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Case Report

Anti-NMDA-receptor antibody encephalitis in infants

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ABSTRACT

Purpose: Anti-N-methyl-D-aspartate (NMDA) receptor antibody encephalitis is an autoimmune disorder manifesting subacutely with prominent aberrant movements and psychiatric symptoms. The clinical course is one of progressive clinical deterioration that can be halted and often reversed by early diagnosis and treatment. Patterns of presentation and etiology of anti-NMDA-receptor antibody encephalitis are dependent on age and can be challenging to recognize in very young children.

Reports: Sequential clinical case observations of anti-NMDA-receptor antibody encephalitis presenting in very young children were examined over a year at a single tertiary pediatric institution. Cerebrospinal fluid confirmed anti-NMDA-receptor antibodies in two cases (a 21-month-old boy and a 29-month-old girl) that demonstrated either bizarre behavioral patterns or status epilepticus both associated with progressive deterioration. Once recognized, the clinical course was arrested and reversed by aggressive treatment with plasma exchange, immunoglobulin, and high dose IV steroids.

Conclusion: Infants with anti-NMDA-receptor antibody encephalitis can present with frank seizures or seizure mimics. Regardless, prompt recognition and aggressive treatment of anti-NMDA-receptor antibody encephalitis, while challenging, can quickly arrest deterioration and hasten recovery, thereby, limiting neurological morbidity.

1. Introduction

Anti-N-methyl-D-aspartate (NMDA) receptor antibody encephalitis is an autoimmune disorder presenting subacutely with prominent aberrant movements and aberrations in behavior associated with clinical deterioration over several weeks [1,8]. In teenagers and adults, the presentation and clinical course are well recognized. Prompt recognition and treatment may reverse the condition, hastening recovery and limiting neurological morbidity. In very young children, the clinical presentation is less well-defined and poses a diagnostic challenge particularly when presenting with prominent psychiatric symptoms.

We report 2 young children presenting with seizure-like movements with CSF-confirmed anti-NMDA-receptor antibody encephalitis at a single tertiary pediatric institution, where all patients with neurological symptoms are evaluated by a primary pediatric neurology team. The tertiary referral children's hospital serves a population catchment area of approximately three million.

2. Reports

2.1. Patient 1

A healthy 21-month-old girl presented with status epilepticus that was not associated with fever. A few days prior to presentation, the family noted a change in behavior with episodes of terrified appearance. This was followed by seizures manifesting with orobuccal automatism and secondarily generalized seizures. Continuous video-EEG demonstrated clinical and electrographic seizures originating independently from the right central and left centrotemporal head regions. Seizures were ultimately controlled with lorazepam, levetiracetam, phenobarbital, and phenytoin. Six days after admission, she developed agitation and severe bilateral upper extremity choreiform movements associated with oral dyskinesias that failed to respond to risperidone and tetrabenazine that were reduced after starting memantine.

Initial and subsequent blood counts, general and metabolic serum panels, urinalysis, and cerebral MR imaging with and without contrast were normal. Cerebrospinal fluid analysis showed white blood count of 53/mm^3 with predominant lymphocytosis, associated with a normal glucose and protein. Cerebrospinal and blood cultures were negative. Antistreptolysin O, antinuclear antibody, lupus anticoagulant, cytoplasmic–antineutrophil cytoplasmic antibodies, perinuclear–antineutrophil

Abbreviations: Anti-NMDA-receptor, anti-N-methyl-D-aspartate-receptor; CSF, cerebrospinal fluid; EEG, electroencephalogram.

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cytoplasmic antibodies, and antiphospholipid antibody titers, thyroid function studies, creatine kinase, lactic acid, and serum ammonia were normal as were serum amino and urine organic acids, carnitine, and acylcarnitine.

A presumptive diagnosis of an autoimmune encephalopathy was entertained, and a course of immunoglobulin and high dose methylprednisolone was administered. Over the course of ten days, she experienced improvement in the dyskinesias, and seizures came under control. The patient was treated with rituximab as maintenance therapy but developed an allergic skin reaction. She was then treated successfully with cyclophosphamide maintenance therapy.

Three weeks after admission, the CSF that had been initially sent for anti-NMDA-receptor antibodies, ultimately confirmed the diagnosis. Over the course of her three months of hospitalization, the patient clinically improved with marked reduction of seizures and the disappearance of agitation and choreiform movements. Her neurological and developmental functions returned to pre–illness baseline, and she continued to make improvement in outpatient follow-up without relapses over the subsequent 5 months.

