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HERPES SIMPLEX 1 ENCEPHALITIS: IMAGING FINDINGS WITH DISEASE COURSE AND TREATMENT.

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ABSTRACT Herpes Simplex Virus (HSV) is a DNA virus causing encephalitis globally across all age groups that has high morbidity and mortality. Early diagnosis and treatment are the keys to minimize potential sequelae of the disease. In adults, herpes simplex virus type 1 (HSV-1) accounts for 95% of all cases of sporadic encephalitis and usually results from reactivation of the latent virus. Magnetic resonance imaging (MRI) is the tool for the detection of the morphologic abnormalities in Herpes encephalitis (HSE). Gold standard for diagnosis is Lumbar puncture with HSV-PCR testing. Acyclovir is the treatment of choice.

KEYWORDS : HSV-1 Encephalitis, MRI-DWI, Acyclovir, PCR.

INTRODUCTION

Encephalitis is an inflammation of the brain parenchyma as a result of an infectious or a noninfectious etiology accompanied by neurologic dysfunction. Herpes simplex virus is the most common non-epidemic and sporadic cause of viral meningoencephalitis with an incidence of approximately 1– 3 cases per million[1,2]. Ninety-five percent of fatal adult cases are a result of type 1 HSV (HSV-1) and typically follow latent viral reactivation in the trigeminal ganglion in immunocompetent patients. MRI is the most sensitive radiological investigation, with changes usually visible within 1–3 days of onset of symptoms.

Presentation

A 41-year-old female, otherwise healthy and fit, came with history of two episode of sudden onset convulsions. There was no history of associated fever or any previous seizure disorder and also there was no history of head injury or any co-morbidities. Her vitals and general examination were within normal limits. Neurological Examination revealed conscious but disoriented patient with irrelevant speech. However, her pupils were reactive and she was moving all the four limbs with 5/5 power. Her meningeal signs were negative.

MRI brain with contrast on Day 01 (Figure-1) showed small foci of restricted diffusion with hyperintensities involving left insular cortex & left temporal lobe showing mild heterogenous enhancement suggestive of vasculitis possibly due to meningoencephalitis. Her chest X-ray done to rule out paraneoplastic syndrome, was clear. Her blood investigations were normal, except for mild elevated total count. Therefore, she was started on Inj Levetiracetam, Tab Clobazam, IV fluids and other supportive medications. Her EEG was abnormal suggestive of left fronto-temporal and occipital seizures with F-7. T-3, O1 Focus and diffuse cerebral dysfunction.

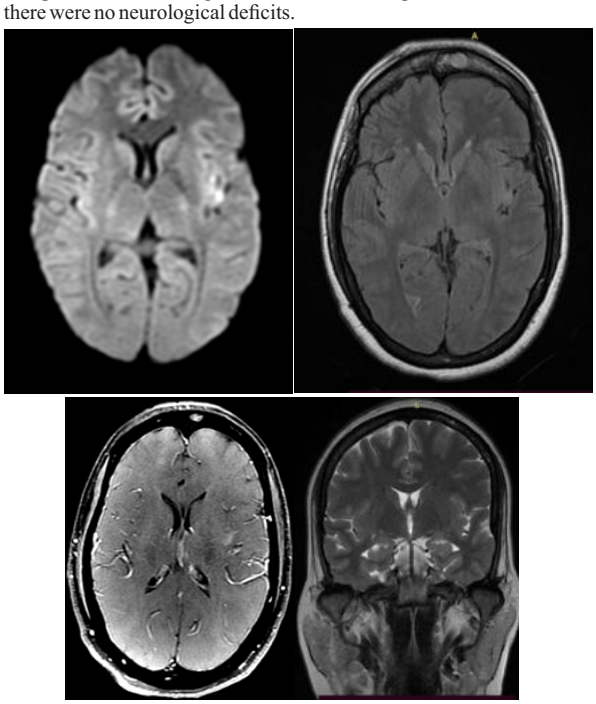
Later, on day 3, the patient developed uncontrolled right focal seizures and decreased consciousness. Therefore, she was intubated and started on Inj Midazolam infusion, Inj Valporate & Inj Lacosamide. Lumbar Puncture - CSF analysis showed protein level of 27mg/dl, elevated sugar level of 92 mg/dl and cell count of 100cells/Cumm constituting neutrophils - 03% and lymphocytes-97%. HSV- PCR was positive for HSV-1 and TB PCR, meningo-encephalitis panel for other disease were negative including VZV. Her serum electrolytes, acid base status, ABG were normal except for total count being 28421 cells/cumm. Therefore, she was started with Inj Acyclovir, Inj Vancomycin, And Inj Meropenem for which she responded well. There was no growth on CSF culture and it was negative for acid fast bacilli on ZN stain.

