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Case Report

Anti NMDA receptor encephalitis: a potentially treatable encephalitis

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ABSTRACT

Anti NMDA receptor encephalitis is autoimmune encephalitis where antibodies are directed against NMDA receptor subunit. It represents a new category of immune-mediated disorder that is often paraneoplastic, presenting with neuropsychiatric symptoms, which is treatable and can be diagnosed serologically affecting both children and adults. Patient can have variable clinical presentation ranging from prodromal illness, neuropsychiatric symptoms, seizures, autonomic instability, hyperkinesias, catatonia, hypoventilation and with or without an associated teratoma. A positive serum or CSF sample screening for antibodies to the NMDA receptor subunit is confirmative. Supportive findings include CSF study, EEG and MRI Brain. The first-line therapies includes IVIG, corticosteroids or plasma exchange. Second line immunotherapy is rituximab or cyclophosphamide or both. Given the high mortality rate (up to 25%), the likelihood of presentation across the age range and the potential for treatment, a high index of suspicion is warranted by clinicians. Authors report a case of a 5 year old child with anti NMDA receptor encephalitis who responded well to IVIG therapy.

Keywords: Anti NMDA receptor encephalitis, IVIG, NMDAR antibodies, Neuropsychiatric manifestations

INTRODUCTION

Anti NMDA receptor encephalitis where antibodies target the NR1-NR2 subunit of the NMDA receptor (NMDAR antibodies) is considered the second most common cause of autoimmune encephalitis after acute disseminated encephalomyelitis in children and adolescents.1The exact prevalence of the disease and the mechanisms that trigger the production of antibodies are unknown.[1] This disorder largely affects young people, and its diagnosis is facilitated by the characteristic clinical picture that develops in association with CSF pleocytosis. The disease presents in three clinical stages; a prodromal stage, an early (psychotic and/or seizure phase), and a late (hyperkinetic) phase. Definitive diagnosis is made by CSF or serum evidence of anti-NMDAR antibodies.[2,3] The clinical symptoms of this disorder correlate well with antibody titre.[4] MRI findings are less predictable in contrast to the consistency of clinical picture as only 55% of patients had increased FLAIR or T2 signal in one or several brain regions, without significant correlation with patients' symptoms.[4] The first-line treatment remains immunotherapy.

The constellation of symptoms in anti-NMDAR encephalitis results in a characteristic syndrome that can suggest alternative diagnoses at different stages. Viral encephalitis and propofol infusion syndrome can mimic anti NMDAR encephalitis.[1] Patients, particularly adults, are often diagnosed with new onset psychosis. The triad of alteration in mental status, rigidity, and dysautonomia can occur in the neuroleptic malignant syndrome (NMS), serotonin syndrome, or lethal catatonia in patients treated with antipsychotic medication such as haloperidol etc.[5] Drugs that block NMDAR function, such as phencyclidine, can produce similar symptoms.[6]

Early identification and treatment may have serious prognostic implications. Delay to treatment with immunosuppressive therapy probably results in worsened outcomes, with evidence for permanent hippocampal damage.[7]

CASE REPORT

Five year old male child, second of a twin child, born of non-consanguineous marriage, born out of infertility conception presented with unprovoked multiple generalized tonic clonic seizures. Patient did not have history suggestive of raised ICT, meningitis, trauma, focal neurological deficits or cranial nerve deficit. Birth and family history was not contributory. Child was neuro-developmentally normal for age.

On examination child was vitally stable, conscious, oriented and obeying commands. He had brisk deep tendon reflexes. Rest of the CNS examination was normal. He did not have signs of raised ICT or meningitis. In view of multiple episodes of convulsion and in status epilepticus child was loaded with antiepileptics phenytoin followed by levetiracetam.

Frequency of seizures decreased. In view of suspected viral encephalitis Inj. Acyclovir was given and started on Inj. Cetriaxone which was later stepped upto Inj. Piperacillin tazobactum as blood culture grew acinetobacter.

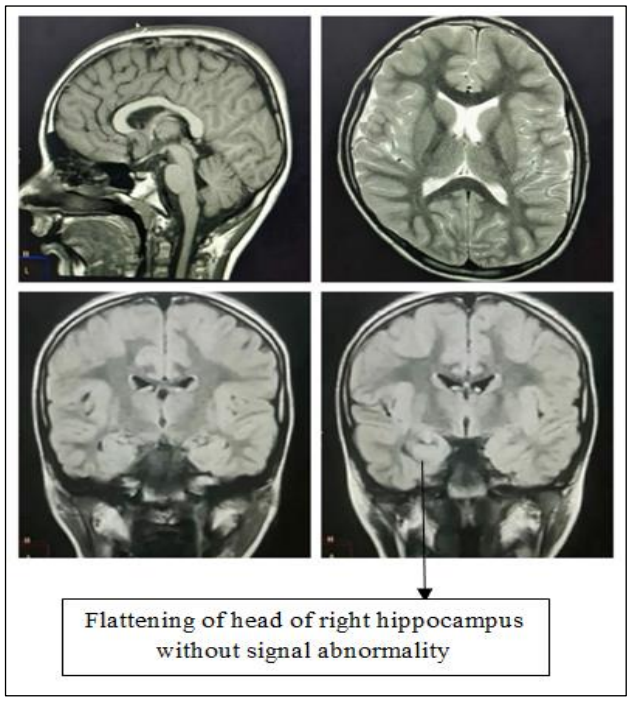

Figure 1: MRI brain, did not reveal any significant abnormality.

