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Case Report

Nonparaneoplastic Anti-*N*-Methyl-D-Aspartate Receptor Encephalitis: A Case Series of Four Children

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ABSTRACT

A rare, severe form of immune-mediated encephalitis recently has been described, associated with antibodies against *N*-methyl-D-aspartate receptors. It is reported mostly in women with ovarian tumors. Nonparaneoplastic presentations are less common. We describe four children with a neuropsychiatric and extrapyramidal syndrome associated with the presence of anti-*N*-methyl-D-aspartate receptor antibodies in cerebrospinal fluid and serum, without evidence of neoplasia. Three children recovered completely after immunomodulatory therapy, i.e., intravenous immunoglobulin and/or steroids, methylprednisolone, and/or adrenocorticotrophic hormone.

Introduction

Anti-*N*-methyl-D-aspartate receptor encephalitis is a neuropsychiatric syndrome first described in 2007 by Dalmau et al. [1,2] and Sansing et al. [3]. The *N*-methyl-D-aspartate receptors are ligand-gated, voltage-dependent channels for nonselective cations. They are heterotetramer of the NR1 and NR2 subunits. The NR1 subunit binds to glycine, whereas the NR2 subunit binds to glutamate. Antibodies against NR1-NR2 heteromers were demonstrated in patients with anti-*N*-methyl D-aspartate receptor encephalitis. The NR1 subunit is widely expressed, and appears to be the target antigen of these antibodies [1,4]. Most of the patients described so far have been young women with ovarian teratoma, suggesting that the presence of a tumor expressing *N*-methyl-D-aspartate receptors likely contributes to the loss of immune tolerance, apart from the presence of other unknown immunologic triggers [1,2,5].

However, in children, nonparaneoplastic anti-*N*-methyl-D-aspartate receptor antibody-mediated encephalitis was recently described as a differential diagnosis of subacute pediatric neuropsychiatric syndrome [4,5].

We describe an index patient in detail, along with three similar pediatric cases from our institute. We also evaluate the clinical syndrome, investigations, and therapeutic interventions in four children with proven anti-*N*-methyl-D-aspartate receptor encephalitis.

Case Reports

Index patient

An 8-year-old, previously normal, healthy boy presented at our Pediatric Neurology Clinic (P.D. Hinduja Hospital, Mumbai, Maharashtra, India) with complaints of difficulty finding "words" and the use of gestures to communicate for the preceding 10 days. His behavior had also changed during this period, i.e., he had become aggressive, and occasionally demonstrated purposeless behavior.

No history of fever, headache, or vomiting was reported. On admission to the hospital, he was observed to sleep excessively, with significant expressive aphasia and fluctuating aggressive behavior. The remainder of his neurologic examination was normal.

Routine hematologic and biochemical tests produced normal results. A cerebrospinal fluid study revealed normal glucose and protein, but the presence of 26 leukocytes. Viral polymerase chain reaction studies for herpes simplex virus, enterovirus, and Japanese B virus produced negative results. The cerebrospinal fluid antimeasles immunoglobulin G antibody was not detectable.

Other investigations producing normal results involved C-reactive protein, sedimentation rate, serum antimycoplasma immunoglobulin M antibody, serum antistreptolysin antibody, a throat swab culture, urine porphobilinogen, and antinuclear antibody.

Contrast-enhanced cranial magnetic resonance imaging produced normal results. An electroencephalogram revealed evidence for recurring subclinical left frontotemporal ictal activity, superimposed on a diffusely slow background (Fig 1).

Parenteral antiepileptic drugs including midazolam, fosphenytoin, sodium valproate, topiramate and leviteracetam were administered. However, the patient's clinical condition worsened during the next few days. His score on the Glasgow Coma Scale steadily decreased to 7/15 (eye response-1; verbal response-2; motor response-4). He then developed odd, stereotypic oromotor movements, which were not associated with ictal activity on electroencephalogram.

