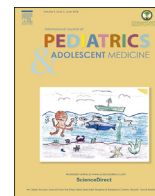


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Instructive case

Anti-NMDA receptor encephalitis in a toddler: A diagnostic challenge

Yasmin Khundakji ^a, Amira Masri ^{b,*}, Najwa Khuri-Bulos ^c

^a Faculty of Medicine, The University of Jordan, Amman, Jordan

^b Department of Pediatrics, Division of Child Neurology, Faculty of Medicine –The University of Jordan, Amman, Jordan

^c Distinguished Professor of Pediatrics and Infectious Disease, Department of Pediatrics, Faculty of Medicine, The University of Jordan, Amman, Jordan

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ABSTRACT

Anti N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disorder and is considered to be one of the most common causes of encephalitis in children. Despite the fact that around half of all reported cases are of children, the number of studies that report infants and toddlers is very small. Furthermore, reports on children from the Middle East particularly are extremely rare.

We report a 21-month-old Jordanian female toddler with NMDAR encephalitis, who initially presented with behavioral changes and some autistic features. She presented a diagnostic challenge due to a concurrent urinary tract infection and gastroenteritis. Multiple investigations were conducted and she was treated with methylprednisolone and intravenous immunoglobulin (IVIg) empirically as well as plasma exchange and rituximab once the diagnosis was confirmed. Her condition improved gradually. We discuss her clinical picture and the diagnostic challenges within this age group; we also review the current related literature.

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1. Introduction

Anti N-methyl-D-aspartate (anti-NMDA) receptor encephalitis is a synaptic autoimmune disorder that was first characterized in 2007 [1]. Since then, the definition evolved to include a wide spectrum of ages and presentations, and it is now considered to be one of the most common causes of encephalitis in children [2]. In children, the most commonly reported clinical manifestations include abnormal behavior, movement disorders, and seizures [2]. Although around 40% of all reported cases with anti-NMDA receptor encephalitis are children [2], however, the number of studies that report infants and toddlers (below 36 months of age) with anti-NMDA encephalitis are rare; not exceeding 20 cases [3–10].

Furthermore, reports on anti-NMDA encephalitis in children from the Middle East are extremely rare [11–13]. Under reporting may be related to the misrecognition of symptoms, as well as the unavailability of diagnostic testing in many countries.

We report a 22-month-old Jordanian female toddler with anti-

NMDA encephalitis who initially presented with behavioral changes and some autistic features.

2. Case report

The patient was a healthy girl. At 21 months, she developed sudden behavioral changes manifesting as bouts of irritability, aggression, inconsolable crying, and self-mutilatory behavior (self-biting). She developed a fever a few days later which was attributed to a urinary tract infection and was followed by vomiting and diarrhea resulting from Rota virus gastroenteritis.

Her condition worsened over the course of two weeks and the fever persisted. She no longer made eye contact nor spoke and developed insomnia which was managed with clonazepam. In addition, she developed a progressive regression in gross and fine motor skills and an inability to swallow. She also had focal seizures which were controlled with valproic acid.

Conducted investigations included a CSF analysis which was normal (WBC 2 cells/mm; one neutrophil and one lymphocyte, protein 15 mg/dl, glucose 69 mg/dl, RBC zero cells/mm, PCR viral work up for enteroviruses, herpes simplex, varicella and mumps viruses were negative, gram stain and bacterial culture were negative), multiple brain images (brain MRI, MRA and MRV), a nerve conduction study, metabolic work up, copper and

* Corresponding author.

E-mail addresses: yasminkhundakji@gmail.com (Y. Khundakji), masriamira69@hotmail.com (A. Masri), najwa.khuri@gmail.com (N. Khuri-Bulos).

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ceruloplasmin levels, rheumatoid factor, and antinuclear antibody testing; all were normal. Sleep electroencephalogram revealed occasional spikes in the left parietal region. She had elevated creatine phosphokinase (524 U/L; normal range: < 190 U/L).

She was transferred to our hospital two weeks following the onset of her symptoms. Her general examination was normal apart from a persistent fever. Her neurological examination revealed poor eye contact, choreoathetotic movements in the right upper limb, oro-buccal dyskinesia, hypotonia with preserved deep tendon reflexes in addition to reduced power (2/5 on the MRC Scale) in her right upper limb.