2.2. Patient 2

A healthy 29-month-old boy presented with 1-week history of bizarre psychiatric symptoms that progressed to behavioral aggression, insomnia, and disuse of the left upper extremity that were thought to be seizures.

He had episodic outbursts of excessive, inconsolable crying and distress that were described "as though he was having nightmares while awake". He had delayed sleep onset from his baseline, decreased appetite, decreased activity level, and emesis. Subsequently, he had dysarthria with progressively decreasing verbal output to the point of mutism with preserved comprehension.

Cranial nerves, muscle bulk and strength, and reflexes were normal. His tone was episodically increased in the left upper extremity with prominent intermittent dystonia and positive Babinski response on left plantar stimulation. Sensory exam was normal to pin prick and vibration. Gait was initially normal but progressively worsened to significant ataxia and frequent falls when trying to stand or ambulate unassisted.

Past history was significant for streptococcal-negative pharyngitis and a motor vehicle accident. The accident occurred at age 19 months when he sustained a pneumothorax that fully recovered. His development was normal, described as an independent, mild-mannered and active toddler. Pregnancy, birth, and family histories were unremarkable.

Because of suspicion of seizures and status epilepticus, an urgent EEG was obtained that captured movements and showed them to be nonepileptic seizure mimics consisting of unilateral extremity quasi-rhythmic movements, and AEDs were withheld.

Cerebrospinal fluid analysis showed 8 WBC and 450 red blood cells without xanthochromia. Cerebrospinal fluid protein was 26 mg/dL, and cerebrospinal lactate and glucose were normal. Cerebrospinal fluid herpes and enterovirus amplifications were negative. Blood counts, chemistries, and urine drug screen were unremarkable. Antistreptolysin O, antinuclear antibody, lupus anticoagulant, cytoplasmic–antineutrophil cytoplasmic antibodies, perinuclear–antineutrophil cytoplasmic antibodies, and antiphospholipid antibody titers, thyroid function studies, creatine kinase, lactic acid, and serum ammonia were normal as were serum amino and urine organic acids, carnitine, and acylcarnitine. Cerebral MRI, EEG, echocardiography, and abdominal ultrasound were normal.

Given his progressive neurological deterioration as well as prominent motor and psychiatric manifestations, an empiric diagnosis of autoimmune-mediated encephalitis was made (and confirmed two weeks later). An empiric trial of intravenous immunoglobulin of 2 g/kg and methylprednisolone 30 mg/kg/day were administered over the course of 5 days. Over the subsequent 6 days, he demonstrated marked improvement in language, behavior, appetite, and sleep. He was able to walk without support, and choreoathetoid movements diminished dramatically. Repeat cerebral and spine MR imaging remained normal.

At this time, results of CSF anti-NMDA-receptor antibodies were positive, and he was placed on mycophenolate with a plan to treat him with immune-modulatory therapy for a full year.

3. Discussion

Two infants presented with aberrant behaviors that were initially unrecognized as pathological. Seizures were suspected in both infants. Only with evolution to seizures or seizure mimics including unilateral quasi-rhythmic movements was neurological involvement suspected. A negative preliminary work-up in the face of further neurological deterioration prompted search for an immune-mediated encephalopathy, which was confirmed serologically to be anti-NMDA-receptor antibody encephalitis.

This report demonstrates the difficulty in identifying behavioral aberration, often a first sign of anti-NMDA-receptor antibody encephalitis, in infants. Seizures or seizure mimics with psychiatric symptoms should raise suspicion. Prompt aggressive empiric treatment was initiated prior to CSF confirmation and was based on symptomatology and absence of common etiologies. Immune therapies rapidly arrested further evolution and were followed by full clinical recovery. During this one-year period, we did not identify children outside infancy with the disorder, although a search of our records for the prior five years identified four older children with anti-NMDA-receptor antibody encephalitis. The clinical presentation of the older children included a movement disorder in three and status epilepticus in one who later developed a movement disorder. Tumors or female preponderance is not observed in pediatric patients with this diagnosis [1,2,8,10,11].

