

Case Report

Post Herpes Simplex Virus -1 Anti -NMDA Receptor Antibody Encephalitis in a 2.5-Year-Old Child: Case Report

Ajay Goenka^{1*} and Vivek Jain²

¹Saul R. Korey Department of Neurology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, USA

²Santokba Durlabhji Memorial Hospital, Bhawani Singh Marg, Jaipur, Rajasthan, India

Introduction

Acute clinical worsening after initial improvement in a patient treated for Herpes Simplex Virus-1 (HSVE) encephalitis is a clinical dilemma. The worsening can be either evolvement of new neurological symptoms or worsening of initial symptoms. 14-27% of children develop a recurrent encephalitic episode after successful treatment of the initial HSV infection [1-3]. The etiology can be secondary to relapse of the HSV encephalitis (can be a reactivation of the replication or delayed symptoms) [1-3] or due to an immune mediated response triggered by the HSV-1 virus [4]. Symptoms of post HSV Anti NMDA receptor encephalitis differs based on the age group. In children, it includes dyskinesia and choreoathetotic movements [5] while in adults symptoms are mostly behavior and cognitive abnormalities. These symptoms usually develop 4 - 6 weeks after the initial episode [6].

There are a few case reports of post HSV-1 anti NMDA receptor encephalitis in adults but limited data is available in the pediatric population. We are reporting a case of 2 1/2 year old girl with post HSV-1 anti NMDA receptor antibody encephalitis.

Case Report

A 2 1/2 year old girl with unremarkable past medical history presented with fever for 1 week, aphasia (irritable, not speaking and occasionally responding to verbal requests) and intermittent seizures from day 2 of her illness. She developed involuntary movements during her treatment on day 8 of illness.

The patient was evaluated by an outside hospital where she presented with one day of fever, headache and vomiting. On day two of her illness she developed seizure and encephalopathy. Cerebro Spinal Fluid analysis showed White Blood Cell 5, Protein 30 mg/dl, Glucose 62 mg/dl and HSV -1 PCR was found to be positive. The HSV-1 infection was confirmed by the western blot analysis. The patient was initially treated with Ceftriaxone, Vancomycin, Valproic acid (25mg/kg/day) and acyclovir (30mg/kg/day). Ceftriaxone and Vancomycin were later stopped based on the positive HSV-1 PCR results. EEG showed diffuse background slowing, suggestive of diffuse cerebral dysfunction. MRI Brain showed cortically based areas of restricted diffusion and foci of signal abnormality involving right temporal and parietal cortex (Fig 1). On day five of her treatment, she was noticed to be more oriented (recognizing mother) and was less irritable. On day 8 of hospitalization she developed acute peri oral dyskinesia / athetosis

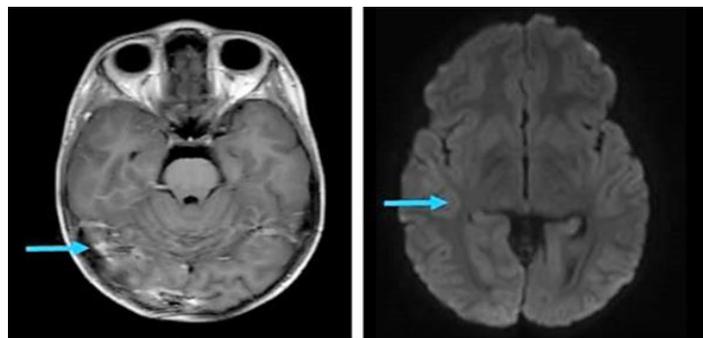


Fig 1. MRI Brain T1 with contrast and diffusion weighted image. Cortically based areas of restricted diffusion involving right temporal and parietal regions.

/ myoclonic jerks with worsening of her cognition and was referred to our centre for further management.