On day 8 of admission child developed left complex partial seizures, inappropriate laughter, dystonia of upper limbs, continuous perioral twitching and speech disintegration as Brocas aphasia. Routine blood investigations and CSF were normal. Hb was 10.4g/dl, WBC 8200 with polymorphs of 56%, Platelet 2.1 lakhs. Sodium 142mg/dl, Potassium 3.9mg/dl. EEG revealed severe diffuse encephalopathy. MRI brain was unremarkable showing non-specific changes like flattening of head of right hippocampus without signal abnormality (Figure 1). Child was in refractory status epilepticus and was loaded with Inj. Sodium Valproate and 3% NaCl infusion started. Autonomic instability in the form of hypotension, bradycardia developed and had worsening of GCS for which child was put on mechanical ventilation and started on inotropic support and midazolam infusion. He was treated with injection IVIG at 0.4gm/kg/day for 5 days in view of suspected autoimmune encephalitis. Anti NMDA antibodies directed against NR2 subunit of NMDA receptor in CSF revealed positive result which clinched the diagnosis. Child gradually improved clinically and was weaned off mechanical ventilator. Aphasia with the comprehension being preserved improved in due course. Patient was discharged on antiepileptics.

DISCUSSION

Anti NMDA receptor encephalitis was originally described as a paraneoplastic syndrome in 2005 in four women with ovarian teratomas, presenting with seizures, acute psychiatric disturbances, cognitive deficits, decreased sensorium, autonomic instability and hypoventilation.[8] Dalmau et al, diagnosed these women and eight others after demonstrating specific autoantibodies to the NMDAR.[5] The exact prevalence of this disease is unknown, but more than 500 cases have been reported.[3] Overall, the disorder predominates in females (80%), although in patients younger than 12 year the frequency of males is higher (40%). The mechanisms that trigger the production of the antibodies are unknown. Given that most patients develop a prodromal viral-like illness, a post infectious immune-mediated etiology has been postulated. In a small number of patients, anti-NMDAR encephalitis occurs simultaneously or after infections with a variety of pathogens like human herpes simplex 1 and 6, enterovirus, influenza and mycoplasma pneumoniae. In a subgroup of patients with noninfectious relapsing neurologic symptoms post HSV encephalitis or choreoathetosis post HSV encephalitis the disorder is in fact anti NMDAR encephalitis.

The disease presents in three clinical stages.[2] The initial prodromal stage as fever, cough, cold or vomiting lasting up to 2 weeks. The early (psychotic or seizure phase) stage, characterized by neuropsychiatric symptoms manifesting in children as behavioral disturbances, short term memory loss, cognitive decline and tantrums. Children are more likely than adults to present with seizures, dystonia, or status epilepticus.[9] Within 3-4 weeks, a more fulminant stage described as the late or hyperkinetic stage develops as rapid speech

disintegration, hyperactivity, mutism, orofacial and limb dyskinesias. Progression to decreased responsiveness, catatonia, autonomic instability, cardiac arrhythmias and hypoventilation. A positive serum or CSF sample screening for antibodies to the NMDA receptor subunit is confirmative.[2,3] Supportive findings include CSF study, EEG and MRI Brain. CSF abnormalities are present in approximately 80% of cases and include a mild lymphocyctic pleocytosis, normally or mildly increased protein concentration and CSF-specific oligoclonal bands in 60% cases. EEG shows non-specific, slow disorganized activity. MRI Brain is often unremarkable in 50% cases or shows transient FLAIR or contrast-enhancing abnormalities in the hippocampi, cerebellar or cerebral cortex, front basal and insular regions, basal ganglia, brainstem.[1]

The first-line treatment remains immunotherapy, typically corticosteroids, intravenous immunoglobulins or plasma exchange, in addition to the removal of any identified teratomas.[3] These treatments have enhanced effectiveness and speed of action when patients have an underlying tumor that is removed.[10] IVIG therapy with 0.4 g/kg daily for 5 days or 1 g/kg on day 1 followed by 0.5 g/kg/day for 2 additional days and methylprednisolone 30 mg/kg (children up to 40 kg) daily for 3 days or daily plasma exchange for six cycles would likely have favorable clinical effects. In refractory cases or critically ill patients, patients without a tumor or with delayed diagnosis second-line immunomodulation with rituximab or cyclophosphamide or both may be attempted.[2,11]

Approximately 75% of patients recover or have mild sequelae, 25% have severe deficits or die.1Recovery from anti-NMDAR encephalitis occurs as a multistage process that happens in the reverse order of symptom presentation. Studies have identified a 12-24% risk of relapse.[3] Delay to treatment with immunosuppressive therapy probably results in worsened outcomes, with evidence for permanent hippocampal damage.[7] Other identified predictors of outcome include: lower severity of symptoms, not requiring ICU admission, prompt initiation of immunotherapy and tumour removal where present.

CONCLUSION

High index of suspicion is necessary in a child presenting with neuropsychiatric manifestations, speech disintegration and autonomic instability for the diagnosis of anti NMDAR encephalitis. Management may prove clinically challenging, from the perspective of treating both the cause and the symptoms. Delay in treatment with immunosuppressive therapy probably results in worsened outcomes, with evidence for permanent hippocampal damage. Early identification and treatment may have serious prognostic implications.

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