CT brain on day 05 & 08 (Figure 2) showed progression of hypodensities to right frontal lobe, left fronto-parietal lobe from previously involved left temporal lobe and left insular cortex. However, her serology and anti-thyroid perioxidase antibodies were negative. The patient improved symptomatically and discharged with education on nature of illness and the need of regular follow up.

Unfortunately, 12 days later, the patient again got admitted with similar complaints. This time her MRI brain (Figure 3) showed increase in extent of cerebral parenchymal involvement with bilateral asymmetric FLAIR hyperintensities at bilateral temporal lobes (L>R), fronto-parietal lobes (L>R) and left thalamus and showing restricted diffusion. Her total count was 45191 cells/cumm and also had mild elevated RFT & LFT levels with D-Dimer levels > 6000. However, her ECG and Echocardiogram were normal and EEG showed abnormality suggestive of right fronto-central seizure.

The patient was treated with acyclovir for 6 weeks, and then discharged. At discharge, the patient's general condition was satisfactory, with full consciousness; global measures, language, memory, visual and frontal functions were improved despite progression of images features. An individual teaching program and Intensive logopedic exercises were conducted in outpatient conditions. There was a constant support from patient's family during rehabilitation, as well as informal training after discharge. The patient was able to regain independence in everyday life at home.

Follow up imaging (Figure 4) after 3 years showed cystic encephalomalacic changes of both medial temporal lobes. However, there were no neurological deficits.



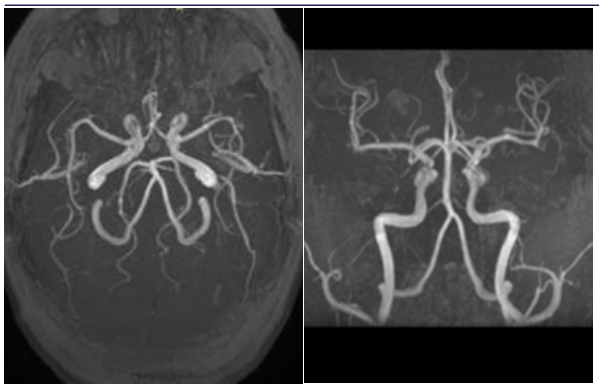


Figure 1: on Day 01, DWI, FLAIR axial, T1FS post contrast and T2 coronal images showing multiple small foci of T2WI /FLAIR hyperintensities involving left left insular cortex with T2 shine through phenomenon on DWI/ADC images. MRA is within normal limit.

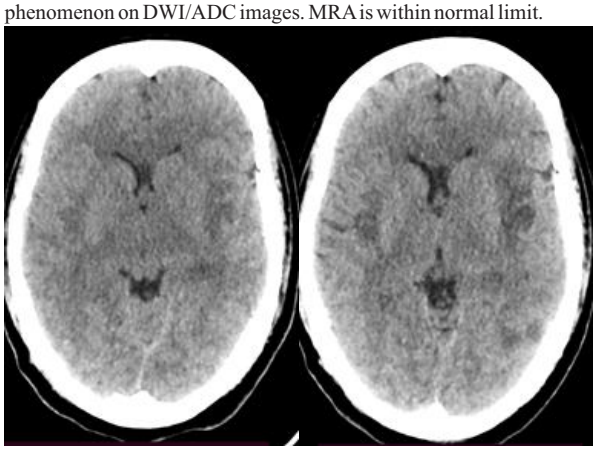


Figure 2: CT brain showing disease evolution on Day 05 & 08 with extended hypodensities at bilateral insular cortex, bilateral fronto-temporo-parietal lobes (L>R) and mild mass effect.

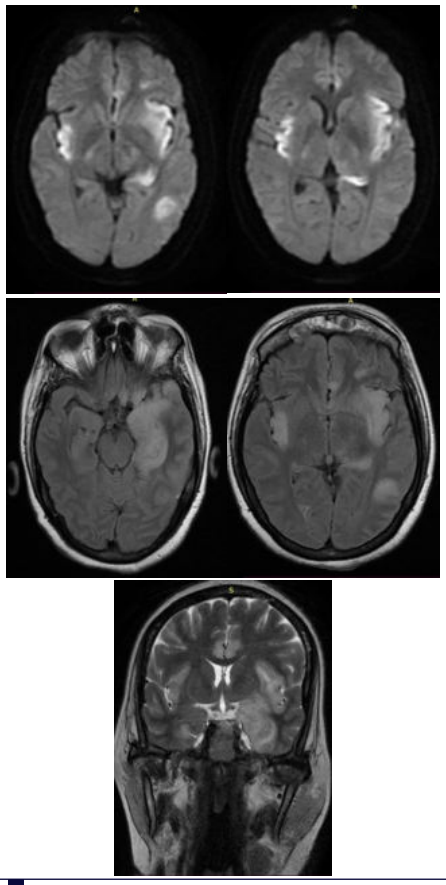


Figure 3: MRI on Day-12, DWI, FLAIR axial and T2 coronal images showing increased in extent of involvement of both temporal lobes (L>R) and fronto-parietal lobes (L>R) with asymmetric FLAIR hyperintensities and restricted diffusion.

