Title: Post Herpes Simplex Virus 1 Encephalitis (HSV1E) induced N-methyl-D-aspartate receptors (NMDAR) Autoimmune Encephalitis ; a case report

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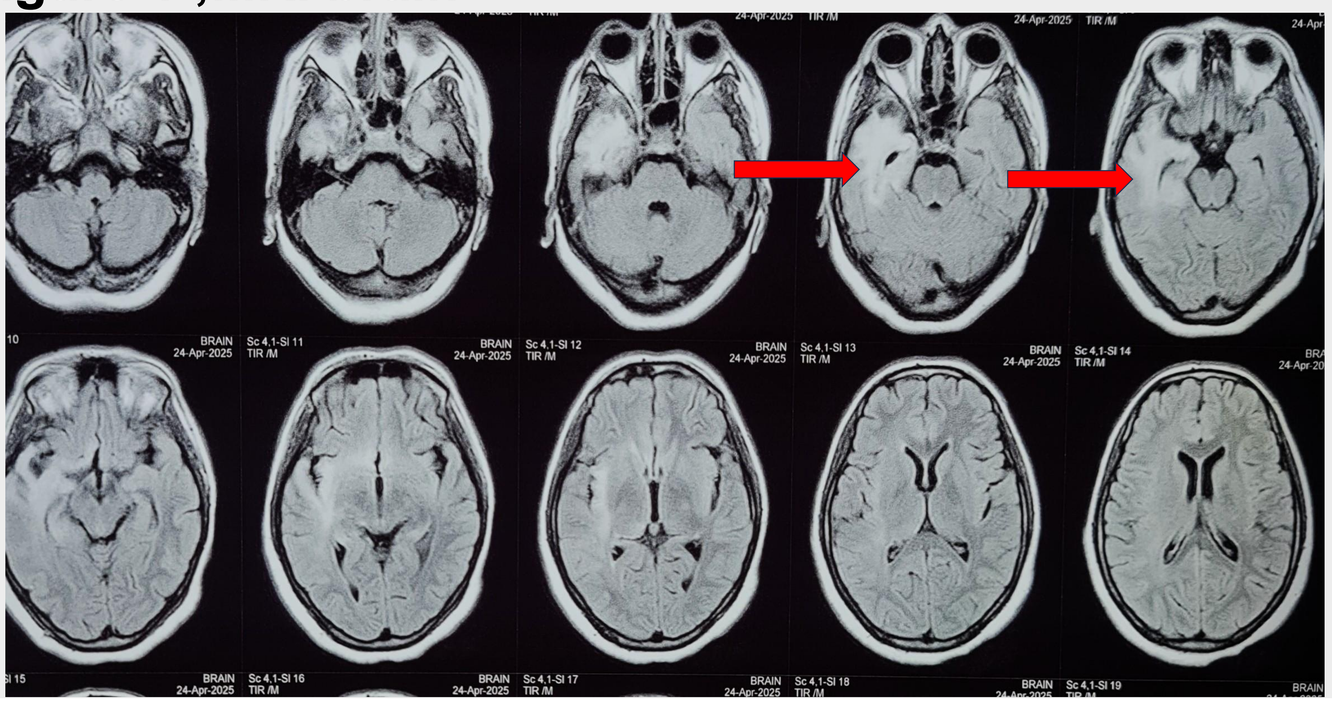
- **Background and Aims** Herpes simplex encephalitis (HSE) is leading cause of severe sporadic encephalitis. Post-HSV1E development of N-methyl-D-aspartate receptor (NMDAR) antibodies resulting in autoimmune encephalitis in the various studies reported from 7.1% to 12.5% in adult patients.[1] Anti-NMDAR develops 1–4 weeks after HSVE, manifesting as choreoathetosis and/or orofacial dyskinesia in children and psychiatric symptoms in young adults. We should consider anti-NMDAR encephalitis in the differentials in patients with clinical decline after improvement of treated acute HSVE.

- **Methodology** A 33 year old previously healthy female presented in March 2025 with history of moderate to high grade fever since 2 days followed by altered sensorium with generalized tonic clinic seizure episode since one day ,on evaluation EEG showed generalized slowing ,CSF; TLC -296 (97%L) ; Glucose - 78 mg/dl Protein- 110 mg/dl ; ZN Stain and CBNAAT for MTB - Negative ,HSV 1 PCR positive in CSF, MRI brain findings suggestive of acute HSV encephalitis, patient was treated with injection acyclovir for 14 days to which responded well. After a month in later 3rd of April 2025 patients presented again with complaints of headache, drowsiness, episodes of perioral movements and during hospitalization had dysautonomia.

- **Result** Routine blood investigation were normal. EEG was showing right side focal temporal lobe epileptic discharges with slowing. CSF showed pleocytosis with slightly increased protein, repeat HSV1 PCR done in CSF in view of possibility of relapse of HSV1 but came out to be negative, no fresh MRI brain necrotic or hemorrhagic lesion ,.

- Further evaluation in view of serum possibility of post infective autoimmune encephalitis came to be positive for NMDAR antibody both in CSF and serum. The patient showed poor response to steroids and IVIG but improved after rituximab therapy.

Figure 1 ;MRI brain



Discussion Anti-NMDAR encephalitis is a well-characterized dysimmune disorder of the central nervous system and represents the most common form of autoimmune encephalitis (AIE). Although it often arises idiopathically, two additional etiological categories are recognized: paraneoplastic and post-infectious forms. Post-infectious encephalitis associated with anti-NMDAR antibodies has been increasingly reported as a secondary form of AIE, with some cases showing the presence of asymptomatic anti-NMDAR antibodies.[2] Notably, all reported AIE cases developed within two months of the triggering event, with an even shorter latency observed in younger patients.Pathogenic mechanism underlying the biphasic HSE followed by HSV induced anti NMDAR encephalitis remain unknown. The proposed hypothesis are virus induced neural injury exposes neural antigen to systemic immunity, molecular mimicry of shared epitopes between HSV. The possibility of delayed post-infectious anti-NMDAR encephalitis should be considered during the long-term follow-up of patients recovering from HSV-1 encephalitis, to enable early recognition and management of this treatable complication. Systematic screening for autoimmune encephalitis–related autoantibodies during the acute phase of infectious encephalitis may also facilitate more effective patient monitoring.

Conclusion Our case highlights the importance of keeping high clinical suspicion for anti-NMDAR encephalitis in biphasic HSE following HSV, as it responds well to immunotherapy.

References:

1 Sköldenberg B, Aurelius E, Hjalmarsson A, et al. Incidence and pathogenesis of clinical relapse after herpes simplex encephalitis in adults. J Neurol 2006;253:163–170.

2 Armangue T, Moris G, Cantarín-Extremera V, Conde CE, Rostasy K,Erro ME,etal.Autoimmune post-herpes simplex encephalitis of adults and teenagers. Neurology. (2015) 85:1736–43.