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# Anti-NMDA-Receptor Antibody Encephalitis in Infants

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## Abstract

**Objective:** Anti-NMDA (N-methyl D-aspartate) receptor antibody encephalitis is an autoimmune disorder manifesting sub-acutely 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 is dependent on age.

**Methods and Findings:** 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. CSF confirmed Anti-NMDA-receptor antibodies in two cases (a 21 month old boy and 29 month old girl) 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 :**Prompt recognition of Anti-NMDA-receptor antibody encephalitis in young children, while challenging, can quickly arrest deterioration and hasten recovery thereby limiting neurological morbidity.

**Key words:** Anti-NMDAR; Encephalitis; Child, Para-neoplastic syndrome; Psychosis, Behavioral outburst; Dyskinesia

**Abbreviations:** Anti-NMDA receptor: N-Methyl-D-aspartate Receptor; CSF: Cerebrospinal Fluid; EEG: Electroencephalogram

## Introduction

Anti-NMDAR (N-methyl D-aspartate)-receptor antibody encephalitis is an autoimmune disorder presenting sub-acutely with prominent aberrant movements and psychiatric symptoms associated with clinical deterioration over several weeks [1,2]. 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 [3].

We present 2 patients with CSF confirmed Anti-NMDA-receptor antibody encephalitis at a single tertiary pediatric institution, all patients with neurological symptoms were evaluated by a primary pediatric neurology team in a tertiary referral children's hospital serving a population catchment area of approximately three million.

## Case Reports

### Patient 1

A healthy 21-month old girl presented with status epilepticus that was not associated with fever. Seizures evolved to include oro-buccal automatism and secondarily generalized seizures. Continuous video-EEG demonstrated clinical and electrographic seizures originating independently from the right central and left centro-temporal head regions. Seizures were ultimately controlled with lorazepam, leviteracetam, phenobarbital, and phenytoin. Six days after admission she developed agitation and severe bilateral upper extremity choreform movements associated with oral dyskinesias that failed to respond to risperidone and tetrabenazine. Ultimately, memantine reduced the movements.

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-anti-neutrophil-cytoplasmic antibodies, peri-nuclear-anti-neutrophil cytoplasmic antibodies and anti-phospholipid antibody titers, thyroid function studies, creatine kinase, lactic acid and serum ammonia were normal as were serum amino and urine organic acids, carnitine and acyl-carnitine. A presumptive diagnosis of an auto-immune encephalopathy was entertained and a course of immunoglobulin and high dose methylprednisolone 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 CSF, 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 function returned to pre-illness baseline and she continued to make improvement in outpatient follow-up without relapses over the subsequent 5 months.

### 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.

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 and 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 frequently 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 full recovered. His development was normal, described as an independent, mild mannered and active toddler. Pregnancy, birth and family histories were unremarkable.

Cerebrospinal fluid analysis showed 8 WBC and 450 red blood cells without xanthochromia. CSF protein was 26 mg/dL, and cerebrospinal lactate, and glucose were normal. CSF herpes and enterovirus amplifications were negative. Blood counts, chemistries and urine drug screen were unremarkable. Antistreptolysin O, antinuclear antibody, lupus anticoagulant, cytoplasmic-anti-neutrophil-cytoplasmic antibodies, peri-nuclear-anti-neutrophil cytoplasmic antibodies and anti-phospholipid antibody titers, thyroid function studies, creatine kinase, lactic acid and serum ammonia were normal as were serum amino and urine organic acids, carnitine and acyl-carnitine. Cerebral MRI, EEG, echocardiography, 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 gm/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 choreo-athetoid 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 mycofenolate with plan to treat him with immune-modulatory therapy for a full year.

## Discussion

Two infants presented with an acute to sub-acute onset of disease that appeared to be post-infectious. Suspicion of an immune mediated encephalopathy was suspected early in the course once preliminary work-up was negative and the patients experienced a progressive course. Prior experience with older children with similar presentation raised suspicion of an Anti-NMDA-receptor antibody encephalitis which was confirmed serologically.

This report of infants with Anti-NMDA-receptor antibody encephalitis further adds to the clinical spectrum in the very young child. Aggressive empiric treatment based on symptomatology and prior to CSF confirmation is validated by rapid arrest of manifestation 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 with later developing movement disorder. Tumors or female preponderance was not observed in pediatric patients with this diagnosis.

Since its initial identification in adult women with ovarian teratoma the spectrum has broadened to include adolescents and young children [1,2,4-6]. 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 [7]. In about 70% of patients, the clinical course of Anti-NMDA-receptor antibody encephalitis is preceded by a non-specific prodromal stage with fever, headache, nausea or upper respiratory symptoms [4]. Psychiatric symptoms include anxiety, insomnia, paranoia and agitation [4], increased agitation and delusional thoughts have been reported [8]. Movement disorder features associated with Anti-NMDA-

receptor antibody encephalitis include dyskinesias exacerbated by ambulation and oro-lingual-facial dyskinesia [4]. Limb and trunk choreoathetosis, dystonia, rigidity have also been reported [1,4], these symptoms finally progress to a hyperkinetic stage [9]. Autonomic deregulation is more commonly seen in adults, although occasionally can be seen 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 manifestations that can be challenging to identify. The EEG usually shows non-specific slowing without epileptiform discharges or subclinical seizures [4]. 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, non-specific T-2 signal hyperintensity may be seen in white matter and appear to have minimal or no correlation with neurological symptoms [1,4,8]. Cerebral positron emission tomography performed in two children was abnormal with reduced uptake in the basal ganglia being the reported. There is suggestion that PET may be superior to cerebral magnetic resonance imaging and electroencephalography [10], 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 non-specific infectious etiology causes production of antibodies that cross a compromised blood brain barrier where they interact with NR1/NR2 subunits of NMDA receptor [1,4,11]. Additionally, evidence of intrathecal synthesis of antibodies have been reported in some patients [1,4]. Recurrence of neurological symptoms after HSV encephalitis with the presence of Anti-NMDA-receptor antibodies suggests the infectious etiology for triggering immune response [2]. A study showed that 30% of HSV encephalitis has Anti-NMDA-receptor antibodies in serum and/or CSF [12].

Tumor removal in cases where an identified tumor is identified, particularly if that tumor is an ovarian teratoma, may be associated with a dramatic reversal of course and full recovery. In tumor negative patients, treatment with high dose steroids and intravenous immunoglobulin or plasma exchange is first line therapy. Relapses occur in 20-25%, may be higher in patients without an associated tumor [6]. Second line immune therapy includes rituximab and/or cyclophosphamide [4,11]. One year of immunosuppression with mycophenolate or azathioprine is recommended to decrease relapse rates [4]. Aggressive immune therapy has reversed the condition, even when administered late in the course.

Increased awareness anti-NMDA receptor associated encephalitis has resulted in increasing recognition in the very young child [1,5,6,8]. The rapid deterioration in our patients prompted an decision to start empiric treatment before CSF confirmatory results were available. This resulted in rapid recovery over the course 2 weeks and minimal neurological morbidity.

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