

Case Report :

Epilepsia Partialis Continua presenting as Anti-NMDA Receptor Antibody Encephalitis

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Abstract:

Anti-N-methyl D-aspartate receptor (anti-NMDAR) encephalitis, recently recognized as a form of paraneoplastic encephalitis, is characterized by a prodromal phase of unspecific illness with fever that resembles a viral disease. The prodromal phase is followed by seizures, disturbed consciousness, psychiatric features, prominent abnormal movements, and autonomic imbalance. Here, we report a case of anti-NMDAR encephalitis with initial symptoms of epilepsy partialis continua in the absence of tumor. A 6-years-old girl was admitted to the hospital with complaint of right-sided, complex partial seizures without fever. The seizures evolved into epilepsy partialis continua and were accompanied by epileptiform discharges from the bilateral hemispheres. Three weeks after admission, the patient's seizures were reduced with antiepileptic drugs; however, she developed sleep disturbances, behavioural abnormalities, cognitive decline, insomnia and mutism. Anti-NMDAR encephalitis was confirmed by clinical findings of the child and her condition slowly improved with methylprednisolone. Moreover, the patient showed gradual improvement of behavioural and cognitive function. This case serves as an example that a diagnosis of anti-NMDAR encephalitis should be considered even with low titres of Anti NMDAR antibodies being positive but with uncontrolled

seizures, insomnias and mutism without evidence of malignant tumour.

Key words: *Anti-N-methyl-D-aspartate receptor encephalitis, Epilepsia partialis continua, Child*

Introduction :

Autoimmune encephalitis comprises an expanding group of clinical syndromes that can occur at all ages (<1 yr to adult) but preferentially affect younger adults and children. Anti-NMDAR encephalitis is becoming increasingly recognized as a cause of acute and subacute encephalopathy in both adults and children [1]. Although first described in young women as a disorder associated with ovarian teratomas [2], pediatric cases may represent 40% of all cases [3]. Anti-NMDAR encephalitis presents as a multistage illness with most patients experiencing a viral-like prodromal illness followed by psychiatric symptoms including changes in behavior and speech, emotional lability, and irritability or psychosis. The illness progresses to neurologic symptoms with catatonia, mutism, and seizures, followed by dyskinesia and autonomic instability [4–7]. Children typically are brought to medical attention because of subtle changes in mood, behavior, personality, or language regression [3]. Awareness of the disease and recognition of its symptoms are key to the early diagnosis and prompt initiation of treatment which may improve outcomes. With

treatment, 75% of patients are estimated to recover completely while 25% may face residual neurodevelopmental impairment or death [4].

Here, we present a case of a young child with anti-NMDAR encephalitis that was not associated with tumor. Initial symptoms of epilepsia partialis continua at onset was observed, followed by sleep disturbances, behavioural abnormalities, cognitive decline, insomnia and mutism. The patient showed significant improvement in symptoms after administration of methylprednisolone.

Report :

A 6 year old female came with the complaints of getting up from sleep on one day with a lingering drowsiness and generalized weakness. Patient was taken to a nearby hospital where she was admitted and prescribed medications despite of which her drowsiness did not improve. On day 3 of admission, she was referred to a private hospital where on the 2nd day of admission she experienced 1 episode of GTCS type of convulsions. An MRI was done which was suggestive of a normal scan. LP was done which was also normal. She was in the private hospital for 15 days after which she was transferred to AVBRH for further management.

In AVBRH, she was admitted in the PICU where she experienced high grade fever with multiple episodes of convulsions. She was started on anticonvulsants (inj phenytoin and inj levetiracetam) and fundus examination was done which was negative for papilledema and she had no signs of meningeal irritation. She developed mutism with intermittent episodes of irrelevant speech and dribbling of saliva from the angle of mouth. Widal was sent which was negative. A CT Brain plain was also done which was normal. She had 72 hours of convulsion free period after which the patient was shifted to ward. Then she experienced 2 episodes of GTCS type of convulsions for which she was shifted back to PICU where she landed up in status epilepticus. At this time, the patient was reloaded with anticonvulsant (inj levetiracetam).