We suspected NMDAR encephalitis, blood and CSF samples were sent to a lab outside of Jordan. Results were received one month later and revealed positive blood and CSF titers (1:320 and 1:160 respectively). Initially, we treated her empirically with intravenous immunoglobulin (IVIg) and intravenous methylprednisolone. This resulted in an improvement in some of her symptoms as the fever and insomnia disappeared; her behavioral and developmental skills however did not improve. Follow-up during the next six months necessitated monthly IVIg. Several relapses occurred during treatment, manifesting as a reemergence of her irritability, insomnia and poor eye contact. She received plasma exchange during her second and third relapses, in addition to rituximab. A dramatic improvement in her social skills and irritability appeared within hours following plasma exchange.

Follow-up at six months after her initial presentation showed continuous improvement. Apart from mild speech delay, her neurological exam and developmental milestones are normal.

3. Discussion

We present the clinical picture of a 22-month-old toddler with NMDAR encephalitis. Previous studies on toddlers with NMDAR encephalitis have shown that the earliest presentation in this age group is behavioral changes, manifesting commonly as temper tantrums, agitation and inconsolable crying [3,4,8,14]. Nevertheless, distinguishing NMDAR encephalitis in infants and toddlers on initial presentation may be quite challenging as initial symptoms could be non-specific. Although the initial symptoms in our patient were behavioral changes, the presence of a fever and gastroenteritis posed an initial diagnostic challenge. Children with NMDAR encephalitis commonly experience prodromal symptoms such as fever and vomiting [10]. Furthermore, persistent fever could be part of the autonomic instability of encephalitis [4,10].

The spectrum of symptoms usually progresses to include seizures, speech and sleep disturbances [15]. In addition to these, our patient also experienced symptoms that are rarely reported in the literature, including autistic-like features such as the loss of eye contact [9], self-mutilatory behavior (self biting) [3,16,17] and dysphagia [3,18]. The choreo-athetoid movements and oro facial dyskinesia noted in our patient are the most commonly reported motor manifestation in toddlers [19].

Investigations are usually necessary to exclude other pathologies that may mimic NMDAR encephalitis, notably other types of encephalitis; in addition to neuro-metabolic disorders, which are reported to be significant causes of childhood developmental disorders and epilepsy in Jordan [20,21].

In our patient, the results of investigations also posed a diagnostic challenge. The CPK was high on initial presentation. High CPK is related to rhabdomyolysis; a rarely reported complication of NMDAR encephalitis as a consequence of the excessive muscle contraction associated with the agitation [22].

Furthermore, the results of CSF analysis and brain MRI were normal in our patient. Normal CSF and normal neuro-imaging are present in more than half of infants and toddlers with NMDAR

encephalitis [4,10,8], posing another challenge for initial diagnosis, especially in countries where diagnostic titers are not available. The diagnosis of anti-NMDAR encephalitis is confirmed upon the detection of anti-NMDAR autoantibodies in serum and cerebrospinal fluid (CSF) [23].

Our patient responded only partially to IVIG and methylprednisolone and she relapsed monthly, which necessitated the use of plasma exchange and Rituximab. Currently, no guidelines exist for the treatment of NMDAR encephalitis in children. Commonly used first line immune-therapies include high-dose corticosteroids, IVIG and plasmapheresis. Second-line therapies include rituximab and cyclophosphamide [14,24]. Within only hours of the plasma exchange there was a marked improvement in our patient's behaviour and social interaction. Plasma exchange was reported to be used in a small proportion of pediatric cases, however, full recovery or partial improvement immediately after plasma exchange was reported in 63.5% of pediatric patients [25].

Our patient improved gradually. Earlier treatment of anti-NMDAR encephalitis is associated with better outcomes [26]. Children have been reported to recover faster than adults [27], usually within six months [27]. Toddlers have a good prognosis, with full recovery in 67% of patients and no reports of mortality [3].

In conclusion, we believe that NMDAR encephalitis is probably underreported in infants and toddlers. This case, initially presenting with behavioral changes and autistic features, highlights the diagnostic challenges presenting in this age group.

Conflicts of interest

All authors declare no conflict of interest.

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