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Review Article

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Pediatric NMDA Receptor Encephalitis: A Case of Speech Regression and Behavioral Changes

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Abstract

Background: Anti-N-methyl-D-asparate receptor (NMDA) receptor encephalitis is a rare autoimmune disorder (estimated prevalence is 1-2 in a million) characterized by the production of antibodies against the N-methyl-D-aspartate receptors in the brain. It often presents with a variety of neurological and psychiatric symptoms, including seizures, speech impairment, and behavioral changes. The disease can be challenging to diagnose due to its variable presentations, rarity, and lack of clear diagnostic signs on neuroimaging.

Patient: We present the case of a 5-year-old girl initially diagnosed with focal epilepsy of unknown etiology and started on Levetiracetam. She later exhibited speech regression and behavioral changes. Despite treatment with antiepileptic medication, her symptoms persisted and worsened over time to full mutism within two months. Throughout this time, she remained fully oriented and did not exhibit any other symptoms of encephalopathy.

Results: Further evaluation, including imaging studies and EEG monitoring, initially revealed no significant abnormalities, though EEG showed some slowing later. However, due to the atypical presentation and lack of response to conventional treatments, autoimmune encephalitis was suspected. The patient was subsequently treated with high-dose steroids for five days, which led to a remarkable improvement in her condition. Serum testing later confirmed the presence of NMDA receptor antibodies. Within a week of discharge, she began speaking in complete sentences again.

Conclusion: This case underscores the need to consider autoimmune encephalitis in children with unusual seizure symptoms and behavioral changes. Treatment with immunomodulatory therapy, like high-dose steroids, can lead to notable clinical improvement and improved outcomes. Additionally, healthcare providers must be cautious when linking mood disturbances solely to Levetiracetam and stay alert for possible NMDA encephalitis.

Keywords

NMDA encephalitis, Autoimmune encephalitis, Speech regression, Levetiracetam-induced aggression, Seizures

Background

Anti-N-methyl-D-asparate receptor (NMDA) receptor encephalitis is a rare autoimmune disorder characterized by the production of antibodies against the N-methyl-D-aspartate receptors in the brain. The exact mechanism is not fully understood, but one hypothesis is that the antibodies target the GluN1 subunit of the NMDA neuronal receptor, and symptoms result from the downstream dysregulation of dopaminergic pathways [1]. While it was initially described in adults, there is increasing recognition of its occurrence in children; it is now considered to be one of the most common causes of encephalitis in children [2]. The clinical presentation can vary widely but often includes psychiatric symptoms, autonomic instability, seizures, and movement disorders, including limb dystonia and dyskinesias [3,4]. This disease has four clinical stages: A prodromal phase, an illness phase, a recovery phase, and a late phase. During the second phase, children present with behavioral changes, irritability, tantrums, coma, manic symptoms, behavioral outbursts, sleep dysfunction, and hyperactivity [5]. Inconsistent neuroimaging results further complicate this diagnosis; MRI changes were only observed in 30% of patients in Titulaer, et al.'s cohort study [6]. When present, there were bilateral

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T2 or FLAIR signal hyperintensities in the hippocampi, frontal cortex, medial temporal lobe, cerebellar cortex, spinal cord, and medulla oblongata [7]. EEG findings in pediatric cases consist of slow, continuous rhythmic, and disorganized activity in delta and theta range superimposed seizures, as 90% of patients have a slowing of EEG at some point during the illness [3]. Extreme delta brush has also been described as a potential diagnostic criterion, though it is not required for diagnosis and may be more variable in pediatric patients [8,9].

When patients present with seizures, Levetiracetam is often used as a first-line therapy [10]. However, Levetiracetam has been reported to cause varying degrees of psychiatric adverse effects, including behavioral disturbances such as agitation, hostility, psychosis, mood symptoms, and suicidality [11]. In the pediatric population, 6-15% of patients on Levetiracetam experience behavioral side effects such as hostility and aggression [12-14]. Consequently, in such patients, the diagnostic challenge emerges from the overlap in symptomatology between Levetiracetam-induced behavioral changes and those characteristic of NMDA receptor encephalitis.

We present the case of a 5-year-old girl initially diagnosed with focal epilepsy of unknown etiology and started on Levetiracetam. She later exhibited speech regression and behavioral changes that progressed to full mutism within two months. Autoimmune encephalitis was suspected, even though classic signs of encephalopathy were absent (given the patient was fully oriented). She responded well to steroids and returned to her baseline within a week of discharge home.

