“Shooting Your Own Foot”: Autoimmune Encephalitis Following A Viral Trigger : A Case Report

Author’s contributions

The authors confirm contribution to the paper as follows: all authors contributed equally to study conception and design, data collection and analysis, draft manuscript preparation and critical revision of final article. All authors reviewed and approved the final version of the manuscript.

Abstract :

Aims :

The aim of this case report is to highlight the frequently overlooked association between Anti-NMDA Receptor Encephalitis and a preceding Herpes Simplex Viral Encephalitis trigger, the clinical settings under which to suspect this autoimmune disease, the need for appropriate workup to clinch the diagnosis and the necessity of speedy initiation of immunotherapy, in a disease where timely treatment is paramount.

Presentation of Case :

A middle aged woman presented with a history of fever and syncope, followed by slurring of speech, quadriparesis, seizures and altered sensorium. She was diagnosed with HSV-1 Encephalitis on basis of CSF studies and MRI brain. Despite a timely 28-day course of intravenous acyclovir therapy, she showed incomplete clinical recovery. A serum and CSF autoantibody panel was performed, which

clinched a diagnosis of Anti-NMDA Receptor Encephalitis. A course of steroids and IVIg was given and the patient was discharged after showing clinical improvement.

Discussion :

Anti-NMDA Receptor Encephalitis is an autoimmune encephalitis characterized by complex neuropsychiatric features and presence of IgG antibodies against NR1 subunit of NMDA receptor detectable in CSF and serum. It is associated with various malignancies, chiefly ovarian teratomas, and with HSV-1 viral encephalitis. Diagnosis involves autoantibody detection in CSF or serum and first line treatment is with steroids, IVIg or plasma exchange, and tumour resection.

Conclusion :

Prompt diagnosis of Anti-NMDA receptor encephalitis is crucial as it enables treatment with timely immunosuppression and tumour resection. This disease must be suspected in adults or children presenting with subacute onset of neuropsychiatric symptoms, with CSF lymphocytic pleocytosis and presence of autoantibodies to NMDA receptor in CSF or serum. Early treatment is associated with good outcomes.

Keywords: Anti-NMDA Receptor Encephalitis, Autoimmune Encephalitis, HSV-1 Encephalitis, Viral Encephalitis, Paraneoplastic Encephalitis

Abbreviations :
NMDA = N-Methyl-D-Aspartate
HSV-1 = Herpes Simplex Virus-1
IVIg = Intravenous Immunoglobulin
CSF = Cerebrospinal Fluid

Introduction :

Anti-NMDA receptor encephalitis is an autoimmune encephalitis targeting the NMDA receptors on neurons in the brain. It presents with subacute onset of psychiatric symptoms, seizures and memory deficits, and most commonly follows some identifiable trigger: classically tumours like ovarian teratomas or post CNS viral infections such as Herpes Simplex viral encephalitis[1]. Here, we present the case report of a woman admitted in our Institute with Herpes Simplex Viral Encephalitis who developed Anti-NMDA receptor encephalitis during her hospital stay. We discuss her presentation, approach to encephalitis, treatment options and prognosis of this unique and often overlooked sequelae, and review the existing descriptions of the same.

Presentation of Case :

A 42-year-old female patient with a history of hypothyroidism presented to medical attention with low-grade fever for two days, followed by an episode of dizziness and fall in the bathroom with associated loss of consciousness for around 20 minutes. She regained consciousness on her own and was taken to a nearby primary care hospital, where she was given IV fluids and sent home without further workup.

The next day, she noticed slurring of speech, drooling of saliva from the angles of her mouth and abnormal twitching of right-sided facial muscles. As the day progressed, she became drowsy and developed weakness in all four limbs. She was rushed to a private hospital where the neurological examination was significant for delirium, quadriparesis and right-sided UMN facial nerve paralysis. MRI was done: showed multiple punctate, confluent areas of infarct in bilateral frontoparietal and insular cortex with frontal leptomeningeal enhancement. The patient was empirically started on intravenous acyclovir because of suspected viral meningitis, with differentials of some other infectious encephalopathy, cerebral vasculitis, other autoimmune conditions like ADEM and autoimmune encephalitis, and non-convulsive status epilepticus.

A lumbar puncture was corroborative of the initial suspicion of viral meningitis: 50 cells/cu.mm with lymphocyte predominance and microproteins of 56mg/dL (See *Table 1*). HSV-1 PCR was positive from CSF sample, which confirmed diagnosis of HSV-1 Encephalitis. The autoimmune panel and EEG were normal, ruling out other causes of presentation.

