Relapsing Anti-NMDAR Encephalitis after a gap of eight years in a girl from North-East India

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Abstract

It has been just 7 years since the discovery of anti-NMDAR encephalitis as distinct immune-mediated encephalitis and we have such cases being reported from our country. Herein, we describe a case of a 13-year-old girl who had relapsing encephalitis consisting of multiple types of difficult-to-control seizures, abnormal behavior, language disintegration, memory loss and abnormal movements eight years after the first clinical attack. In 2005, when she was 5 yearsold, anti-NMDAR encephalitis was not yet discovered and she was provisionally diagnosed as a case of viral encephalitis. During her second attack in 2013, antibodies against NMDAR were demonstrated by immunofluoresence in serum (1:10). This is the first report from our country of a case of relapsing anti-NMDAR encephalitis of such a long duration, successfully treated by immunotherapy.

Key Words

Anti-NMDAR encephalitis, autoimmune encephalitis, relapsing encephalitis

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Introduction

Anti–N-methyl-D-aspartate Receptor (NMDAR) Encephalitis was first described by Josep Dalmau in 2007 as an immune mediated disorder of memory, behavior and cognition in patients with ovarian teratoma.[1] Later as more patients were identified, it was recognized as a distinct type of autoimmune encephalitis that may present without a tumor.[2] It is a multistage illness that progresses from psychosis, memory deficits, seizures and language disintegration into a state of unresponsiveness with catatonic features, abnormal movements, and autonomic and breathing instability. It predominantly affects children and young adults, and responds to treatment but can relapse.[3] The main epitope targeted by the antibodies is in the extracellular N-terminal domain of the GluN1 subunit. Persistence of these antibodies has been described as long as six years after clinical remission.[4] Since its discovery, many cases have been reported from our country.[5,6] We report a unique case of anti-NMDAR encephalitis from North East India, who had relapse after a gap of "eight years". To the best of our knowledge, relapsing anti-NMDAR encephalitis of such a long duration has not been reported so far.

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Case Report

A 13-year-old girl was admitted in our hospital with difficult-to-control seizures. Her symptoms started with worsening of handwriting. Parents noticed that she had involuntary, repetitive pill-rolling hand movements on the right side. She then developed seizures of multiple phenotypes (focal seizures, GTCS, facio-brachial dystonic seizures) and had distinct periods of agitation with unresponsiveness and mutism [Figure 1, Video 1]. She appeared lucid between these episodes, attempting to form words but without speech production. Subsequently, she developed bruxism and dystonic posturing, and at times full body rigidity approaching opisthotonic posturing. She had insomnia, appeared afraid and agitated and cried abnormally and spontaneously. Her reflexes were brisk with unsustained clonus bilaterally, and at times she had waxy catatonia. Opsoclonus was noted during some time. After 10 days of admission, she developed high-grade fever and her sensorium deteriorated. She developed orofacial dyskinesia, autonomic instability, and irregular respiration. Her hospital stay was complicated by sepsis, urinary tract infection and colitis. During this time her modified Rankin Scale (mRS) score was 5. Blood investigations including hemogram, liver function tests, renal function tests,

serum electrolytes, thyroid function and viral markers were normal. Initial MRI Brain and repeat MRI Brain two weeks later were normal. The electroencephalogram (EEG) showed delta slowing in left hemispheric regions. The cerebrospinal fluid (CSF) analysis showed normal cell count, sugar and protein and was negative for Herpes Simplex and Japanese Encephalitis viruses. Serum antinuclear antibody (ANA) was negative. The girl was examined thoroughly for evidence of malignancy. Chest X-ray, contrast enhanced computed tomography (CECT) of abdomen with screening of thorax, ultrasound pelvis and skeletal survey using X-rays were done, and they did not reveal any associated tumor. Tumor markers (CA-125, CEA, α-fetoprotein) were advised, but could not be done due to financial constraints. She was initially started on empirical Acyclovir on benefit of doubt, and her seizures were being managed with multiple antiepileptic drugs (AEDs). Anti-NMDAR antibody was detected by indirect immunofluorescence using cell-based assay with substrate as transfected HEK (human embryonic kidney cells) with NMDA-NR1 receptor protein [Figure 2]. She was started on a combination of intravenous methylprednisolone and intravenous immunoglobulins followed by oral prednisolone. Her symptoms started improving and by four weeks her mRS became 4. She continued improving on oral prednisolone as the AEDs were being tapered. At four months follow-up, her mRS was 1 [Video 2] and her residual deficits included amnesia, mild language disintegration and occasional agitation. She has been advised regular follow-up with repeat ultrasound/magnetic resonance imaging (MRI) of abdomen and pelvis and screening by tumor markers.