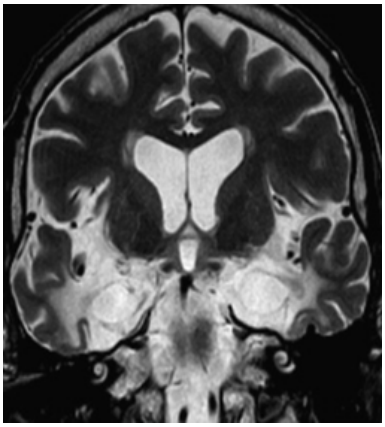


Figure 4: Follow up MRI, T2 coronal image after 3 years shows cystic encephalomalacia of both temporal lobes.

DISCUSSION

There are prevailing doubts regarding whether HSE is caused by reactivation of a latent HSV-1 infection or a primary infection. But HSV-1 remains latent in the trigeminal ganglia of asymptomatic patients after the acute illness subsides, and encephalitis is a result of reactivation of the latent virus. An alternative theory is that HSE is a primary infection in which the virus travels to the brain either through the trigeminal nerves or olfactory tracts[1,2,3].

Clinically, Herpes encephalitis presents with nonspecific neurologic findings of an acute (<1 week) duration[1,2,3]. Fever is the most prominent finding, present in 90% of patients. There is a progressive prodromal phase at the beginning of the disease, after which a rapid decline may follow[4, 5]. Some patients show behavioral or psychiatric disorders, plus amnesic or language disturbances. Neurologic findings include hemiparesis, dysphagia, aphasia, ataxia, or focal seizures. Patients often have a prodromal syndrome of upper respiratory tract infection[8].

Herpes encephalitis leads to early development of cytotoxicity, and diffusion-weighted imaging is therefore sensitive in the acute and subacute phase of the disease[6, 7]. DWI is the most sensitive sequence for HSE detection until approximately 2 weeks of disease duration, at which point FLAIR shows more pronounced signal abnormality[9,10]. Large intraparenchymal and petechial variety of hemorrhage is seen in less than half of cases. Contrast-enhancement can be seen on CT and MR but is less frequent than FLAIR hyperintensity or restricted diffusion[11]. Of all MR imaging findings in the acute stage, the only one that is predictive of disease morbidity is restricted diffusion. The presence of hemorrhage or contrast enhancement does not portend a worse prognosis.

The cerebrospinal fluid can be normal in 5% to 10% of patients at initial evaluation, but MRI will show lesions earlier with areas of hypointensity, edema and a mass effect in the temporal and orbitofrontal lobes. Finding DNA in the cerebrospinal fluid, using the polymerase chain reaction technique is gold standard for diagnosis[12]. The treatment of choice for HSE is acyclovir; it is absorbed by virus infected cells and leaves healthy cells unaffected. The compound is activated by viral thymidine kinase within the cell. It competitively inhibits viral DNA and inactivates viral DNA polymerase, causing a break in the nucleoside chain and ultimately stopping the replication of viral DNA without damage to normal cells.

In our patient, MRI documented widespread abnormalities on admission, and progression, despite the clinical improvement[13,14].

This pattern could be due to following factors:

1. Persistent MRI abnormalities may not correspond to disease activity, but may simply reflect a process that takes time to be completed with atrophy and cystic transformation of signa changes.

2. These changes could represent relapsing or chronic HSE.

3. immune-mediated tissue damage may result in progressive changes.

4. Wallerian degeneration of fibers can also further lead to signal changes.

Imaging studies of a cohort of patients surviving PCR confirmed HSV-1 encephalitis are needed to determine whether this pattern is occasional or represents a frequent form of progression.

Finally, HSE continues to confer high morbidity and mortality with overall mortality over 70 % and only 2.5 % of patients fully recovered. Therefore, prompt diagnosis and initiation of treatment with intravenous acyclovir are key to reduce neurologic sequelae among survivors and reduces mortality[15,16].

CONCLUSION

CSF analysis and PCR remains the gold standard for diagnosis of HSV encephalitis. Advanced MRI imaging has been increasingly used to aid with diagnosis. In the era of increasing use of immunologic therapy, prompt empirical Acyclovir may be warranted to decrease morbidity and mortality. Proper rehabilitation care should be given for patient's recovery for their day-to-day activities.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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Declaration of Competing Interest
The authors declare that they have no competing interests.

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