Table 1: CFS analysis at day 2 and day 28

CSF Analysis	Day 2	Day 28
Appearance:	Clear	Clear
WBC (/cu.mm):	50 (80% Lymphocyte)	10-12 (100% Lymphocyte)

RBC:	0	0
Protein:	56 mg/dl	99 mg/dl
Glucose:	85 mg/dl	69 mg/dl
HSV-1 RNA:	Detected	Not detected
Other Virus Panel PCR:	Not detected	Adenovirus Enterovirus EBV Human Parechovirus Human Parvovirus B19 HSV-2 VZV CMV HHV-6 HHV-7 ..were all not detected
CSF Autoimmune Panel:	Negative	Anti NMDA + Anti AMPA 1 - Anti AMPA 2 - CASPR - LGI-1 - GABAb receptor -
CSF Oligoclonal Band:	Not done	Negative
Gram Stain and Culture	No growth	No growth
KOH Mount	Normal	Normal

On Day 3 of coming to medical attention, the patient condition worsened: sensorium dipped to E2V2M2 and she developed focal onset seizures. Neurological examination was significant for the power of 0/5 in all four limbs. She was intubated and shifted to ICU. Acyclovir therapy and supportive management continued. However, the patient failed to show clinical improvement, and was tracheostomised after seven days on ventilator support.

The patient presented to our institute on Day 12 of her illness, with GCS of E1VtM1, on inotrope support and acyclovir therapy. She was managed for multiple secondary issues over a rocky month in the ICU: septic shock, aspiration pneumonitis, bedsores and UTIs, and status epilepticus. With the completion of 28-day course of acyclovir therapy, she regained consciousness and her power improved to 2/5 in bilateral upper and lower limbs. However, she had also developed spasms of masticator muscles with a mouth opening of less than 1 cm, an inability to swallow liquids, and episodes of excessive crying.

Because of the incomplete recovery despite timely initiation and completion of anti-viral therapy, a repeat LP (including CSF autoimmune panel) and MRI Brain (See *Image A*) were done. The autoimmune panel was positive for anti-NMDA receptor antibodies in

both CSF and plasma and negative for other autoantibodies (See *Table 1*), thus confirming the diagnosis of anti-NMDA receptor Encephalitis. Tumour markers, transvaginal ultrasonogram, and CT chest/abdomen ruled out any paraneoplastic etiology. The vasculitis profile was negative. Repeat MRI brain showed T2 hyperintense lesions in B/L temporal lobes and insular cortex, consistent with the original diagnosis of HSV-1 Encephalitis, attributed to be the trigger for the subsequent autoimmune encephalitis.

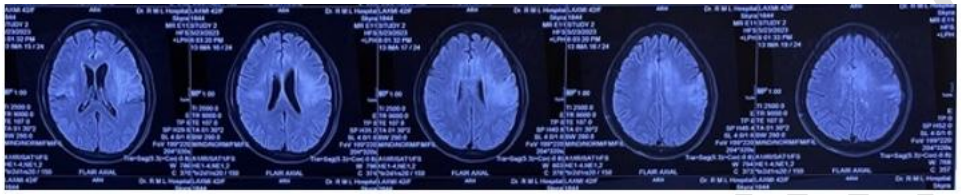

Image A: *T2/FLAIR hyperintensities with patchy gyriform enhancement in bilateral temporal lobes, insular cortex, cingulate gyrus, posterior limb of left internal capsule, left thalamus and left hippocampus.*

The patient was started on a five-day course of IVIg and pulse Methylprednisolone therapy. Her GCS improved to E4VtM6, and power improved to 3/5 in bilateral upper and lower limbs. Her masticator spasms stopped, her mouth opening improved to over 2 cm and emotional lability subsided. She continued to not be able to tolerate more than a few oral sips and was discharged with tracheostomy and RT, on a tapering dose of oral prednisolone.

On 2 month follow-up, patient was seen in the outpatient department: Her power had improved slightly to 4+ and plateaued, she was off tracheostomy and RT feed, and able to tolerate small oral feeds.

