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Original Article

Extended Clinical Spectrum of Anti–*N*-Methyl-D-Aspartate Receptor Encephalitis in Children: A Case Series

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ABSTRACT

OBJECTIVE: There is a wide spectrum of clinical manifestations in children with anti–*N*-methyl-D-aspartate (NMDA) receptor antibody encephalitis from two different health care settings. **METHODS:** We describe our experience with 13 patients (median age, 7 years; range, 5 months to 19 years) presenting to tertiary referral centers in India and the United States. **RESULTS:** Initial manifestations were neurological (seizures or movement disorders) in eight patients, and psychiatric (e.g., emotional lability and hallucination) in five patients. Symptoms during the clinical course included seizures in ten patients, movement disorders (dyskinesia and choreiform movements) in 11 patients, and behavioral changes (aggressiveness and insomnia) in ten patients. Concomitant infections (herpes simplex virus 1, tuberculous meningitis, and influenza A) were present in three patients. Analysis of the cerebrospinal fluid in all except two cases preceded by infection (herpes simplex virus encephalitis and tuberculous meningitis) was unremarkable. Treatment included intravenous immunoglobulin/methylprednisolone (11 patients), rituximab (eight patients), plasmapheresis (two patients), and cyclophosphamide (two patients). Six patients recovered completely. Two patients had mild residual neurological deficits, whereas four had severe residual neurological deficits. Two patients had profound autonomic instability, which was the cause of death for one of them. Two patients relapsed at two and six months after the initial recovery. **CONCLUSIONS:** We describe the differences and similarities of clinical presentation, test results, and response to treatment of children with anti–*N*-methyl-D-aspartate receptor encephalitis from India and the United States. Included is a description of one of the youngest patients with anti–*N*-methyl-D-aspartate receptor encephalitis (five months) and the first patient to be reported in association with tuberculous meningitis.

Keywords: seizures, acute psychosis, movement disorder, autonomic instability

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Introduction

Anti–*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis was first described by Dalmau et al.[1] in 2007 and is now recognized as one of the most common etiologies of encephalitis in the pediatric population.[2-4] It is estimated that approximately 37% of cases of anti-NMDAR encephalitis occur in infants and children.[5] In almost half of these individuals, anti-NMDAR encephalitis initially presents with a prodrome of fever, headache, and vomiting, followed by neurological or psychiatric manifestations.[6]

Paralleling the increased awareness of anti-NMDAR encephalitis, the realization that this condition needs to be considered and treated before confirmation of the diagnoses. Multiple studies have shown that earlier treatment of the anti-NMDAR encephalitis in children results in better outcome.[5,7] We describe 13 pediatric cases from tertiary care centers in the United States and India to emphasize the similarities in the clinical spectrum, disease progression, and treatment outcomes of anti-NMDAR encephalitis in different parts of the world.

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Methods

Thirteen patients were identified between 2010 and 2016 after evaluation in tertiary care hospitals in India (Santokba Durlabhji Memorial Hospital, Jaipur, India) and the United States (Montefiore Medical Center and Jacobi Medical Center, Bronx, NY). Five patients were referred to centers following onset of symptoms, whereas eight children presented directly to these centers. All patients were diagnosed with anti-NMDAR encephalitis based on cerebrospinal fluid (CSF) and plasma anti-NMDAR antibody positivity by enzyme-linked immunosorbent assay (ELISA). At the time of admission, all patients were provisionally diagnosed with encephalitis (infective/autoimmune). Although no standard guidelines were followed for the performance of diagnostic studies, most patients underwent a magnetic resonance imaging (MRI) of the brain, an electroencephalogram (EEGs), and a lumbar puncture with CSF studies including bacterial and viral culture, herpes simplex virus (HSV), and enterovirus polymerase chain reaction. For each patient, treatment was based at the attending physician's discretion.

Results

Patient characteristics

The median age of the 13 patients (seven female) was seven years (range, 5 months to 19 years). In the Indian cohort the median age was 2.5 years, whereas in the US cohort it was nine years. Anti-NMDAR antibodies were identified in the serum and in the CSF of all but one patient, who had CSF positivity only. The median follow-up period was six months (three months to two years). Clinical information for each case is summarized in the Table.

Presenting symptoms

Prodromal symptoms were identified in eight patients (62%). The most common symptoms were fever (50%), nausea and emesis (25%), and irritability and insomnia (17%). In eight patients, the initial manifestations were neurological (six with seizures and two with a movement disorder). The most common movement disorders were orofacial dyskinesia and choreoathetoid movements of the limbs. In five patients, the initial manifestations were psychiatric (emotional lability and hallucinations).

