Case report

"Shooting Your Own Foot": Autoimmune Encephalitis Following AViral Trigger - A Case Report

Abstract :
Aims :

The aim of this case study is to highlight the often overlooked association between HSV-1 encephalitis and subsequent anti-NMDA receptor encephalitis, and to sensitise physicians to recognise the same in clinical practice.

Presentation of Case :

A middle aged woman presented with history of fever and syncope, followed by slurring of speech, quadriparesis, seizures and altered sensorium. She was diagnosed with HSV Encephalitis on basis of CSF studies and MRI brain. Despite timely 28 day course of intravenous acyclovir therapy, she showed incomplete clinical recovery. Serum and CSF auto-antibody panel was performed, which clinched a diagnosis of Anti NMDA receptor encephalitis. A course of steroids and IVIg was given and patient was discharged after showing clinical improvement.

Discussion :

Encephalitis most commonly is due to viral or autoimmune etiology. HSV encephalitis, which presents with fever, altered sensorium, seizures and neurological deficits is treated with intravenous acyclovir. About 30% of these cases progress to anti-NMDA receptor encephalitis. Diagnosis involves autoantibody testing and treatment is with steroids, IVIg or plasma exchange

Conclusion :

HSV encephalitis requires prompt diagnosis and timely initiation of intravenous acyclovir therapy for best outcomes. Anti-NMDA receptor encephalitis, occurring in 30% post-HSV encephalitis cases, is often overlooked to the detriment of the patient. This case report highlights the association between the two, and the importance of keeping vigilance in HSV encephalitis patients with lack of response to anti-viral therapy or with development of fresh psychiatric and neurological symptoms.

Ketwords: HSV Encephalitis, Autoimmune Encephalitis, Anti NMDA Receptor Encephalitis

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 andinfections such as Herpes Simplex viral encephalitis. Here, we present the case report of a woman admitted in our Institutewith Herpes Simplex Viral Encephalitis who developed Anti-NMDA receptor encephalitis during the course of 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 association in the Indian setting.

Presentation of Case :

A 42-year-old female patient with history of hypothyroidism presented to medical attention with low grade fever for two days, followed by anepisode 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 carehospital, where she was given IV fluids andsent home without further workup.

The next day, shenoticedslurring 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 developedweakness of all four limbs. She was rushed to a private hospital where 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. Patient wasempirically started onintravenous acyclovir in view 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 puncturewas corroborative of initialsuspicion 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. Autoimmune panel and EEGwas 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 - LGl-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, patient condition worsened: sensorium dipped toE2V2M2 and she developed focal onset seizures. Neurological examination was significant for power of 0/5 in all four limbs. She was intubated and shifted to ICU. Acyclovir therapy and supportive management continued. However, patient failed to

show clinical improvement, and was tracheostomised after seven days on ventilator support.

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 the course of 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 mouth opening of less than 1 cm, an inability to swallow liquids, and episodes of excessive crying.

In view 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.Autoimmune panel was positive for anti NMDA receptor antibody 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. Vasculitis profile was negative.Repeat MRI brain showed T2 hyperintense lesions in B/L temporal lobes and insular cortex, consistent with original diagnosis of HSV-1 Encephalitis, attributed to be the trigger for the subsequent autoimmune encephalitis.

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

Patient was started on a five day course of IVIg and pulse Methylprednisolone therapy. Her GCS improved to E4VtM6, power improved to 3/5 in bilateral upper and lower limbs. Her masticator spasms stopped,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 tapering dose of oral prednisolone.

On 2 month follow up, patient was seen in the outpatient department : Her power had improved slightly to 3+ 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 autoimmuneetiology. 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[1]. Autoimmune encephalitis is most commonly due to anti NMDA receptor autoantibody, and less frequently other autoantibodies[2].

HSV encephalitis presents with fever, altered sensorium, seizures and hallucinations. Examination can reveal virtually any type of neurological deficit: hemiparesis,CN palsies, aphasias and involuntary movements have all been seen in clinical practice[3].As meninges are usually not inflamed, signs of meningeal irritation are absent. CSF studies show characteristic lymphocytic pleocytosis with slightlyraised proteins, and HSV PCR in CSF sample remains the gold standard for diagnosis[4]. HSV serology may be positive, though it is less sensitive and specific than PCR. MRI Brain shows bilateral temporal lobe hyperintensities on T2 imaging, with predilection for the medial temporal lobe, insular cortex, para-hippocampal area and frontal lobe[5].

HSV encephalitis has a grave prognosis if untreated : up to 75% of patients die without therapy, which reduces to 30% with timely acyclovir therapy started within 2-3 days. Even with timely intervention, up to 50% of patients have permanent neurological deficits[6].

Anti NMDA receptor encephalitis is a complication that developsin around 30% of cases post HSV encephalitis. It is most commonly seenin the initial 2 months post the HSVE episode, butcases presenting many years later have also been documented in medical literature[7].

The association between HSV-1 encephalitis and 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[8].Further research is needed to elucidate the exact mechanisms involved.

Autoimmune encephalitis isconfirmed by testing for a panel of autoantibodies in CSF and plasma. With timely immunosuppressivetherapy, anti NMDA receptor encephalitis has an excellent prognosis: 1st line measures are IVIg, plasmapheresis and pulse steroid therapy, 2nd line measures include rituximab and cyclophosphamide[9]. Upto 90% patients showimprovement with timely treatment.Long term outcomes vary among

patients, with some having complete recovery while others have residual neurological deficit[10].

Recognition of this association between HSVE 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 treatment.

Conclusion :

HSV encephalitis is the most common cause of viral encephalitis and is a neurological emergency requiring timely acyclovir therapy to reducemortality andneurological deficit. A low threshold to start empirical therapy with acyclovir must be kept in all patients presenting with features suggestive of encephalitis, and clinicians must not wait for HSV PCR reports or MRI brain before initiating therapy.

Anti NMDA receptor encephalitis is a complication that can develop in up to 30% patients with HSV encephalitis. As this easily treatable disease is under diagnosed in the Indian context, it is important to sensitise young physicians to it.

This case report highlights the not uncommon, yet grossly overlooked association between HSV-1 encephalitis and anti-NMDA receptor encephalitis. Physicians should maintain a high index of suspicion in patients presenting with new-onset psychiatric symptoms or neurological deterioration after HSV-1 encephalitis. Timely diagnosis and initiation of immunotherapy are essential for improving outcomes in affected individuals. Further research is needed to enhance our understanding of the underlying mechanisms and explore targeted treatment strategies for this unique neurological sequalae.

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