Discussion :

Encephalitis, or inflammation of the brain, is usually due to viral or autoimmune etiology. Sporadic viral encephalitis cases are caused by Herpes family group (HSV-1, 2, VZV, EBV) and enteroviruses, while Arboviruses are the most common cause of epidemics of viral encephalitis[2]. Autoimmune encephalitis is most commonly due to anti NMDA receptor autoantibody, and less frequently other autoantibodies such as anti-AMPA, anti-Caspr2, anti-LG1, anti-GABA and many more[3].

HSV encephalitis presents with fever, altered sensorium, seizures and hallucinations. HSV PCR in CSF samples remains the gold standard for diagnosis[4], and HSV serology may also be positive. MRI Brain shows bilateral temporal lobe hyperintensities on T2

imaging, with a predilection for the medial temporal lobe, insular cortex and para-hippocampal area.

Anti-NMDA receptor encephalitis is a complication that develops in around 20-30% of patients with HSV encephalitis[5]. It is most commonly seen in the initial 1-2 months post the HSV-1 Encephalitis episode, but cases presenting many years later or even alongside the triggering viral infection have also been documented in medical literature[6]. Symptoms of anti-NMDA receptor encephalitis primarily include a subacute onset of prominent psychiatric symptoms, seizures, frequent dyskinesias and autonomic instability. Anti NMDA receptor encephalitis may also develop as a paraneoplastic syndrome in association with several malignancies, and its diagnosis must always initiate a thorough workup to rule out these malignancies[7]. Almost half of adult females have a unilateral or bilateral ovarian teratoma, while the detection of a tumour is much rarer in men. Other malignancies seen include teratomas of the mediastinum, ovarian cystadenofibromas, neuroblastomas, small cell lung cancers, Hodgkin's lymphoma and testicular germ cell tumours[8].

The association of HSV-1 encephalitis and malignancies with anti-NMDA receptor encephalitis is intriguing. Several hypotheses have been proposed to explain the pathogenesis of this association. It is postulated that the initial viral infection triggers molecular mimicry, leading to the production of antibodies against NMDA receptors. Alternatively, the viral infection may cause a dysregulated immune response, resulting in the breakdown of immune tolerance to NMDA receptors[9]. In the case of malignancies, autoantibodies are generated in response to the neural elements within tumours such as teratomas[10]. Further research is needed to elaborate the exact mechanisms involved.

Autoimmune encephalitis is confirmed by testing for a panel of autoantibodies in CSF and to a lesser extent, serum. CSF shows lymphocytic pleocytosis, and detection of IgG antibodies to NR1 subunit of NMDA receptor in CSF is confirmatory for diagnosis of Anti-NMDA Receptor Encephalitis[11]. MRI brain may be normal or show transient contrast enhancing abnormalities in cortical and subcortical regions. A set of clinical criteria in the absence of autoantibody testing in low-cost settings have also been proposed and can be used to make a decision to initiate treatment[12].

Treatment consists of immunosuppressive therapy and tumour resection. 1st line medical measures are pulse steroid therapy followed by either IVIg or plasmapheresis. If there is minimal clinical improvement, 2nd line immunosuppressive therapies such as Rituximab, Cyclophosphamide or both are tried[13]. Maximum clinical improvement occurs in the first 4 weeks of immunosuppression and may continue for up to 18 months after treatment. Up to 80% of patients treated with immunosuppression achieve a good outcome, defined as a score of 0 to 2 on modified Rankin Scale[14]. Long term outcomes vary, with some having complete recovery while others have residual neurological deficit. Treatment initiated within 30 days on disease onset was associated with the best outcome. About 15-20% of patients may experience a relapse, with relapse being less likely if patient underwent tumour resection or received timely immunosuppression[15].

Recognition of the association between Herpes Simplex Virus-1 Encephalitis and Anti-NMDA Receptor Encephalitis is vital for timely diagnosis and initiation of appropriate treatment. Clinical suspicion should arise when patients with a history of HSV-1 encephalitis develop new-onset psychiatric symptoms or neurological deterioration beyond the expected course. Prompt evaluation, including CSF analysis for anti-NMDA receptor antibodies, is crucial in confirming the diagnosis and initiating immunosuppression.

Conclusion :

Anti NMDA receptor encephalitis is a complication that can develop in up to 20-30% of patients with HSV-1 encephalitis. It can also occur in the setting of paraneoplastic encephalitis, and its diagnosis necessitates a screening to rule out associated malignancies. With early diagnosis and speedy initiation of treatment measures such as immunosuppression and tumour resection, it has a good prognosis with minimal permanent neurological deficit. Due to the chances of relapse even after full clinical recovery, it mandates close follow up of the patient post discharge.