One patient developed anti-NMDAR encephalitis 6 days after initiating treatment for HSV encephalitis with acyclovir, and another patient developed anti-NMDAR encephalitis 4 weeks after Influenza A infection. A third patient was diagnosed with anti-NMDAR encephalitis 1 week after starting treatment for tuberculous meningitis. He developed acute severe oromotor and limb dyskinesia, leading to the diagnosis.

Clinical course

During the course of the disease, almost all patients developed either seizures or movement disorders. Among the ten patients that developed seizures, 40% were focal, 40% were generalized, and 20% had both focal and generalized seizures, 20% of these patients had status epilepticus. In total 11 patients developed movement disorder during the clinical course, the common movements were orofacial dyskinesia and choreoathetoid movements of the limbs. Changes in behavior (e.g., aggressiveness, insomnia, and irritability) were observed in ten patients. Autonomic features were seen in six patients including temperature instability (five patients, hyperpyrexia; two patients, fluctuating core temperature) and bradycardia. Two patients required mechanical ventilation. There was a major difference in the duration of hospital stay in India (1 to 21 days) versus the United States (14 to 56 days). Seven patients were transferred to a rehabilitation center for further care and one patient died in India.

The EEG was abnormal in all the patients and typically revealed diffuse background slowing. Epileptiform activity was observed in two patients. An extreme delta brush pattern, characteristic of anti-NMDAR encephalitis,[8] was identified in only one patient. Thirteen patients underwent MRI of the brain. In all except two patients the test was deemed to be normal. MRI abnormalities were seen in the patients with previous HSV encephalitis (multiple lesions bilaterally in the subcortical white matter and hemorrhagic lesions in the left temporal region) and tuberculous meningitis (diffuse basal enhancement with enhancing exudates). These lesions were assumed to reflect the prior infections and not anti-NMDAR encephalitis-related changes.

Routine CSF studies were normal in 11 of 13 patients. The results were abnormal in the children with post-HSV infection and tuberculous meningitis. Oligoclonal bands were absent, and CSF bacterial and viral cultures were negative in the other 11 patients. One patient underwent brain biopsy, which showed infiltration with inflammatory cells including monocytes and macrophages with immunostaining positive for CD3 (T cell) and CD20 (B cell).

All patients underwent screening for underlying tumors with MRI of the chest, abdomen, and pelvis or a testicular ultrasound in males. An ovarian mass was suspected in two patients and both underwent oophorectomy. A mature cystic teratoma was found in one patient and the pathology was normal in the second patient.

Treatment

On the basis of the clinical suspicion, patients were treated empirically for presumed anti-NMDAR encephalitis pending antibody conformation. All but one patient, whose parents refused treatment, were treated initially with methylprednisolone (30 mg/kg/day for 5 days with a slow taper), intravenous immunoglobulin (IVIG) (2 g/kg divided over 2 to 5 days), or with both agents simultaneously. IVIG was preferred in patients with unexplained fever. Plasmapheresis was performed in two patients whose symptoms proved to be refractory to steroids and IVIG. Second-line therapy was initiated when there was little or no improvement after the initial treatment. Weekly infusions of rituximab were administered (three to four cycles) in eight patients, with two patients also receiving cyclophosphamide.

Antiepileptic drugs were used in 11 patients for a duration of three to six months. None of the patients developed seizures after cessation of treatment. Antipsychotic medications were used for behavioral control (e.g., risperidone). All patients underwent neurorehabilitation evaluations and received services based on their clinical needs.

TABLE.
Demographics, Clinical Features, Treatment and Outcomes of Children With Anti NMDAR Encephalitis