In PICU, she had remission of seizures but continued to have intermittent mutism, irrelevant talks and dribbling of saliva. EEG was done of the patient which showed sharp and high amplitude waves which were generalised and reflecting ongoing ictogenic discharges secondary to underlying cause. She was kept on anticonvulsants and after a convulsion free period of 72 hours, she was shifted to ward. Neurophysician opinion was taken and USG abdomen and pelvis along with complete autoimmune encephalitis antibody panel was advised. USG abdomen and pelvis revealed no abnormality, but due to financial issues, only anti-NMDA receptor antibody titres out of the complete autoimmune encephalitis panel were sent which came out to be negative. Patient later also developed 2 episodes of focal seizures for which she was again shifted to PICU initially and started on Inj Valproic acid. She kept having focal seizures after adding another anticonvulsant due to which Pulse therapy with Methyl Prednisolone was started after which the patient improved and her other symptoms also started to regress. The patient was then shifted to ward and phenytoin was tapered and omitted. The patient currently is seizure free and is showing improvement in speech and other symptoms post Pulse therapy with Methyl Prednisolone.

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Photo 1. Clinical Photograph of the Patient

Table 1. Clinical features and laboratory findings of reported cases of anti-NMDAR encephalitis.

Reference	Age (yrs) /sex	Onset time and type of seizure	EEG at diagnosis	Brain MRI
Goldberg et al. ^[8] (2011)	9/F	Five days after prodromic symptoms Altered mental status with a right hemianopsia, partial right sixth nerve palsy, and increased tone in right arm	12–13 Hz, sharply contoured activity from the left occipitotemporal region	Elevated arterial spin labeled perfusion in the left occipital lobe
Finne Lenoir et al. ^[9] (2013)	17/M	Three days after prodromic symptoms Repeated lateral rotations of the head to the right and mild paresis and paresthesia in the right hand and foot	Epileptiform discharges in the left central and fronto-temporal areas	No focal abnormality
Barros et al. ^[10] (2014)	7/M	Four days after prodromic symptoms Repetitive version of eye and head to the right with secondarily generalization	Left parietal-occipital paroxysmal activity	Mild hyperintensity of the left temporal occipital cortex
Present study (2017)	6/F	Fever with drowsiness with multiple episodes of GTCS and focal convulsions. intermittent mutism with irrelevant talks and drooling of saliva.	Sharp and high amplitude waves which were generalised and reflecting ongoing ictogenic discharges secondary to underlying cause.	No focal abnormality

Discussion :

Anti-NMDAR encephalitis has been recognized as the most frequent autoimmune encephalitis in children after viral encephalitis or acute demyelinating encephalomyelitis[7]. As noted in previous case reports, clinical presentation of

anti-NMDAR encephalitis in children is often different from that in adults[2-4]. Adult patients usually present with acute behavioral change and psychosis followed by seizures, dyskinesia, memory and language impairment, and autonomic and breathing dysregulation[1]. However, most children with anti-NMDAR encephalitis have more

frequent neurological symptoms, such as seizures and oro-facial dyskinesias or choreoathetoid movement of limbs rather than psychiatric symptoms at the disease onset. In the present study our patient had alogia, multiple seizures, altered behavior and mutism as the patients of all ages frequently experience progressive decline in speech and language, including alogia, echolalia, perseveration, mumbling, and mutism reported by Dalmau et al and Florence et al[3,4]. These alterations in speech often persist throughout other stages of disease. In sum, the initial psychiatric phase of the syndrome appears to last 1-3 weeks[2,10], though some cases raise the possibility of a longer course of behavioral and personality changes at attenuated levels preceding symptomatic presentation[1,3]. Children with anti-NMDAR encephalitis have the rare development of mono-symptomatic illness with less severe autonomic manifestations[2-4]. A recent study showed that seizures at the onset of anti-NMDAR encephalitis were predominant within a group of pre-pubertal children, suggesting that modification of hormonal activity related to puberty could represent a key factor in the progression of the clinical presentation of anti-NMDAR encephalitis at different ages[4]. In some cohorts, most pediatric patients presented with partial motor or complex seizures, whereas generalized tonic-clonic seizures or status epilepticus were infrequently presented[3,8]. Cases of *epilepsia partialis continua* in pediatric anti-NMDAR encephalitis were rarely reported[9-11] (Table 1). Our patient also presented with *epilepsia partialis continua* following repetitive partial seizures. The uncommon initial symptom in anti-NMDAR encephalitis leads to diagnostic difficulties in the course of the first days following the onset. However, subsequent repetitive orofacial dyskinesia, dystonic or choreoathetoid movements of the limbs, and cognitive deficits were important clinical clues to suspect and diagnose anti-NMDAR encephalitis eventually. Although laboratory findings of CSF, EEG, and brain MRI are not diagnostic tools for anti-NMDAR encephalitis, some characteristic