When the girl was 5 years of age, she had similar history of subacute onset AED resistant seizures, abnormal behavior and abnormal body movements. Routine investigations were normal. CSF analysis was unremarkable. MRI Brain was normal. Remission of seizures and abnormal movements took more than three months and then she recovered gradually. There was no record of immunotherapy given then. She was fully functional before the second attack eight years later.

Discussion

The family of NMDARs consists of three different subunits termed GluN1-3. GluN2 and N3 subunits are encoded by four (GluN2A-D) and two (GluN3A and B) genes respectively. Functional NMDARs are heterotetramers containing two obligatory GluN1 subunits in combination with two GluN2 and/or GluN3 subunits [Figure 3]. For activation, the GluN1/GluN2 NMDARs require co-agonist glycine and agonist glutamate and GluN1/GluN3 NMDARs require only glycine.[7] The NMDARs are widely distributed throughout the brain including the limbic system (GluN1 ubiquitously, GluN2A in the postnatal brain, GluN2B in the embryonic brain and postnatally in the forebrain, GluN2C in the postnatal cerebellum and GluN2D in the diencephalon and the brainstem at embryonic and neonatal stages). They play a crucial role in synaptic plasticity, learning and memory.[8]

About 70% of the patients with anti-NMDAR encephalitis have prodromal symptoms like headache, fever, nausea, vomiting, diarrhea, rhinitis and sore throat. Within 2 weeks, patients develop psychiatric symptoms such as anxiety, insomnia,

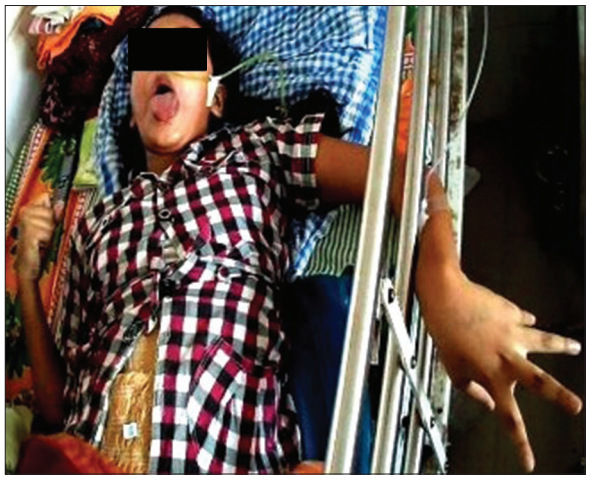

Figure 1: Photograph of our case during an attack of facio-brachial dystonic seizure

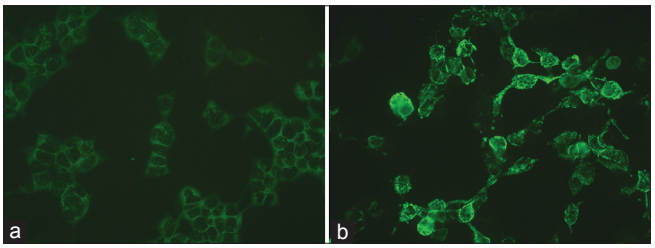

Figure 2: Negative control (a) and our positive case (b) of Anti-NMDAR antibody by Indirect Immunofluorescence

