N-Methyl-d-Aspartate (NMDA) Receptor Encephalitis, Post Herpes Encephalitis in Two Pediatric Cases

Amna Al Futaisi1, Wafa Bani Uraba1, Naji Al Dhawi2, Eiman Al Ajmi3, Mahmood Al Kindi4, Jalila Al Shukaili4 and Azza Al Adi5

1Pediatric Neurology Unit, Department of Child Health, College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman
2General Pediatrics Department, Al Nahda Hospital, Muscat, Oman
3Department of Radiology and Molecular Imaging, Sultan Qaboos University Hospital, Muscat, Oman
4Department of Microbiology and Immunology, Sultan Qaboos University Hospital, Muscat, Oman
5Nursing Department, Sultan Qaboos University Hospital, Muscat, Oman

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*Corresponding author: amnaf@squ.edu.om

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Abstract

Commonly, Herpes simplex virus (HSV) causes infectious encephalitis among children. A neurological relapse after primary HSV encephalitis (HSE) in the weeks or months after presentation is well recognized. Relapsing symptoms of post-HSV encephalitis can present either as a true relapse or an immune-mediated disorder. A relationship is predicted between immune-mediated disorder and N-methyl-D-aspartate receptor (NMDAR) antibodies. This study presents two cases of patients suffering from anti-NMDAR encephalitis who appeared after treatment for proven herpes-simplex virus (HSV) encephalitis. The first patient was treated immediately after the presentation as autoimmune encephalitis and had an excellent outcome. The second patient had delayed initiation of treatment and suffered from intractable epilepsy and severe global developmental delay. An important role is played by recognizing anti-NMDAR encephalitis symptoms and its variable presentation for timely diagnosis and quick initiation of treatment for anti-NMDAR encephalitis, thus, improving the outcome for those patients.

Keywords: HSV; Encephalitis; NMDAR; Antibodies.

Introduction

Herpes simplex virus (HSV) encephalitis is the most prevalent infectious cause of sporadic encephalitis (1), with an estimated frequency of 2-4 occurrences per 1,000,000 people worldwide. The morbidity and mortality rate is high with HSV encephalitis even after anti-viral therapy with acyclovir (2). Although the disease frequently has a monophasic course, 5% - 27% of individuals experience a neurologic recurrence within a few weeks or months of the initial occurrence. When symptoms of post-HSV encephalitis recur, they may be a real relapse (CSF PCR positive for HSV) or an immune-mediated illness (CSF negative for HSV) (3). The immune-mediated presentation of HVS encephalitis is frequently associated with NMDAR antibodies. It manifests as a multistage sickness, with most patients first experiencing a prodromal illness that resembles a viral infection, then psychiatric symptoms such as altered irritability, behavior, speech, psychosis, or emotional lability (4). Neurologic symptoms (seizures, catatonia, and mutism), followed by autonomic instability and dyskinesia, might develop as the illness progresses (5). The study reports two cases of post-herpetic encephalitis to highlight the importance of early detection of immune-mediated pathogenesis and early intervention in the disease course to improve the outcome.
Case Reports

Case one

A ten-year-old boy, previously well and developmentally normal presented at a local hospital with a history of fever and focal motor seizures. He was hospitalized, and the initial cranial computed tomography (CT scan) revealed no significant abnormalities. His treatment started with giving him intravenous (IV) ceftriaxone, vancomycin, and acyclovir for presumed meningencephalitis. The seizures were treated with Levetiracetam, reaching a 40mg/kg/day dose. Complete blood count and biochemical analysis were normal. Cerebrospinal fluid (CSF) was positive for herpes simplex virus type 1 on polymerase chain reaction (PCR) testing. He was treated with Acyclovir for a total of three-week duration and then discharged home in good condition to the extent that he resumed his normal activities and attended school in the same week.

One week later, he was brought back to the hospital with altered sensorium, abnormal movements, irritability, and hallucination. Physical examination revealed a child with a GCS of 9/15 (E4M4V1), oral dyskinesia, and choreoathetoid movements. He had left hemiparesis with a power of 3/5 on the left side with brisk deep tendon reflexes and extensor planter response. He was commenced on intravenous Immunoglobulin of one gram per kg per day for two consecutive days and intravenous acyclovir treatment. Cerebral magnetic resonance imaging (MRI) showed bilateral hyperintensities involving temporal areas, limbic system, insular cortex, cingulate gyrus, and basifrontal region with bilateral asymmetry (Right more than Left). Electroencephalograms (EEG) showed diffuse delta slowing, not associated with clinical epileptic events or epileptiform abnormalities. CSF analysis revealed normal protein and glucose levels. Microscopic analysis of CSF revealed, ninety leucocytes with 80% lymphocytes. Herpes PCR testing was negative. CSF sample detected at a titer of 1:10 using indirect immunofluorescence (a cell-based indirect immunofluorescence assay) (Euroimmun, Lubeck, Germany) was positive for anti-NMDAR autoantibodies. The patient was treated with a pulse IV methylprednisolone 30 mg/kg/day for five days, followed by prednisolone 2 mg/kg/day with slow tapering for twelve weeks. Trihexyphenidyl was started for the movement disorder. His condition worsened clinically with the suppressed level of consciousness and constant violent jerking abnormal movements, despite the immediate immunotherapy initiation. Subsequently, rituximab (375 mg/m2) was added to be taken every week for four weeks for his anti-NMDAR encephalitis.