The incidence of anti-NMDA-receptor antibody encephalitis in pediatrics remains to be defined, although recent studies suggest that it is the second most common immune-mediated encephalitis, after acute disseminated encephalomyelitis [3]. In about 70% of patients, the clinical course of anti-NMDA-receptor antibody encephalitis is preceded by a nonspecific prodromal stage with fever, headache, nausea, or upper respiratory symptoms [2]. Psychiatric symptoms include anxiety, insomnia, paranoia, and agitation [2]; increased agitation and delusional thoughts have been reported [5]. Movement disorder features associated with anti-NMDA-receptor antibody encephalitis include dyskinesias exacerbated by ambulation and orolingual-facial dyskinesia [2]. Limb and trunk choreoathetosis, dystonia, and rigidity have also been reported [1,2]; these symptoms finally progress to a hyperkinetic stage [4]. Autonomic deregulation is more commonly seen in adults, although it can be seen occasionally in children. Unrecognized, the condition may progress to a pseudo-vegetative state.

In the very young child, presentation is either one of status epilepticus or behavioral seizure mimics that can be challenging to identify. The EEG usually shows nonspecific slowing without epileptiform discharges or subclinical seizures [2]. Much more difficult to recognize are psychiatric symptoms as evidenced by Patient 2, where multiple visits to the emergency room were dismissed as very young child separation anxiety and temper tantrums.

Cerebral MRI is normal in the majority of patients, even late in the disease course, although nonspecific T-2 signal hyperintensity may be seen in white matter and appear to have minimal or no correlation with neurological symptoms [1,2,5]. Cerebral positron emission tomography performed in two children was abnormal with reduced uptake in the basal ganglia being reported. There is a suggestion that PET may be superior to cerebral magnetic resonance imaging and electroencephalography [7], although this finding remains to be more widely confirmed.

While anti-NMDA-receptor antibodies can be detected in both serum and CSF, only CSF titers have been correlated with severity of disease [1]. It is hypothesized that immune response initiated by a tumor or a nonspecific infectious etiology causes the production of antibodies

that cross a compromised blood–brain barrier where they interact with NR1/NR2 subunits of the NMDA-receptor [1,2,6]. Additionally, evidence of intrathecal synthesis of antibodies has been reported in some patients [1,2]. Recurrence of neurological symptoms after HSV encephalitis with the presence of anti-NMDA-receptor antibodies suggests the infectious etiology for triggering immune response [8]. A recent study showed that 30% of HSV encephalitis has anti-NMDA-receptor antibodies in serum and/or CSF [9].

In tumor-negative patients, treatment with high dose steroids and intravenous immunoglobulin or plasma exchange is the first line therapy. Relapses occur in 20–25%; the rate may be higher in patients without an associated tumor [6]. Second-line immune therapy includes rituximab and/or cyclophosphamide [2,6]. One year of immunosuppression with mycophenolate or azathioprine is recommended to decrease relapse rates [2]. Aggressive immune therapy has reversed the condition, even when administered late in the course.

Increased awareness of anti-NMDA-receptor-associated encephalitis has resulted in increasing recognition in the very young child [1,5,10,11]. The rapid deterioration in our patients prompted a decision to start empiric treatment before CSF confirmatory results were available. This resulted in rapid recovery over the course of 2 weeks and minimal neurological morbidity.

Conflict of interest

There are no conflicts of interest by any of the authors.

References

[1] Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDAR encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008;7(12):1091–8.
[2] Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld M, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011;10(1):63–74.
[3] Granerod J, Ambrose HE, Davies NW, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicenter, population-based prospective study. Lancet Infect Dis 2010;10(12):835–44.
[4] Iizuka T, Sakai F, Ide T, et al. Anti-NMDA receptor encephalitis in Japan: long-term outcome without tumor removal. Neurology 2008;70:504–11.
[5] Tamma PD, Agwu AL, Hartman AL. Behavior outbursts, orofacial dyskinesias, and CSF pleocytosis in a healthy child. Pediatrics 2011;128(1):e242–5.
[6] Peery HE, et al. Anti-NMDA receptor encephalitis. The disorder, the diagnosis and the immunobiology. Autoimmun Rev 2012;11:863–72.
[7] Salvucci A, Devine IM, Hammond D, Sheth RD. Pediatric anti-NMDA (N-methyl D-aspartate) receptor encephalitis. Pediatr Neurol 2014;50:507–10.
[8] Bale JF. Virus and immune-mediated encephalitides: epidemiology, diagnosis, treatment and prevention. Pediatr Neurol 2015;53:3–12.
[9] Prüss J, Finke C, Höltje M, et al. N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. Ann Neurol 2012;72:902–11.
[10] Armangue T, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis—clinical analysis and novel findings in a series of 20 patients. J Pediatr 2013;162:850–6.
[11] Goldberg EM, et al. Anti–N-methyl-D-aspartate receptor-mediated encephalitis in infants and toddlers: case report and review of the literature. Pediatr Neurol 2014;50:181–4.