A further evaluation for possible immune-mediated encephalitis, including antibasal ganglia antibody, antithyroid antibody, antiendomysial antibody, and antivoltage-gated potassium channel antibody, all produced negative results. No improvement in his sensorium was evident, and he continued to manifest limb and

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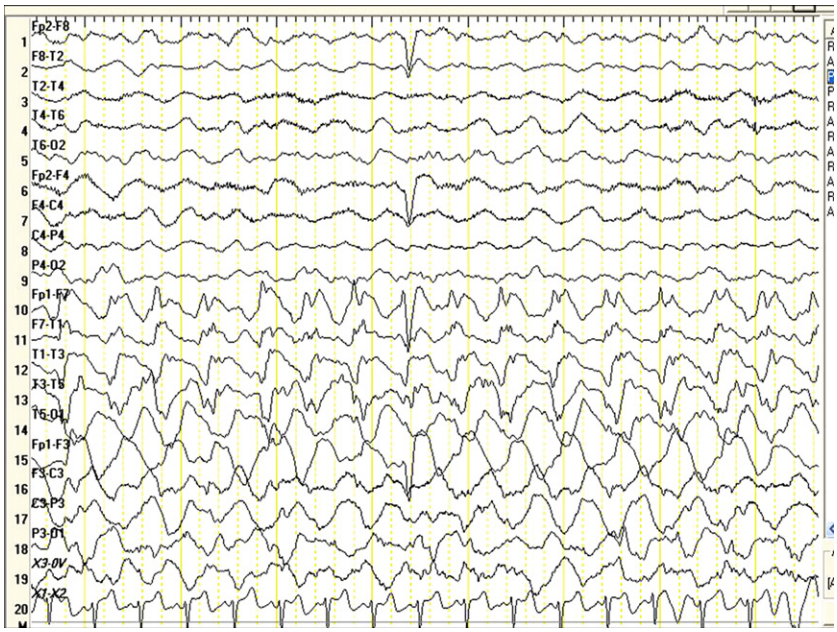

Figure 1. Video electroencephalogram reveals regional left frontotemporal seizure pattern with no clinical signs (electrographic seizures only) in patient 1, diagnosed with anti-*N*-methyl-D-aspartate receptor encephalitis.

oromotor stereotypies. He appeared to be minimally conscious and catatonic at times. He also developed signs of autonomic dysfunction (bradycardia, increased salivation, urinary retention, and temperature instability). His sleep-wake cycle was significantly disturbed.

Pending the results of cerebrospinal fluid and serum anti-*N*-methyl-D-aspartate receptor antibody analyses, a course of intravenous immunoglobulin produced significant improvement, as evidenced by the complete disappearance of ictal activity on electroencephalogram. However, he demonstrated little clinical improvement. A screening for neoplasms included abdominal and testicular ultrasounds, which both produced negative results.

To intensify the patient's immunomodulation, methylprednisolone (25 mg/kg/dose) was administered by injection for 5 days. Later, adrenocorticotropin (70 units per square meter of body surface area) was injected and the dose tapered. After about 2 weeks of therapy, definite improvement was evident in his sensorium and autonomic signs. After 2 months, following an attempted reduction of corticotrophin therapy, he exhibited a worsening of his movement disorder, and corticotrophin therapy was reintroduced. His cerebrospinal fluid and serum tested positive for anti-*N*-methyl-D-aspartate receptor antibodies, according to two laboratories.

At the end of 4 months, he became ambulant and spoke a few words, but demonstrated obvious features of autism, including stereotypical behavior and a lack of adequate visual and auditory attention. He was discharged on gradually reduced doses of corticotrophin, which were administered for a total of 9 months. The clinical improvement continued, and during his 15-month follow-up, he was observed to demonstrate age-appropriate motor and cognitive skills. He had resumed mainstream school, and retained no memory of his stay at the hospital. However, he continues to demonstrate odd behavioral traits, involving periods of reclusive behavior in the form of a refusal to interact or talk, sometimes for hours on end.

Further cases

We have treated three more children with anti-*N*-methyl-D-aspartate receptor encephalitis. We present a cumulative summary of all four patients, including their clinical features, investigations, treatments, and outcomes (Tables 1 and 2).

Our patients comprised schoolchildren who had demonstrated initially prominent neuropsychiatric deficits, with subsequent mutism and swallowing difficulty and a movement disorder characterized by limb, facial, and oromotor stereotypies or choreodystonia. Seizures were common, although they usually did not involve overt status epilepticus. Fever at onset was prominent in only one patient.

