level of consciousness • Autonomic dysfunction or central hypoventilation 2. At least one of the following laboratory study results: • Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush) • CSF with pleocytosis or oligoclonal bands 3. Reasonable exclusion of other disorders (infective, vasculitis, demyelinating, metabolic) Diagnosis can also be made in the presence of three of the above groups of symptoms accompanied by a systemic teratoma
Definite anti-NMDA receptor encephalitis
Diagnosis can be made in the presence of one or more of the six major groups of symptoms and IgG anti-GluN1 antibodies, after reasonable exclusion of other disorders (infective, vasculitis, demyelinating, metabolic)

Table 1: *Diagnostic criteria for anti-NMDA receptor encephalitis [12].*

Treatment

Immunomodulation and neoplasm removal targeting both symptomatic and causal factors are mainstays of table 2. Symptomatic therapy needed for seizure, behavioural changes, movement disorder and cognitive decline. As in most other inflammatory disorders, corticosteroids are used in the treatment of AE, acting to broadly inhibit the inflammatory process in acute phase. However, it has less specificity for the antibody-mediated immune process, and their efficacy is limited in cases of AE, along with it systemic steroids possess several side effects. Therapeutic targets for these treatments include autoantibodies and other immune mediators (IVIg and PLEX), B cells and short-lived plasma cells (rituximab), and specific cytokines associated in the autoimmune and inflammatory process [tocilizumab and low-dose interleukin (IL)-2]. Antiproliferative agents targeting lymphocyte proliferation (cyclophosphamide, azathioprine, mycophenolate mofetil, etc.) are also used in refractory cases or to maintain remission [13].

First-line immunotherapy
Methylprednisolone
Intravenous immunoglobulin
Plasma exchange/immunoadsorption
Second-line immunotherapy
Rituximab
Cyclophosphamide
Alternative therapy
Tocilizumab
Low-dose interleukin-2
Steroid-sparing agents used for maintenance therapy
Azathioprine
Mycophenolate mofetil

Table 2: *Treatment modalities.*

Good recovery from illness is generally good with 75% of patients achieving full recovery or with minimal residual deficits [2]. Severe disability may result in the remaining 25% with low mortality rates of 4 - 7%. Reported relapse rates range between 12% and 24%, more often in those without ovarian teratoma [2].

Bibliography

1. Kayser MS and Dalmau J. "Anti-NMDA receptor encephalitis in psychiatry". *Current Psychiatry Reviews* 7.3 (2011): 189-193.

2. Barry H., *et al*. "Anti-N-methyl-d-aspartate receptor encephalitis: review of clinical presentation, diagnosis and treatment". *BJPsych Bulletin* 39.1 (2015): 19-23.

3. Wong D and Fries B. "Anti-NMDAR encephalitis, a mimicker of acute infectious encephalitis and a review of the literature". *ID Cases* 1.4 (2014): 66-67.

4. Dalmau J., *et al*. "Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis". *Lancet Neurology* 10.1 (2011): 63-74.

5. Hughes EG., *et al*. "Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis". *Journal of Neuroscience* 30.17 (2010): 5866-5875.

6. Moscato EH., *et al*. "Mechanisms underlying autoimmune synaptic encephalitis leading to disorders of memory, behavior and cognition: insights from molecular, cellular and synaptic studies". *European Journal of Neuroscience* 32.2 (2010): 298-309.

7. Lee SK and Lee ST. "The laboratory diagnosis of autoimmune encephalitis". *Journal of Epilepsy Research* 6.2 (2016): 45-50.

8. Titulaer MJ and Dalmau J. "Seizures as first symptom of anti-NMDA receptor encephalitis are more common in men". *Neurology* 82.7 (2014): 550-551.

9. Schmitt SE., *et al*. "Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis". *Neurology* 79.11 (2012): 1094-1100.

10. Lancaster E., *et al*. "Immunoglobulin G antibodies to the N-Methyl-D-aspartate receptor are distinct from immunoglobulin A and immunoglobulin M responses". *Annals of Neurology* 77.1 (2015): 183.

11. Masdeu JC., *et al*. "Serum IgG antibodies against the NR1 subunit of the NMDA receptor not detected in schizophrenia". *American Journal of Psychiatry* 169.10 (2012): 1120-1121.

12. Graus F., *et al*. "A clinical approach to diagnosis of autoimmune encephalitis". *The Lancet Neurology* 15.4 (2016): 391-404.

13. Shin YW., *et al*. "Treatment strategies for autoimmune encephalitis". *Therapeutic Advances in Neurological Disorders* 11 (2018): 1756285617722347.

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