Case Presentation

A previously healthy 5-year-old female initially presented to the Emergency Department (ED) with concerns about focal seizure activity. While on an outing with her family, she exhibited slurred speech, drooling, right head turning, and clonic movements of her head and right upper extremity, lasting approximately 2 minutes, with the patient remaining conscious throughout. Before the seizures, she had rhinorrhea and nasal congestion but no fevers or other sick symptoms. Notably, there was no family history of seizures but a strong history of migraine on her father's side. In the ED, she experienced two seizures lasting about 30 seconds each, described as eye deviation and right upper extremity jerking, then a loss of tone and strength in the right upper extremity. She received Ativan and a loading dose of Levetiracetam (40 mg/kg), which successfully stopped further seizure activity, and she returned to her baseline. Lab results were appropriate; both Head CT and Angio CT scans showed no abnormalities. A routine EEG showed no focal abnormalities or seizures, and an epilepsy genetic panel revealed no pathologic mutations. She was discharged on a maintenance dose of Levetiracetam (20 mg/kg/day) with Diastat as needed for seizures lasting over 5 minutes.

She presented to the ED thirty-two days later with right-sided headaches, photophobia, phonophobia, vomiting, and "seeing rainbows." She had a normal neurological exam then, and ibuprofen provided minimal relief. The family noted then that she had not yet started Levetiracetam as her parents had not yet picked up the prescription from the pharmacy- yet she had been seizure-free in the meantime. Upon discharge from the ED, she was prescribed Levetiracetam as well as Periactin. At home, her parents stopped administering the seizure medication after two doses due to perceived behavioral changes [She was irritable and not acting like herself]. Five days after discharge, the patient presented again to the ED with two breakthrough seizures in 24 hours, described as right facial droop, twitching, and right-sided weakness. A head CT and labs were standard, and she returned to baseline in the ED. Levetiracetam was restarted at 24.5 mg/kg/day with Pyridoxine 25 mg daily for mood side effects. She went home, where she had another seizure at home with arm jerking, loss of control of motor functions, and loss of responsiveness.

Two days later, the patient became non-verbal, isolating herself and exhibiting incomprehensible speech. Alongside this, she developed episodes of right-hand twitching, drooling, and urinary incontinence despite prior full potty training. Despite the family's full compliance with medications, including Levetiracetam, Periactin, and Pyridoxine, she continued to experience 2-3 seizures daily, accompanied by uncharacteristic aggressive behavior and destructive behavior. Levetiracetam was increased to 35 mg/kg/day to address the hand twitching and seizures. Over the following week, her aggressive and harmful behaviors persisted, along with several seizures and irregular flickering of her right arm. Despite an increase in Levetiracetam dosage to 49 mg/kg/day, her symptoms only moderately improved. Due to the concern about levetiracetam-induced behavioral changes, it was weaned, and Oxcarbazepine was started at 15 mg/kg/day. Imaging studies [MRI Brain with and without contrast] showed no abnormalities (Figure 1), yet her condition continued to deteriorate, with speech difficulties [at this point expressive aphasia] and refusal to eat. Although her seizures ceased after discontinuing Levetiracetam, her behavior worsened, prompting suspicion of electrical status epilepticus of sleep or autoimmune encephalitis.

A repeated EEG showed intermittent focal sharp waves noted over left frontal and temporal regions during sleep states, occurring in clusters as well as bilateral hemispheric slowing (left anterior quadrant maximum); hence, there was a decreased seizure threshold originating from the left frontal and temporal regions, along with mild-moderate encephalopathy. However, there were no seizures, no status epilepticus during sleep, and no evidence of extreme delta brush. At that point, she was started on five days of empiric high-dose IV methylprednisolone while blood and CSF studies for autoimmune encephalitis were pending. By day 3 of treatment, she significantly improved her speech [saying three words] and behaviors. Subsequent testing confirmed NMDA encephalitis, but by then, the patient had fully recovered, displaying normal behavior and speech, requiring no further treatment beyond the initial course of methylprednisolone.

A follow-up two weeks after her treatment with Methylprednisolone showed that she had returned to her baseline. Her neurological exam and developmental

milestones are normal. Repeated Brain MRI was normal, and EEG showed intermittent slowing noted from both posterior quadrants, specifically the left posterior quadrant, indicative of a bi-posterior region of subcortical dysfunction (Figure 2). Additionally noted are two bursts of irregular generalized epileptiform activity that do not consistently localize or lateralize, suggestive of an underlying tendency for seizures. The remainder of the EEG was appropriate for the patient's stated age.