Magnetic resonance imaging produced normal results or indicated nonspecific abnormalities. Cerebrospinal fluid studies produced normal results or indicated mild pleocytosis. Anti-*N*-methyl-D-aspartate receptor antibodies were demonstrated in the cerebrospinal fluid of all four patients. Tumor screening produced negative results in all four children.

Intravenous immunoglobulin and pulse methylprednisolone was administered to three patients, whereas two patients received high-dose, prolonged corticotrophin therapy, reduced to a minimum alternate-day dose. One patient required oral prednisolone, reduced to a minimum alternate-day dose for 6 months.

Two of four patients demonstrated complete recovery at the end of 4 and 6 months. The index case demonstrated significant improvement at the end of 8 months. Patient 4 demonstrated a fatal outcome secondary to central apnea, before the initiation of adequate therapy.

Discussion

Dalmau et al. [1,2] and Sansing et al. [3] first described anti-*N*-methyl-D-aspartate receptor encephalitis in 2007, whereas the first few cases of teratoma-associated encephalitis were described by Viataliani et al. in 2005 [6]. The early literature described this encephalitis as a paraneoplastic syndrome in women with ovarian teratoma. The more recent literature further described this neuropsychiatric syndrome in the absence of teratomas in men and children [1,4,5]. Dale et al. described anti-*N*-methyl-D-aspartate positive and negative encephalitis lethargica, wherein those with the presence of antibodies demonstrated prominent dyskinesia, agitation, seizures, and insomnia, and those with an absence of antibodies demonstrated Parkinsonism with somnolence [7]. Episodic agitation, insomnia, mutism, stereotypies, oromotor dysfunction, catatonia, and choreodystonia of the limbs comprised the prominent clinical features in our patients. Complex, stereotyped motions involving the face and limbs, raising suspicious of seizures, were observed in all four patients; similar movements were described in the literature among both adults and children [4,8].

As discussed in regard to the index patient, the differential diagnosis for anti-*N*-methyl-D-aspartate receptor encephalitis includes various forms of autoimmune encephalitis (such as those associated with voltage-gated potassium channel antibodies and Hashimoto encephalopathy), systemic autoimmune disorders

Table 1. Clinical details and investigations of four children with nonparaneoplastic anti-*N*-methyl-D-aspartate receptor encephalitis

	Patient 1 (Index)	Patient 2	Patient 3	Patient 4
Age	8 years	9 years	8 years	5 years, 6 months
Sex	Male	Female	Male	Female
Presenting features	Expressive aphasia, behavioral changes	Episodic abnormal movements	Seizures	Headache, fever-associated seizures
Neuropsychiatric complaints	Insomnia, episodic aggression	Insomnia, irrelevant speech	Episodic aggressive behavior	Confusion
Speech abnormality	Mute	Mute	Mute	Mute
Seizures according to EEG	Subclinical (only detected in EEG)	A few focal motor seizures	Generalized tonic-clonic seizures (twice)	Status epilepticus (once, recovered)
Movement disorders	Oromotor and facial dyskinesias, stereotypic behavior, catatonia	Episodic stereotypies of right upper extremity	Episodic hypermotor stereotyped behavior, oromotor dyskinesia	Near continuous choreodystonia of upper extremities
Autonomic instability	Tachycardia, bradycardia, and temperature instability	No	No	Tachycardia, excessive sweating
Central hypoventilation	No	No	No	Yes
Other signs	Stupor and oromotor dysfunction	Oromotor dysfunction	Oromotor dysfunction	Oromotor dysfunction
CSF study	26 WBCs, 72 G, 21 P	0 WBCs, 67 G, 16 P	1 WBC, 63 G, 23 P	20 WBCs, with normal G and P
Cranial magnetic resonance imaging	Normal results	T_2 hyperintensity in right corona radiata, hyperintensity in caudate nuclei	Normal results	Normal results of first scan; subsequent scan indicative of mild cortical atrophy
Tumor screening	Negative results	Negative results	Negative results	Negative results

Abbreviations:
CSF = Cerebrospinal fluid
EEG = Electroencephalogram
G = Glucose (mg/dL)
P = Protein (mg/dL)
WBC = Leukocytes

(such as systemic lupus erythematosus cerebritis), metabolic disorders (such as porphyria), viral encephalitides, and other disorders such as neuroleptic malignant syndrome [3].