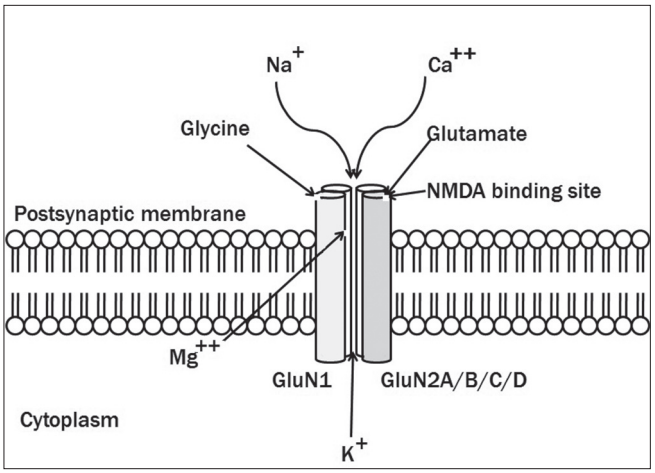

Figure 3: Illustrative structure of NMDA receptor

fear, grandiose delusions, hyper-religiosity, mania, and paranoia. There is usually short-term memory loss and rapid disintegration of language. In children, the first symptom to be recognized is often non-psychiatric — e.g., seizures, status epilepticus, dystonia, verbal reduction, or mutism. This initial phase is followed by decreased responsiveness that can alternate between periods of agitation and catatonia, abnormal movements and autonomic instability. Hypoventilation, requiring respiratory support, can occur. Investigations demonstrate variable CSF lymphocytic pleocytosis, elevated protein levels, and oligoclonal bands, although in a number

of patients the CSF can be unremarkable. MRI can be normal or demonstrate medial temporal fluid attenuated inversion recovery high signal or focal areas of hyperintensity in the frontal or parietal cortex.[3]

Treatment of anti-NMDAR encephalitis consists of immunotherapy. First-line immunotherapy includes steroids, intravenous immunoglobulins, and plasmapheresis alone or combined or tumor removal. Rituximab or Cyclophosphamide or both can be used as second-line therapy. More than 50% have improvement in 4 weeks with treatment (immunotherapy or tumor removal) and more than 80% have clinical improvement at 24 months. In a recently published observational cohort study, 12% had clinical relapses during the 24-month follow-up. Compared with the initial episode, 67% of relapses were less severe, more often mono-symptomatic relapses, and resulted in fewer admissions to the intensive care unit. Patients without a tumor had a higher frequency of relapses than did those with a tumor. The use of immunotherapy was associated with fewer relapses.[9]

In the largest case series on autoimmune encephalitis from India, seven patients had anti-NMDAR encephalitis. CSF analysis and MRI Brain were normal in four patients. The longest duration of illness was reported to be five years. One patient had reduced seizure frequency following treatment with oral steroids. No relapse was reported in the follow-up (> six months).[10]

Our case is a girl who, at the age of 5 years, had difficult-to-control seizures (generalized as well as focal motor), behavioral abnormalities and abnormal movements. During that time, anti-NMDAR encephalitis was not yet discovered. She was provisionally diagnosed as a case of viral encephalitis and treated symptomatically. We did not find any records of immunotherapy given then. She took more than three months to recover. Recovery without immunotherapy is known in anti-NMDAR encephalitis, albeit with the consequences of prolonged hospitalization and higher risk of relapse. Quite uniquely, our case was apparently well for eight years, when she presented again with AED resistant seizures of multiple types, memory loss, behavioral abnormalities and abnormal movements of body. Because we now know about the immune-mediated disorders causing limbic encephalitis and because of case reports and series of their existence in our country, we could identify the etiology in our case. Rise in NMDAR antibody titers in relapsing cases is known.[11] So this second attack after eight years could possibly be a relapse of the same disease. Unfortunately, we cannot prove anti-NMDAR encephalitis as the cause of her symptoms eight years ago. But given the age and gender, the description of typical symptoms, normal MRI Brain, exclusion of other causes and gradual recovery, we presume that the first attack then was probably due to anti-NMDAR encephalitis, which was not a known entity then.

Conclusion

Anti-NMDAR encephalitis is an increasingly recognized etiology of previously unexplained encephalopathy and encephalitis. We report a case of anti-NMDA receptor encephalitis from our country, first of its kind with probable relapse after a gap of eight years. Such cases may have been missed previously due to recent recognition of these immune- mediated disorders and due to lack of awareness. A combination of seizures, memory loss, behavioral abnormalities and abnormal movements should give a clue to the diagnosis. The role of anti-NMDAR antibodies in follow-up of these patients needs to be addressed, as there may be risk of relapse even after a long duration.

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