Early Onset Refractory Anti-NMDAR Encephalitis in a 13-Month-Old Infant

Anti-N-methyl-D-aspartate (anti-NMDAR) encephalitis is a common cause of encephalitis in children. Previous studies on toddlers with NMDAR encephalitis have shown that the earliest presentation in this age group is behavioral changes [1,2]. Nevertheless, distinguishing anti-NMDAR encephalitis in infants and toddlers on initial presentation may be quite challenging as initial symptoms could be non-specific. We report the clinical picture of an infant with anti-NMDAR encephalitis.

A 13-month-old girl presented with a history of cough and cold followed one week later by irritability and intermittent brief episodes of staring look. After 4-5 days, she developed sleep disturbances, sleeplessness, excessive crying, right focal seizure and brief intermittent twitching movement of right face, lasting 5-15 seconds. She had no significant birth history, past history or family history. Her developmental milestones were normal for age. On examination, she was irritable and had oromotor and limb dyskinesia. She had received a course of oral antibiotics before being referred to our center. Her hemogram, C-reactive protein (CRP), serum electrolytes, and liver and renal function tests were within normal range. At this stage, acute encephalitis syndrome/ herpes simplex viral (HSV) encephalitis was suspected and magnetic resonance imaging (MRI) brain was done, which was normal. EEG showed left hemispheric seizure onset with background slowing. Her cerebrospinal fluid (CSF) cell count was 23/mm^3 (100% lymphocytes) with normal protein and glucose. Her CSF HSV-DNA polymerase chain reaction (PCR) was negative. Based on clinical presentation of seizure/ abnormal movements and altered sleep pattern, anti-NMDAR encephalitis was suspected. Her CSF was sent for anti-NMDAR antibody levels, and treatment with intravenous methylprednisolone was started. Her CSF anti-NMDAR IgM antibody was reported positive.

After 4 days of hospitalization, she developed loose stools, gaseous abdominal distension with raised CRP. She had intermittent episodes of moderate to high grade fever, which went on for about a month. Her blood, urine, stool and CSF cultures had no growth. Due to fever, loose stools and high CRP, treatment with intravenous antibiotics (piperacillin, metronidazole) was started empirically. Repeat MRI brain after one week showed right cerebellar and left hippocampus T2W/FLAIR hyperintensity without diffusion restriction. Her stool frequency reduced over the next three weeks. Her ultrasound (USG) whole abdomen and pelvis was normal. She had ongoing dystonia /dyskinesia during awake state. She was given tetrabenazine, trihexphenidyl and clonidine for involuntary movements, to which she responded partially. After methylprednisolone, she also received two days of intravenous immunoglobulin (zg/kg). But due to partial response to these immunosuppressive therapy, she was started on weekly doses of rituximab after one month after the onset of illness.

After one month of hospitalization, child was followed-up for weekly rituximab for total of three doses and maintenance dose of IVIG every three weeks. After 3 doses of rituximab, her CD19 count was 0 cells. At 3 month follow-up, she was afebrile with significant reduction of involuntary movements and improvement in alertness. Her follow-up EEG at 3 months showed low amplitude background with poorly formed age appropriate sleep background. Due to persistent clinical symptoms and CSF antibodies, treatment was started with cyclophosphamide dose every 3 weeks for total of five doses. As repeat CSF anti-NMDAR antibody was negative at 6 months from disease onset, she was not given long-term immune therapy. Follow-up MRI at one year showed diffuse cortical atrophy. At one year follow-up, she had some clinical improvement in developmental milestones with minimal dyskinesia. She could achieve head control, sitting balance with support, and could reach out for objects using hands, but was non-verbal.

The clinical symptoms of anti-NMDAR encephalitis are complex, especially in younger pediatric patients, and many clinicians cannot promptly distinguish them from those of other diseases such as viral encephalitis or psychological conditions. Patients typically present with psychiatric symptoms, behavioral dysfunction, seizures, speech and cognitive impairment, movement disorders, decreased consciousness, autonomic instability, and central hypoventilation [1,2]. In children, most commonly, the first presentation may be nonpsychiatric, including seizures [2]. Although paroxysmal events may appear as intractable epileptic seizures, recording of these events often discloses no epileptic discharge and these events prove not to be epileptic [3].

Fever and diarrhea in this girl was probably due to autonomic dysfunction, which are well described in anti-NMDAR encephalitis [2,4]. Cardiac arrhythmias, hypotension, hypertension, hypoventilation, and hyper-or hypothermia have all been described. Although, the initial symptoms in our patient were seizures, movement disorder and altered sleep pattern, the presence of a fever and gastroenteritis posed an initial management challenge. Children with NMDAR encephalitis commonly experience prodromal symptoms such as fever and vomiting [4]. The spectrum of symptoms usually progresses to include seizures and sleep disturbances [5]. The dystonia, involuntary movements and orofacial dyskinesia noted in our patient are

the most commonly reported motor manifestation in toddlers [6]. In a case series from India [7], among 11 patients of pediatric anti-NMDAR encephalitis (age 2.5 to 18 years, mean 9 years) common presentations were progressive extrapyramidal syndrome with neuroregression, seizure (generalized: 64%, focal:36%), sleep disturbances, psychiatric manifestations and autonomic instability [7].

Investigations are usually necessary to exclude other pathologies that may mimic NMDAR encephalitis, notably other types of encephalitis. Currently, commonly used first line immune-therapies include high-dose corticosteroids, IVIG and plasmapheresis. Second-line therapies include rituximab and cyclophosphamide [8,9]. Earlier treatment of anti-NMDAR encephalitis is associated with better outcomes [10]. Children have been reported to recover faster than adults, usually within six months [11]. Toddlers have a good prognosis, with full recovery in 67% of patients and no reports of mortality [1]. Cases in children and adults reported generalized/fronto-temporal and potentially reversible cortical atrophy as sequelae of anti-NMDAR encephalitis leading to changes in behavior, learning, and memory. NMDAR is present in high density in the fronto-temporal area, suggesting an immunological cause of the brain atrophy of these area [12].

In conclusion, we believe that Anti-NMDAR encephalitis is probably underreported in infants and young children due to its varied clinical presentation. Its early diagnosis can hasten initiating proper management and early recovery.

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