This case report demonstrates such an association between HSV-1 encephalitis and subsequent anti-NMDA receptor encephalitis. Physicians should maintain a high index of suspicion in patients presenting with new-onset psychiatric symptoms or neurological deterioration after a diagnosis of HSV-1 encephalitis, especially in the first 2 months. Timely diagnosis and initiation of immunotherapy are crucial for improving outcomes in affected individuals. Further research is needed to enhance our understanding of the underlying mechanisms and exploring targeted treatment strategies for this unique neurological sequelae.

Ethical Approval:

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

Consent

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

References :

1. Peery HE, Day GS, Dunn S, Fritzler MJ, Prüss H, De Souza C, Doja A, Mossman K, Resch L, Xia C, Sakic B. Anti-NMDA receptor encephalitis. The disorder, the diagnosis and the immunobiology. Autoimmunity reviews. 2012 Oct 1;11(12):863-72.

2. Ellul M, Solomon T. Acute encephalitis–diagnosis and management. Clinical medicine. 2018 Apr;18(2):155.

3. Gole S, Anand A. Autoimmune Encephalitis. 2023 Jan 2.

4. Atkins JT. HSV PCR for CNS infections: pearls and pitfalls. The Pediatric infectious disease journal. 1999 Sep 1;18(9):823-4.

5. Armangue T, Spatola M, Vlagea A, Mattozzi S, Cárceles-Cordon M, Martinez-Heras E, Llufriu S, Muchart J, Erro ME, Abraira L, Moris G. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. The Lancet Neurology. 2018 Sep 1;17(9):760-72.

6. Tyler KL. Update on herpes simplex encephalitis. Rev Neurol Dis. 2004 Jan 1;1(4):169-78.

7. Lancaster E, Martinez-Hernandez E, Dalmau J. Encephalitis and antibodies to synaptic and neuronal cell surface proteins. Neurology. 2011 Jul 12;77(2):179-89.

8. Leypoldt F, Titulaer MJ, Aguilar E, Walther J, Bönstrup M, Havemeister S, Teegen B, Lütgehetmann M, Rosenkranz M, Magnus T, Dalmau J. Herpes simplex virus–1 encephalitis can trigger anti-NMDA receptor encephalitis: case report. Neurology. 2013 Oct 29;81(18):1637-9.

9. Dalmau J, Armangué T, Planagumà J, Radosevic M, Mannara F, Leypoldt F, Geis C, Lancaster E, Titulaer MJ, Rosenfeld MR, Graus F. An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models. The Lancet Neurology. 2019 Nov 1;18(11):1045-57.

10. Swayne A, Warren N, Prain K, Gillis D, Wong R, Blum S. Analysing triggers for anti-NMDA-receptor encephalitis including herpes simplex virus encephalitis and ovarian teratoma: results from the Queensland Autoimmune Encephalitis cohort. Internal Medicine Journal. 2022 Nov;52(11):1943-9.

11. Mann AP, Grebenciucova E, Lukas RV. Anti-N-methyl-D-aspartate-receptor encephalitis: diagnosis, optimal management, and challenges. Therapeutics and clinical risk management. 2014 Jul 1:517-25.

12. Kaneko A, Kaneko J, Tominaga N, Kanazawa N, Hattori K, Ugawa Y, Moriya A, Kuzume D, Ishima D, Kitamura E, Nishiyama K. Pitfalls in clinical diagnosis of anti-NMDA receptor encephalitis. Journal of neurology. 2018 Mar;265:586-96.

13. Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, Honig LS, Benseler SM, Kawachi I, Martinez-Hernandez E, Aguilar E. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. The Lancet Neurology. 2013 Feb 1;12(2):157-65.

14. Raja P, Shamick B, Nitish LK, Holla VV, Pal PK, Mahadevan A, Thomas PT, Maya B, Saini J, Shantala H, Netravathi M. Clinical characteristics, treatment and long-term prognosis in patients with anti-NMDAR encephalitis. Neurological Sciences. 2021 Nov;42:4683-96.

15. Gabilondo I, Saiz A, Galán L, González V, Jadraque R, Sabater L, Sans A, Sempere A, Vela A, Villalobos F, Viñals M. Analysis of relapses in anti-NMDAR encephalitis. Neurology. 2011 Sep 6;77(10):996-9.