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Case Report

Pediatric anti N-methyl-D-aspartate receptor encephalitis: a case report

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ABSTRACT

Anti-N-methyl-D-aspartate receptor encephalitis (NMDARe) is a form of autoimmune encephalitis commonly associated internal malignancy. In this report, we present the case of a 6 years girl with acute onset of left partial seizures rapidly progressed to status epilepticus. The patient had recurrent generalized convulsions requiring multiple admissions. She had dominant neuropsychiatric manifestations, polymorphic seizures, agglomeration of movement disorders and cognitive decline. She did not respond to intravenous steroids and immunoglobulins. She responded to rituximab. She was on maintained on azathioprine for eight months and stopped. Presently she is on two anti-epileptic agents and seizure free. She returned back to school with reasonably good scholastic performance. Early detection, immunomodulation and regular follow up gives good long-term outcomes.

Keywords: Encephalitis, Autoimmune, NMDA, Immunotherapy, IVIg, Cancer, Paraneoplastic, Psychiatric manifestations

INTRODUCTION

The autoimmune encephalitis syndromes are a rare group of inflammatory disorders of brain associated with antibodies against neuronal cell surface, synaptic and intra-neuronal proteins. They are often associated with cancer.[1] A significant number tumors are associated with this condition e.g., ovarian and extra-ovarian teratomas, neuroendocrine tumors, thymoma, breast cancer, lung cancers, testicular cancer, lymphomas, B-cell neoplasms, adenocarcinomas and list is ever growing. The pathogenetic mechanisms involved are T-cell mediated or antibody mediated and, in some conditions, still undetermined. The list of antibody markers is ever increasing. N-methyl-D-aspartate receptor encephalitis (NMDARe) is one of these complex syndromes. It is one of the more commonly encountered autoimmune encephalitides. It occurs mostly in above 45 years age, sometimes children are also affected.[2] Its recognition has increased due to greater awareness within the neurology community and availability of diagnostic testing. This condition typically presents with subacute neuropsychiatric symptoms, seizures encephalopathy and is associated with ovarian teratomas in 20% to 59% of patients.

Clinical features

Prominent psychiatric manifestations

Symptoms include anxiety, agitation, bizarre behaviour, hallucinations, delusions, disorganized thinking and psychosis. In rare cases the disease can present as isolated psychosis and psychiatric symptoms may be the only manifestations of recurrence.

Sleep disorders

These include reduced sleep at the onset of the disease and hypersomnia during recovery.

Memory deficits

These include impairment in memory function.

Seizures

It includes occurrence of seizures.

Decreased level of consciousness

This can progress to stupor with catatonic features.

Frequent dyskinesias

These include involuntary movements such as orofacial, choreoathetoid movements, dystonia, rigidity, and opisthotonus postures.

Autonomic instability

Symptoms include hyperthermia, fluctuations in blood pressure, tachycardia, bradycardia, cardiac pauses, and sometimes hypoventilation requiring mechanical ventilation.

Language dysfunction

This includes diminished language output, mutism, and echolalia.

Diagnosis is confirmed based on detection of antibodies in the CSF. However seronegative cases do occur and the following diagnostic approach would be helpful.[3,4]

Rapid onset of working memory impairment (short-term memory loss), changes in mental status, or psychiatric symptoms.

Exclusion of well-defined autoimmune encephalitis syndromes (such as limbic encephalitis, acute disseminated encephalomyelitis, and Bickerstaff brainstem encephalitis).

Absence of well-characterized autoantibodies in blood and cerebrospinal fluid (CSF), along with at least two of the following: magnetic resonance imaging (MRI) findings indicative of autoimmune encephalitis, CSF pleocytosis, CSF-specific oligoclonal bands, or an elevated CSF IgG index, and brain biopsy revealing inflammatory infiltrates and ruling out other conditions (e.g., vasculitis or tumours).

Reasonable exclusion of other potential causes.

There is rapid evolution in the management strategies.[5] The basic principle is immunomodulation and periodic evaluation for malignancy and removal tumour if feasible.[6] Improvement of symptoms might take some time. Relapses are quite common. Diagnosing a relapse of anti-NMDAR encephalitis could be challenging due to the lack of well-defined monitoring guidelines and an incomplete understanding of its natural history.[7]

CASE REPORT

Six years old girl, a local resident, grade-I student, without any prodrome presented with the following.