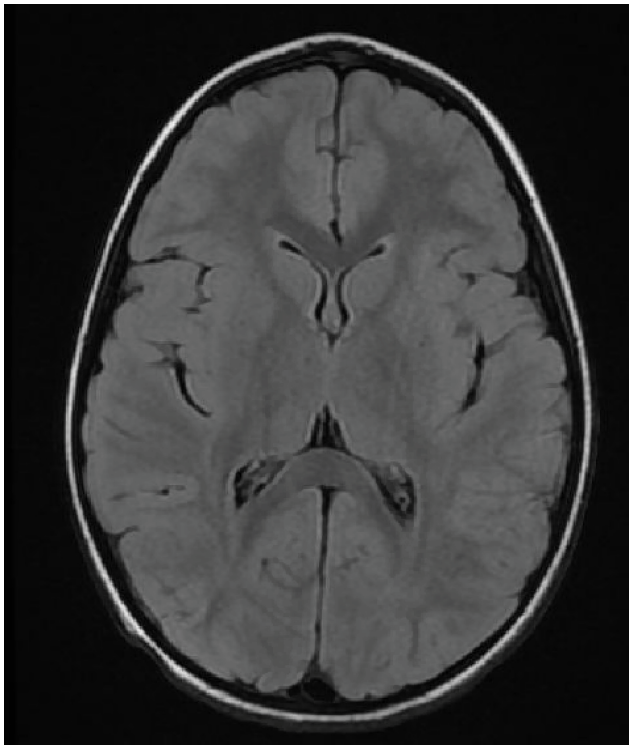

Figure 1: The patient's brain MRIs were consistently normal.

Discussion

NDMA encephalitis, while relatively rare, poses significant diagnostic and therapeutic challenges, particularly in pediatric populations with an incidence of 1-2 per million per year, and is more prevalent in non-Caucasian race individuals [15,16]. The disease exhibits a predilection for young individuals, with a median age of onset of around 20-21 years and a female predominance of 4:1 [6]. The disease is often associated with ovarian teratoma, small-cell lung cancer, and other neoplasms and is frequently paraneoplastic [17]. In line with age and sex, our patient was female and five-years-old at symptom onset. She did not present with an ovarian teratoma, but the prevalence of ovarian teratoma has been hypothesized to be lower in pediatric patients [15-18].

Typical symptoms of NMDA encephalitis include psychosis, memory loss, and dystonia. These psychotic and cognitive impairments may have a gradual onset over several weeks and may be difficult to distinguish from primary psychiatric disease [18,19]. Seizures are a common symptom of NMDA encephalitis, occurring in around 75% of patients [9,18,20]. However, seizures are not usually the first symptom of the disease. In one study of 167 pediatric NMDA encephalitis cases, only 18% of patients had seizures as their first symptom [20]. It is worth noting that our patient did not have any seizures for 32 days after her first one, even though she was not taking any anti-seizure medication during this period.

EEG findings compound diagnostic challenges, which may not always indicate seizure activity. Regarding our patient's EEG results, the initial test showed normal results. However, during subsequent tests, while the patient was sleeping, intermittent focal sharp waves were noted over the left frontal and temporal regions, occurring in clusters. Additionally, bilateral hemispheric slowing was observed, with the left anterior quadrant showing maximum slowing. After the patient's symptoms had resolved, another EEG