On examination at our centre she was found to have poor cognition, aphasic (irritable, not speaking and not following any verbal or visual clues) with normal cranial nerve examination and no weakness in any extremity. She was also found to have involuntary movements of the extremities in form of myoclonic jerks as well as peri oral dyskinesia. The patient underwent a repeat lumbar puncture and blood work including serology for anti NMDA receptor antibodies. A repeat MRI and EEG did not suggest any new finding. After an extensive literature search her symptoms were attributed to post HSV-1 anti NMDA receptor encephalitis, which is a very rare diagnosis in pediatric population. She was empirically started on treatment for autoimmune encephalitis with IVIG (2 gm/kg over 2 days) followed by IV Methylprednisolone

***Corresponding author:** Ajay Goenka, Saul Korey Department of Neurology, Albert Einstein College of Medicine, Children Hospital at Montefiore, 3415 Bainbridge Avenue, Bronx NY 10467, Tel: 718-920-4378; E-mail: agoenka@montefiore.org

Sub Date: December 30, 2016, **Acc Date:** January 6, 2017, **Pub Date:** January 7, 2017.

Citation: Ajay Goenka and Vivek Jain (2017) Post Herpes Simplex Virus -1 Anti -NMDA Receptor Antibody Encephalitis in a 2.5-Year-Old Child: Case Report. BAOJ Neuro 3: 026.

Copyright: © 2016 Ajay Goenka and Vivek Jain. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

30mg/kg/day for 3 days starting on day 14. She was continued on Acyclovir (30mg/kg/day) for a total of 21 days. She underwent a whole body MRI (chest, abdomen and pelvis) to screen for any primary malignancy and was found to be negative.

The patient completed her course of IVIG and Methylprednisolone with minimal improvement. Her anti NMDA receptor antibodies were found to be positive in both serum as well as cerebro spinal fluid. Due to the persistence of her neurological deficits, she was treated with Rituximab 375 mg/m². Rituximab was repeated after 1 week with marked improvement in her speech and her cognition. Her involuntary movements also slowly subsided. She was initially treated with Risperidone 0.25 mg twice a day for her involuntary movements and encephalopathy, which was later tapered and stopped completely.

The patient was discharged after 4 weeks of hospitalization. At the time of discharge she showed significant improvement in her speech and cognition with no involuntary movements. The patient was able to name few objects but was lacking fluency. During her follow up visit (6 months from onset of her disease) she showed remarkable improvement in her cognition and language. She was speaking 2-3 words sentences with no involuntary movements and had no neurological deficits on examination. .

Discussion

Anti-NMDAR encephalitis is recently described autoimmune encephalitis with the first description by Dr. Dalmau in 2007[7]. It is an acute onset, life threatening but treatable disease that is pathophysiologically defined due to IgG antibodies against NR1 subunit of the NMDA receptors[8].

There is a prodrome of fever, vomiting in about 50 % of patients followed by either predominantly neurological manifestations of seizure and movement disorder or psychological and cognitive changes including behavior alteration, psychosis, and memory deficits[8].

The etiology is however unclear, in young women there has been a strong correlation with underlying ovarian teratoma. Other possible tumor associated includes testicular tumor, colon cancer and other gastrointestinal tract and lung cancer.⁸ Most of these studies are adult based and there is no good correlation of any malignancy associated with this clinical entity in pediatrics population.

Our case focuses on the role of Anti NMDA receptor antibodies as etiology in worsening of symptoms and involvement of new symptoms (choreoathetoid movements) after initial improvement in a patient getting treated for HSV-1 encephalitis.

The pathogenesis of immune response triggered by HSV is unclear. In a recent adult study IgG NMDAR antibodies were detected in 7% of patients with HSVE [9]. The symptoms of post HSV encephalitis includes prolonged abnormal movements (choreoathetosis) and are often refractory to acyclovir therapy.