Case Number	Age	Sex	Neurological Symptoms	Psychiatric Symptoms	Autonomic Dysfunction	Investigation	Treatment	Outcome	Atypical Features
Albert Einstein cohort (Montefiore/Jacobi) (United States)									
1	5 years	M	Seizures (generalized), facial twitching	Aggression, emotional labiality, insomnia	Fever	Unremarkable MRI, EEG, and CSF	Steroids, IVIG	Improved but not back to baseline	Influenza A positive on presentation
2	7 years	F	Seizures (generalized, status epilepticus), dystonia, orofacial dyskinesia	Insomnia, agitation	Fever	Unremarkable MRI, slow EEG, and CSF	Steroids, IVIG, plasmapheresis, rituximab	Improved to baseline	Status epilepticus
3	7 years	M	Seizures (focal), orobuccal dyskinesia	Emotional labiality, aggression, aphasia	None	Unremarkable MRI and CSF. EEG with focal seizures.	Steroids, IVIG, and plasmapheresis (for relapse)	Still having behavioral issues	None
4	9 years	M	Seizures (focal and generalized), orobuccal dyskinesia	Aggression, akathisia, emotional lability, insomnia	None	Unremarkable MRI and CSF, slow EEG	Steroids, IVIG, rituximab	Improved to baseline	Status epilepticus
5	13 years	F	Choreiform movement	Insomnia, inappropriate behavior	Severe autonomic storms	EEG-delta brush, MRI normal. Ovarian teratoma	IVIG, methylprednisolone, cyclophosphamide, rituximab, plasmapheresis, oophorectomy	Multiple cardiac arrests because of autonomic instability. Trach/G-tube dependent	Severe autonomic storms
6	17 years	F	Choreiform movement	Insomnia, inappropriate behavior	None	Unremarkable MRI, EEG, and CSF	Steroids, IVIG, rituximab	Improved to baseline	None
7	19 years	F	Seizures (focal and generalized), choreiform movement	Intermittent fluctuation of alertness, aphasia	None	Unremarkable MRI, slow EEG, CSF with mild lymphocytosis	Oophorectomy, steroids, IVIG, plasmapheresis	Improved to baseline	None
Santokba Durlabhji Memorial Hospital cohort (India)									
8	6 months	M	Fever, altered mental status	None	Fever	Initially MRI and LP consistent with tubercular meningitis	IVIG, steroids	Global developmental delay	Post-tuberculous meningitis
9	5 months	M	Seizure (focal), choreiform movement	Irritability	Fever	Unremarkable MRI and CSF, slow EEG	IVIG, methylprednisolone, rituximab (for relapse)	Global developmental delay	Infantile onset
10	2.5 years	F	Seizure (focal and generalized) status epilepticus, choreiform movement	Altered sleep pattern, aphasia	Fever, temperature instability	Unremarkable MRI and CSF, slow EEG	IVIG, methylprednisolone, cyclophosphamide, rituximab	Died	Temperature instability, death
11	2.5 years	F	Seizure (generalized), choreiform movement	Irritability	Fever	Initially MRI and LP consistent with HSV encephalitis	IVIG, methylprednisolone, cyclophosphamide, rituximab	Language regression	Post-HSV
12	5 years	F	Seizure (focal status), choreiform movement	None	Fever	Unremarkable MRI and CSF, slow EEG	IVIG, methylprednisolone	Improved to baseline	None
13	11 years	M	Seizure (generalized), expressive aphasia	None	Fever	Unremarkable MRI and CSF, slow EEG	None	Improved to baseline	Expressive aphasia

Abbreviations:
CSF = Cerebrospinal fluid
EEG = Electroencephalograph
HSV = Herpes simplex virus
IVIG = Intravenous immunoglobulin
LP = Lumbar puncture
MRI = Magnetic resonance imaging

Outcomes

Seven patients required critical care monitoring and two needed mechanical ventilation for autonomic instability. The clinical course was followed for up to one year in ten patients. The median time to improvement was two months (seven days to 12 months). Six patients had complete recovery, whereas six patients were left with a mild to moderate neurological deficit, most commonly language deficits and ataxia. Two patients had a relapse (two and six months after initial recovery, respectively) requiring initiation of second-line therapy. The patient who died was a two-and-a-half-year-old girl presenting with fever, new onset seizures, and choreoathetoid movements. She subsequently developed profound temperature instability and bradycardia. She was treated with IVIG and methylprednisolone followed by rituximab and cyclophosphamide with no improvement. She died four weeks after the onset of symptoms in a secondary care hospital because of sudden cardiac arrest likely due to profound autonomic instability (bradycardia, hypotension, and hypothermia). One patient was treated in a critical care unit for profound autonomic instability and multiple cardiac arrests for more than two months and eventually transferred to a rehabilitation facility. During her acute care, this patient underwent emergent bilateral oophorectomy after cardiac arrest. The right ovary contained a mature cystic teratoma.