The methods used for detecting the anti-*N*-methyl-D-aspartate receptor antibody include rat brain incubation with representative cerebrospinal fluid (revealing a hippocampal "neuropil" binding pattern), the culturing of nonpermeabilized live rat hippocampal neurons incubated with cerebrospinal fluid, and human embryonic kidney (HEK293) cells transfected with the NR1-NR2B subunits, reacting with a patient's cerebrospinal fluid or serum [1,9]. All four patients manifested the presence of antibodies according to these methods (courtesy of Josep Dalmau, MD, PhD, University of Pennsylvania, Philadelphia, PA, and Angela Vincent, MBBS, John Radcliffe Hospital, Oxford, United Kingdom).

Table 2. Treatments and outcomes in four children with nonparaneoplastic anti-*N*-methyl-D-aspartate receptor encephalitis

Treatment	Patient 1	Patient 2	Patient 3	Patient 4
Intravenous immunoglobulin	Yes	Yes	Yes	No
Injection of methylprednisolone	Yes	Yes	No	Yes
Oral prednisolone	No	6 months	No	No
Injection of adrenocorticotrophic hormone	9 months	No	7 months	No
Duration of hospital stay	40 days	16 days	15 days	14 days
Scores of modified Rankin scale at 2 months*	4	1	2	6
Scores of modified Rankin scale at 4 months	3	0	1	
Scores of modified Rankin scale at 6 months	2	0	0	
Scores of modified Rankin scale at 12 months	1			
Outcomes†	B	A	A	F

* Scores of modified Rankin scale: 0, no signs at all; 1, no significant disabilities; 2, cannot perform all previous activities, but no assistance is needed; 3, moderate disabilities, requiring some help, can walk without assistance; 4, dependent on others for activities of daily living; 5, severe disabilities, bedridden, and requiring constant nursing care; 6, dead.

† Outcomes: A, full recovery; B, >75% recovery, with substantial improvement; C, 50-75% recovery, with some remaining deficits; D, <50% recovery, with severe signs remaining; E, no recovery; F, dead.

As described in the literature, younger patients exhibit a lower likelihood of an associated tumor [1,4,5]. None of our patients manifested the presence of any neoplasm. They were screened using ultrasound of the abdomen, including the ovaries and testes. Some case series recommend the use of magnetic resonance imaging or computed tomography of the abdomen for the same purpose [4,5].

First-line immunotherapy, involving immunoglobulin, corticosteroids, and plasma exchange, were used to treat most of these patients, whereas some required second-line agents such as cyclophosphamide and rituximab [1,4,5].

In addition to the use of immunoglobulin, methylprednisolone, and oral steroids, two of our patients exhibited definite improvement with corticotrophin therapy. Because corticotrophin has proven effective in opsoclonus-myoclonus-ataxia, a paraneoplastic syndrome in which an autoimmune process against neuronal surface protein may occur, this therapy was attempted in two of our patients with anti-*N*-methyl-D-aspartate receptor encephalitis [10]. Moreover, an opsoclonus-myoclonus-ataxia-like clinical syndrome was also described in a patient with anti-*N*-methyl-D-aspartate receptor encephalitis [11]. We propose that immunotherapy with corticotrophin injections should be attempted in patients with anti-*N*-methyl-D-aspartate receptor encephalitis, at least before they are started on a second-line therapy such as rituximab.

The outcomes in three patients were very gratifying, although course of their illness was prolonged. A better prognosis in nonparaneoplastic encephalitis, as opposed to paraneoplastic encephalitis, is not surprising. One fatality in our series involved a girl from another country, already a couple of months into her illness; she died of central hypoventilation.

All three of our patients retained no memory of their illness, which occurred secondary to the disruption of their mechanism of synaptic plasticity, and which constitutes a well known phenomenon in anti-*N*-methyl-D-aspartate receptor encephalitis [1,12].

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