Left partial seizures involving distal lower limb. Jerky movements lasting for 2-10 minutes, recurring many times serially, spreading to involve left upper limb, and face. No H/O loss of consciousness. Attended a local nursing home. Seizure activity terminated by iv Lorazepam and loading dose of Phenytoin sodium and referred to government teaching hospital, where she developed epilepsia partialis continua. Admitted for 6 days: routine biochemical tests - blood counts, renal, liver functions, electroencephalography (EEG), computed tomography (CT) scan brain, C-reactive protein (CRP), Dengue, and Chikungunya were normal. Seizures controlled in 2 days with intravenous DPH 15 mg/kg/day + midazolam 0.1 mg/kg. Discharged with oral DPH 5 mg/PO/day.

Four days later left partial seizures recurred lasting for 30 minutes, re-admitted for 18 days. Recurrent episodes of seizures were treated with multiple anti-epileptic drugs (AEDs) such as valproate, levetiracetam, phenytoin sodium, lacosamide, oxcarbazepine, and clonazepam, but without significant relief. She developed transient left hemiparesis. Additional tests CSF analysis, MRI brain and virological tests were normal.

The patient was taken to another tertiary care hospital, where she was re-evaluated. Routine biochemical tests, virological tests, S IL-6, US abdomen, MRI, MRA, PET scan whole body were normal, however EEG showed diffuse slowing right hemisphere more than the left and CSF showed NMDA-R antibodies positive, other auto-antibodies were negative. Search for any internal malignancy was negative. A definitive diagnosis of NMDARe was made. Semiology changed to GTCS, developed myoclonic jerks, chorea, opisthotonus and dystonic posturing, weakness in all limbs more on left side. Cognitive decline in cognitive domain, aphasia, not recognizing family members and double incontinence. She developed behavioral abnormality: shouting, excessive crying, biting herself and others, echolalia, excessive drinking water. Seizures got controlled but her psychiatric manifestations continued for several weeks in spite medication. After one year she made steady improvement in behavior and is seizure free.

Treatment history

Treatment included: IV methyl prednisolone for 3 days without any response; IVIg 2 gms/kg over 2 days at rate 0.5 ml/kg/min every 4 weeks for four months, still without much benefit; four cycles of rituximab 250 mg 3 doses /cycle after 2 months of onset, she received totally 4 cycles; monitoring TC/DC, ALC CD19+ and CD20+ counts; oral prednisolone in appropriate doses on tapered and stopped due to adverse events; the patient has been on a combination of AEDs including sodium valproate

(VPA), lacosamide (LCM), brivaracetam (BRT), and clobazam (CLB). Currently, she is on two AEDs: VPA and BRT; and azathioprine was administered as maintenance immunosuppressive therapy at a dose of 0.5 mg/kg/day for 8 months, then discontinued.

Clinical course

The patient did not respond to IV steroids, IVIg and multiple antiepileptic agents. There were 6 admissions in four months for seizures and behavioural problems. After two cycles of rituximab, the patient started improving steadily. After 4 cycles rituximab was stopped. She regained continence, limb power, speech and cognitive functions. Her scholastic performance at school was reasonably good unlike those described in the literature.[8] Though she had a turbulent initial course but subsequently did fairly well without any relapses or deficits.

DISCUSSION

Our patient was only six years old, which is uncommon for NMDARe, although there are cases of much younger patients described in the literature. There were no preceding illnesses. She had intractable seizures and landed up with status epilepticus. The patient did not respond first line of treatments. There was time lapse for procuring free rituximab at government facility. Her return to school is a testament to the effectiveness of the treatment and the importance of early detection and consistent management.

CONCLUSION

This pediatric patient had a masquerading left partial seizures with secondary generalization with status epilepticus without a structural lesion, defied detection for nearly two months. Recognizing NMDARe is crucial in clinical practice because it responds well to immunotherapy despite having 7% fatality rate. Regular follow-up and meticulous management yield rewarding outcomes.

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