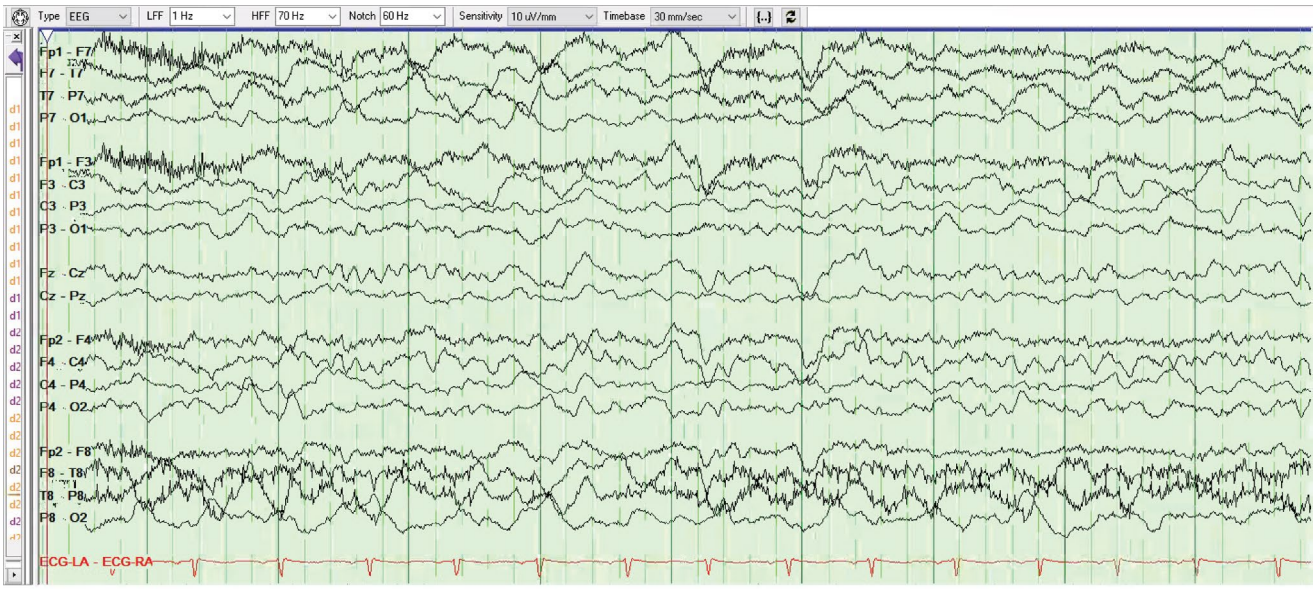

Figure 2: An EEG of the patient that demonstrated left hemisphere slowing.

showed intermittent slowing from both posterior quadrants, specifically the left posterior quadrant (Figure 2). These findings are similar to a study of 81 patients, aged less than 18-years-old, who presented with new onset of neurological or psychiatric symptoms of unknown etiology. CSF studies were consistent with NMDA receptor encephalitis. Out of the 81 patients, 25 EEGs were available to review, and 88% of them showed focal or diffuse delta/theta wave or disorganized activity, with 28% showing some epileptic activity [3,21,22]. Our patient's EEG did not show extreme delta brush; it has been reported in around 30% of adult patients with NMDA encephalitis. It has been listed as a potential diagnostic criterion, although it is not required for diagnosis and may be more variable in pediatric patients [8,9]. Its prevalence in pediatric patients varies widely, and its absence does not exclude NMDA encephalitis. Studies have reported a range of extreme delta brush prevalence of 11-53% in pediatric NMDA encephalitis patients [21,23,24].

Aggression is often observed in NMDA encephalitis, with one study reporting its presence in 57% of 571 patients [4]. However, this presented a diagnostic challenge in our patient, whose behavioral changes were initially attributed to Levetiracetam side effects. About 6-15% of pediatric patients may experience behavioral side effects, including hostility and aggression, while taking Levetiracetam [12-14]. However, the persistence of aggression despite medication changes raised suspicion of an autoimmune etiology, which led us to NMDA encephalitis despite the patient remaining fully oriented and not exhibiting classic symptoms of encephalopathy (she was not confused and seemed to understand what was said to her).

Similarly, speech deficits, although less common in adults, were evident in our patient. They are described in the literature as well, estimated to occur in 50% of pediatric patients by the time of diagnosis, emphasizing the diverse clinical manifestations of the disease [3,18]. Our patient was unique in that she progressed to full mutism with occasional intervals of unintelligible babbling quickly within two months of her first symptom. However, receptive language was less impeded, and she could follow commands well throughout the ordeal. She recovered her speech quickly after immunotherapy, beginning to say words on day three of her five-day course of methylprednisolone and returning to her baseline within a week post-treatment.

Timely initiation of immunotherapy is crucial for favorable outcomes, with delayed treatment associated with poorer prognosis [25]. Investigations have also found that recovery takes several months, with only 50% of patients improving within one month of diagnosis [6]. Despite the delayed initiation of methylprednisolone in our case, the patient exhibited rapid improvement following a 5-day course, highlighting the potential efficacy of early intervention.

Conclusion

This case highlights the importance of considering autoimmune encephalitis in children presenting with atypical seizure manifestations and behavioral changes. Prompt recognition and treatment with immunomodulatory therapy, such as high-dose steroids, can result in significant clinical improvement and better outcomes for these. Furthermore, healthcare providers should exercise caution in attributing mood disturbances solely to Levetiracetam treatment and remain vigilant for the potential occurrence of NMDA encephalitis.

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