Discussion

Apparent increased incidence of anti-NMDAR encephalitis in all age groups is likely, at least in part, because of the increasing awareness of the disorder and the relatively easy accessibility of the autoantibody diagnosis test. The increased incidence emphasizes the need for standardized guidelines for its both diagnosis and treatment. In fact, the California Encephalitis Project found anti-NMDAR encephalitis to be more common than any single viral encephalitis.[9] Autoimmune encephalitis comprises an ever-expanding group of potentially treatable disorders that should be in the differential diagnosis when patients present with signs of encephalitis. Clinically, they can resemble infectious encephalitis, and on occasion can be triggered by infectious encephalitis (e.g., herpes simplex encephalitis).[10]

One difficulty with the rapid diagnosis and treatment of anti-NMDAR encephalitis is its varied presentation. Prominent clinical manifestations in adults are psychiatric, whereas children generally present with seizures and movement disorders.[5] Children with anti-NMDAR encephalitis, unlike affected adults, are likely to experience prodromal symptoms such fever, vomiting, or headache.[11] Our patients support this observation, as 67% of them experienced prodromal symptoms. Importantly, the presenting symptoms within our cohort differed with age. All our adolescent patients presented with psychiatric manifestations similar to adults, whereas younger children generally presented with neurological symptoms (77%). Although data in infants with anti-NMDAR encephalitis are limited, our five-month-old patient presented with irritability for three weeks followed by seizures and choreoathetoid movements.

Although the specific cause of anti-NMDAR encephalitis remains unknown, most reports have postulated a virus-induced etiology.[10,11] In our series, one patient developed anti-NMDAR encephalitis as a complication of HSV encephalitis, whereas in a second patient, it followed infection with influenza A. Of note, four of seven patients in our US cohort presented during a short period between January and February, which also suggests an infectious etiology.

The significant difference regarding age range (median age 2.5 years in Indian cohort versus nine years in the US cohort) may possibly indicate a geographical difference with younger children being affected more in India, but more epidemiologic studies are needed to replicate these observations. Similarly, outcomes were generally worse in the Indian cohort (global delays and deaths were 50% in Indian cohort versus 15% in the US cohort). This finding may be because the Indian cohort comprised younger children or availability of better medical resources in the United States. However, there are no prior studies to evaluate the prognostic differences between the infants, toddlers, and young children in anti-NMDAR encephalitis.

The longer hospital stay in the US cohort (median, 21 days; range, 14 to 56 days) in comparison to Indian cohort (median, 10 days; range, 1 to 21 days) can be multifactorial. Although severity of illness clearly impacts length of stay (13-year-old girl in the United States with multiple cardiac arrests had a prolonged hospitalization), other factors, such as reimbursement schemes, may also play a role. In India, most patients self pay and have no insurance, pressuring family and health care providers for shorter stays, more aggressive treatment at presentation, and discharge to a less costly secondary care rehabilitative facility.

The child who developed anti-NMDAR encephalitis after tuberculous meningitis, which we report for the first time, is quite relevant for countries where tuberculosis is endemic. In this, clinicians must remain aware of this potential complication of tuberculous meningitis.

Diagnosis of autoimmune encephalitis by standard testing is problematic because there are few clinical or investigational markers that distinguish anti-NMDAR positive cases from those with negative titers.[12] Recently published guidelines help in the differential diagnosis of autoimmune encephalitis using criteria based on conventional clinical neurological assessments and standard diagnostic tests (MRI, EEG, and CSF studies). The guidelines authors proposed levels of evidence for autoimmune encephalitis (possible, probable, or definite) through use of an algorithm, which can lead to prompt immunotherapy. Unfortunately, these guidelines have been suggested only for adults.[13] MRI of the brain is routinely normal and CSF analysis will typically reveal nonspecific lymphocytic pleocytosis (70%) and possibly oligoclonal bands (50%).[5] EEG patterns are typically nonspecific, characteristically generalized background slowing. Only one patient had an EEG showing the classic exaggerated delta brush pattern, which has been associated with anti-NMDAR encephalitis.[8] In one patient who underwent brain biopsy, findings were nonspecific but was consistent with the previous findings of intrathecal synthesis of plasma cells and immunopositivity to CD 20 (B cell marker).[14]

One patient had spontaneous resolution of his symptoms and did not require intervention. This spontaneous resolution occurred in an 11-year-old boy who presented with a ten-day history of an expressive aphasia. Only a few individuals with spontaneous resolution have been described.[15,16]

Finally, we report what may be the youngest patient with anti-NMDAR encephalitis, a five-month-old child who benefited from aggressive treatment including plasmapheresis even at this young age.

Conclusions

Anti-NMDAR encephalitis should be considered in children presenting with acute onset of prolonged or difficult to control seizures, a movement disorder or psychiatric symptoms, especially if preceded by bacterial or viral infections. Teens, like adults, are more likely to present with the acute onset of a psychiatric disorder. Strong clinical suspicion is needed to make an early diagnosis and initiate treatment before confirmation by detecting antibodies in blood or CSF. Herein, we suggest that the presentation and prognosis may be similar throughout the world.

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