On day 48, he was discharged with constant choreoathetoid movements, expressive aphasia with left hemiparesis, irritability, and aggressive behavior. He had head control but could not sit or speak any words. Eight weeks later, he was readmitted with sleep disturbance and aggressive behavior in addition to swallowing difficulty. He required psychiatry evaluation, neuro-rehabilitation, gastroenterology consultation, and dietitian review. Six months later, he presented with complete resolution of symptoms. He was back to baseline status with completely normal neurological examination including speech and cognititive functions. NMDAR antibodies were positive at three- and six-months follow-up with subsequent negative results at 9 and 12 months with a titer of > 1:100 using indirect immunofluorescence (a cell-based indirect immunofluorescence assay) (Euroimmun, Lubeck, Germany). Follow-up MRI at 12 months showed interval partial improvement of the previous hyperintensities noted in the first MRI (Fig 1).
Figure 1. Atrophy and gliosis of the right hippocampus are seen in coronal (A) and axial (B) T2 weighted images (arrows). (C) Susceptibility weighted image showing old hemorrhage in the mesial right temporal lobe. (D,E,F) Coronal FLAIR images show mild swelling and abnormal signal intensity in the inferior right frontal lobe (white arrow), right insula (yellow arrow), right temporal lobe with loss of gray-white matter differentiation (blue arrow), posterior medial temporal lobes bilaterally (green arrows), and right cingulate gyrus (red arrow).

Case two

An eight-month-old infant presented with a history of fever and focal seizures. She was treated with ceftriaxone, vancomycin, and acyclovir, in addition to phenytoin, to control her seizure. The Lumbar puncture was offered but refused by the parents. The initial blood workup was normal, with negative blood and urine culture. The Head CT showed hypodensities in bi-temporal areas. She was discharged in good condition after getting a 14-day course of acyclovir and antimicrobial therapy. However, she was readmitted after two weeks with irritability, altered sleep pattern, and involuntary limb and facial movements. Brain MRI revealed areas of increased signal intensity in the MRI of the frontal, hippocampal, thalamic, and temporal areas. EEG showed slow activity with sharp waves over the right front-temporal area. She was administered acyclovir intravenously. The parents were dissatisfied and left against medical advice. Her condition had progressed, and she lost her ability to swallow the liquid and continued to have frequent seizures with choreoathetoid movements. Two months later, she was diagnosed with anti-NMDAR-autoimmune encephalitis in a pediatric hospital in the United Arab Emirates. She received IVIG 1g/kg/day for two days, IV methylprednisolone pulse therapy for three doses, and three sessions of plasmapheresis. The steroid therapy was then continued orally over a course of two months. In addition to antiseizure medications consisting of levetiracetam, phenobarbitone, and clonazepam.

On subsequent follow-up visits, she continued to have uncontrolled seizures with impaired neurological development. Repeated anti-NMDAR was negative in serum. Her brain MRI showed a Gliotic area in the right temporal lobe and T2 hyperintensity in periventricular white matter in the parietal & occipital region (Fig 2). The Electroencephalogram showed focal EDs over the right hemisphere. Her current assessment at the age of 5 revealed that she has a significant language delay, limited social-communication skills, repetitive behavior, and
sensory sensitivity. She continues to have myoclonic seizures and focal motor seizures with impaired awareness. She has drug-refractory epilepsy despite being on the optimum dose of sodium valproate, Levetiracetam, and clobazam.

**Figure 2.** Coronal (A) and axial (B) T2 weighted images show significant encephalomalacia of the right temporal lobe (arrows). (C) An axial FLAIR image demonstrates gliosis and volume loss in the right parietal lobe and right insula (arrow). (D) Gliosis and significant atrophy of the right hippocampus (arrow).