In a recent case series of children with post HSV-1 Anti NMDA receptor encephalitis, the most common symptoms reported were

chorea-like movements, while other symptoms includes irritability, sleep disorder, and unresponsiveness. Bases on the recent literature in majority (80%) of the cases, symptoms occur after complete recovery from HSE while in 20% of the cases, symptoms develops in contiguity with HSVE [4,6]. The average duration of development of choreoathetosis post HSV is 4 - 6 weeks after the initial episode [6]. Our case had a unique presentation and possibly the first pediatric case of post HSV-1 Anti NMDA receptor encephalitis to develop choreoathetoid movements on day 8 of illness.

The standard diagnostic workup includes a lumbar puncture that is non-specific and can show lymphocytic pleocytosis and oligoclonal bands. In majority of the cases there are no specific EEG findings, the common findings includes focal or generalized slowing or epileptogenic foci [10]. There are a few case reports of EEG showing delta brush in this clinical entity which is associated with poor prognosis[11]. MRI brain is mostly normal or shows transient T2 hyper intensities. Diagnosis is made by detection of IgG antibodies against NR1 subunit of the NMDA receptors in serum and CSF.

There are no standard guidelines for the treatment of this disease. Based on the current literature IVIG, Methylprednisolone and plasmapheresis are considered first line treatment. Rituximab and Cyclophosphamide are considered as second line therapies which are used in cases of either poor response or disease relapse [10].

Based on the case there are few clinical implications

- 1) Patient with acute worsening post HSVE treatment or evolving of new symptoms (choreoathetoid movements/cognitive changes) should be evaluated for Anti NMDA receptor encephalitis.
- 2) Anti NMDA receptor encephalitis is an under diagnosed entity in pediatric population especially post infectious and needs further research.
- 3) Our case exhibited atypical manifestations in terms of early development of Anti NMDA receptor Encephalitis after HSV-1 (Day 8 of illness).

References

1. De Tiege X, Rozenberg F, Des Portes V (2003) Herpes simplex encephalitis relapses in children: differentiation of two neurologic entities. *Neurology* 61(2):241-243.
2. Ito Y, Kimura H, Yabuta Y (2000) Exacerbation of herpes simplex encephalitis after successful treatment with acyclovir. *Clin Infect Dis* 30(1):185-187.
3. Kimura H, Aso K, Kuzushima K, Hanada N, Shibata M, et al. (1992) Relapse of herpes simplex encephalitis in children. *Pediatrics*.89(5 Pt 1):891-894.
4. Armangue T, Leypoldt F, Malaga I (2014) Herpes simplex virus encephalitis is a trigger of brain autoimmunity. *Ann Neurol*75(2):317-323.
5. Hoftberger R, Armangue T, Leypoldt F, Graus F, Dalmau J, et al.(2013) Clinical Neuropathology practice guide 4-2013: post-herpes simplex encephalitis: N-methyl-Daspartate receptor antibodies are part of the problem. *ClinNeuropathol*32(4):251-254.

6. Skoldenberg B, Aurelius E, Hjalmarsson A (2006) Incidence and pathogenesis of clinical relapse after herpes simplex encephalitis in adults. *Journal of neurology* 253(2):163-170.
7. Sansing LH, Tuzun E, Ko MW, Baccon J, Lynch DR, et al. (2007) A patient with encephalitis associated with NMDA receptor antibodies. *Nature clinical practice Neurology* 3(5):291-296.
8. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R, et al. (2011) Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 10(1):63-74.
9. Pruss H, Finke C, Holtje M (2012) N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. *Ann Neurol* 72(6):902-911.
10. Florance NR, Davis RL, Lam C (2009) Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Ann Neurol* 66(1):11-18.
11. Di Capua D, Garcia-Ptacek S, Garcia-Garcia ME, Abarrategui B, Porta-Etessam J, et al. (2013) Extreme delta brush in a patient with anti-NMDAR encephalitis. *Epileptic disorders: international epilepsy journal with videotape* 15(4):461-464.