findings have been suggested by some studies. For our patient, CSF studies revealed no abnormal finding other than an oligoclonal band. CSF analysis in patients with anti-NMDAR encephalitis usually identifies lymphocytic pleocytosis with frequent oligoclonal banding[1]. However, a recent study reported that the frequency of CSF alteration was lower in children than in adults[2]. On EEG, our patient showed sharp and high amplitude waves which were generalised and reflecting ongoing ictogenic discharges on EEG. Disorganized and diffuse or focal (predominantly fronto-temporal) slowing of electrical activity in the delta-theta range, sometimes with rhythmical appearance or epileptic activity on EEG, has been described in children with anti-NMDAR encephalitis similar to that reported in adults[3,5]. Our patient had normal brain MRI. In most cases, MRI of the brain is usually normal or shows non-specific focal changes at the initial stages of anti-NMDAR encephalitis. Increased signal on T2 or FLAIR MRI sequences could be revealed in basal ganglia, medial temporal lobes, brainstem, or cerebellum[1,3]. White matter changes and cerebral atrophy have been noted as atypical MRI changes in a few cases of anti-NMDAR encephalitis[5]. As noted in previous case reports, most children with anti-NMDAR encephalitis do not have an underlying tumor[2,3]. Similarly, our patient had no identifiable tumor. Although the mechanisms that initiate this disorder are unknown, it has been suggested that the presence of a tumor that expresses NMDAR likely triggers the immune response. However, the low frequency of paraneoplastic etiology in children with anti-NMDAR encephalitis suggests that other immunological triggering mechanisms are associated with postinfectious auto-immune process or an underlying genetic predisposition for disease onset[3]. Although the triggering mechanism remained unclear in our patient, the absence of a malignancy and good clinical outcome without relapse suggest that a postinfectious auto-immune process is possibly involved. *In vivo* and *in vitro* studies have shown that the structural and functional effects of anti-NMDAR antibodies

would result in specific reduction of the levels of synaptic NMDAR by a mechanism of antibody capping, cross-linking, and internalization of the receptors[12]. In addition, the anti-NMDAR antibodies abrogate NMDAR-mediated currents, potentially altering the mechanisms of synaptic plasticity and enhancing the excitability of the motor cortex[13]. Overall, these antibody effects coupled with the characteristic clinical syndrome have contributed to the development of treatment strategies by not only removing antibodies from the serum, but also abrogating the inflammatory infiltrates and the synthesis of antibodies within the CNS. Although there is no uniform systematic treatment approach, treatment of anti-NMDAR encephalitis in childhood is focused on the empirical use of immunosuppressive therapies and supportive care. In initial studies largely involving patients with paraneoplastic disease, response rates to tumor removal and first-line immunotherapies (such as corticosteroids, IVIG and plasmapheresis) were high[1]. However, it is recognized that tumor negative patients may not respond to first line immunotherapy. A recent review of anti-NMDAR encephalitis suggested that cyclophosphamide and rituximab should be used as second-line immunotherapies in these patients[14]. Our pediatric case with nonparaneoplastic anti-NMDAR encephalitis was treated with methylprednisolone without apparent side effects. Her outcome was good, although her recovery was slow. Some studies reported that most children with anti-NMDAR encephalitis had remarkable clinical improvement or full recovery[2,4]. Recent research by Armangue et al.[2] reported that 85% of pediatric patients had remarkable improvement or full recovery, although the recovery was achieved 8-12 months after the symptom onset. These results suggest that the production of anti-NMDAR antibodies within the central nervous system as well as systemic production might have contributed to the systemically slow response to immunotherapy and prolonged the duration of disease. Lower severity of symptoms and early treatment of immunotherapy as well as tumor removal are likely to

reduce relapses and limit morbidity associated with anti-NMDAR encephalitis[4].

In summary, we report the case of a Indian child with anti-NMDAR encephalitis, initially presenting with focal status epilepticus followed shortly by other characteristic manifestations such as mutism and altered behaviour. Anti-NMDAR encephalitis is an important cause of neuropsychiatric deficits in children, which has to be considered as the differential diagnosis in children with uncontrolled seizures followed by the development of dyskinesias, even if they are young age without evidence of a malignant tumor. Early recognition and aggressive treatment therapies are essential in order to improve outcomes.

Contribution Of Authors –Anjali Kher-manuscript ,Jayant Vagha-guidance and final scrutiny,Ayush Shrivastav-initial work up ,Shreyas Borkar-scanning of literature,Rupali Salve- treatment and follow up

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Conflicts of Interest :

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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