**Discussion**

HSVE-induced anti-NMDA receptor encephalitis is known as autoimmune encephalitis, associated with the production of antibodies directed against the GLuN1 subunit of the NMDA receptor. We have presented two cases of early presentation of anti-NMDAR AIE post-HSV-1 encephalitis in two pediatric age groups and two different outcomes. Though the etiology is unclear, it is hypothesized to be caused by the induction of synaptic antigens due to neuronal damage by viruses or by a molecular mimicry process (given the homology between...
NMDAR and HSV proteins) (8,9). In a recent prospective cohort study, Armangue T et al. looked at 51 patients with HSV encephalitis and found that 14 (27%) of them went on to develop autoimmune encephalitis. Among all the 14 participants, nine had antibodies against NMDAR, and 5 had antibodies against other neuronal proteins (10). Because of their similar presentations, autoimmune encephalitis and herpes virus reactivation should be considered in patients with worsening neurological impairments or emerging new neurological or psychiatric symptoms (11,12).

The clinical manifestations often appear within three months after a successful course of anti-viral therapy (10). According to studies, presenting symptoms vary depending on the patient's age, with children exhibiting mostly neurological symptoms compared to adults, whose symptoms are more likely to emerge as behavioral and psychiatric problems. (8,10,12). Additionally, variations in clinical presentation between pediatric groups were also discovered. In their cohort study, Armangue T et al. also showed that children under the age of 4 frequently presented with frequent seizures, decreased level of consciousness, infantile spasms, or choreaathetosis with a worse outcome at one year, while those over the age of 4 frequently experienced changes in cognition and behavior that may be related to seizures (10). Choreoathetosis is the most encountered clinical feature in young children, in addition to drug-resistant epilepsy or status epilepticus (13-15). Most children and adults acquire the same clinical condition, which manifests with neurological and psychological symptoms, regardless of the presenting complaints. (12).

This report provides two examples of early anti-NMDAR AIE presentation within a month of HSV-1 encephalitis in two pediatric age groups (8 months and ten years). Despite having a very identical (1-2 week) time for the onset of illness following HSE infection, the outcomes of the patients were vastly different. The fact that younger age at presentation tends to carry a worse prognosis and a delay in detection and treatment may account for the devastating outcome in the younger child. The first case highlights the value of prompt therapy with a successful outcome. The first case received first-line immunotherapy from the first day of his admission, and 72 hours later, second-line therapy commenced. However, the second case had significantly delayed treatment initiation and consequently developed significant brain damage. These manifested as uncontrollable seizures, global developmental delay (primarily speech and language), and autism spectrum disorder secondary to anti-NMDAR encephalitis. However, behavior and psychosis are challenging to assess in the younger age group, the older child presented with neurological, behavioral, and psychiatric symptoms as opposed to the infant who had more evident neurological symptoms. Infants and young children may experience significant neurological impairments and developmental disabilities, although older children and adults typically respond well to therapy with satisfactory results (8). There are no standard treatment protocols for managing autoimmune encephalitis. However, the consensus from systemic reviews is to initiate immunotherapy early, start first-line immunotherapy, and consider second-line immunomodulators for a better outcome and fewer relapses in case of no or poor response (7). In their study of 501 patients with NMDR encephalitis resulting from various etiologies, Shin YW et al. found that 53% of patients responded well to first-line medication and tumor excision and 81% of patients had a good prognosis after a 24-month follow-up. (7).

Corticosteroids, IVIG, and plasmapheresis are among the first-line treatments that can be administered separately or in combination. The most popular combination is corticosteroids plus either IVIG or plasma exchange. (16, 17). Until the diagnosis of autoimmune encephalitis is confirmed, steroids should be deferred as they might aggravate infectious encephalitis, and their role in infectious encephalitis is controversial. (11,18, 19). In addition to their systemic manifestations, they can exacerbate the psychological symptoms linked to autoimmune encephalitis (7). IVIG is less expensive and more readily accessible for urgent therapy than plasma exchange. (11). The second-line therapy needs to be commenced in case of little to no clinical response. The two alternatives are cyclophosphamide and Rituximab (20). An improved safety profile for Rituximab has been demonstrated (7). There is an option of long-term maintenance with prednisolone or steroid-sparing medications such as mycophenolate mofetil and azathioprine in case if patient’s substantial neurological impairment persists and their response to treatment has been insufficient.

Conclusions

Clinical signs of HSVE-induced anti-NMDA receptor encephalitis, autoimmune encephalitis, can arise months after a successful course of anti-viral medication. The patient's age affects the symptoms, with youngsters more likely to have neurological symptoms than adults, whose symptoms are more likely to manifest as behavioral and
psychiatric issues. Children with autoimmune encephalitis might have a better prognosis and outcome when the condition is identified early, and immunotherapy is initiated promptly.

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References