A tale of concealed source and bizarre CSF in an immunocompetent HSV-2-associated encephalitis patient

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ABSTRACT

Background: HSV-2-associated encephalitis is a rare occurrence, described in neonates and immunocompromised individuals.

Case Presentation: We describe a case of HSV-2-associated encephalitis associated with genital herpetic lesions. MRI brain showed large confluent T2/FLAIR hyperintensities involving the left medial temporal lobe, left insula, and left anterior cingulate gyrus. LP-CSF showed the presence of marked neutrophilic leukocytosis mimicking a pyogenic meningoencephalitis etiology. Cerebrospinal fluid (CSF) Biofire ME test was positive for HSV-2. The patient was treated with IV acyclovir for 14 days and after improvement in symptoms was discharged. On account of the recurrence of symptoms; post 10 days of discharge, he required readmission and was given a further 14-day course of IV Acyclovir. Our patient thus required an IV acyclovir course extending beyond 3 weeks.

Conclusion: This case report serves to highlight that marked neutrophilic leukocytosis can be a presenting feature and treatment in HSV-2 encephalitis may need to be prolonged if the patient does not have resolution of symptoms or acellularity in CSF/ negative PCR report has not been achieved.

Keywords: HSV-2-associated encephalitis, viral CSF pleocytosis, temporal lobe encephalitis, genital herpes.

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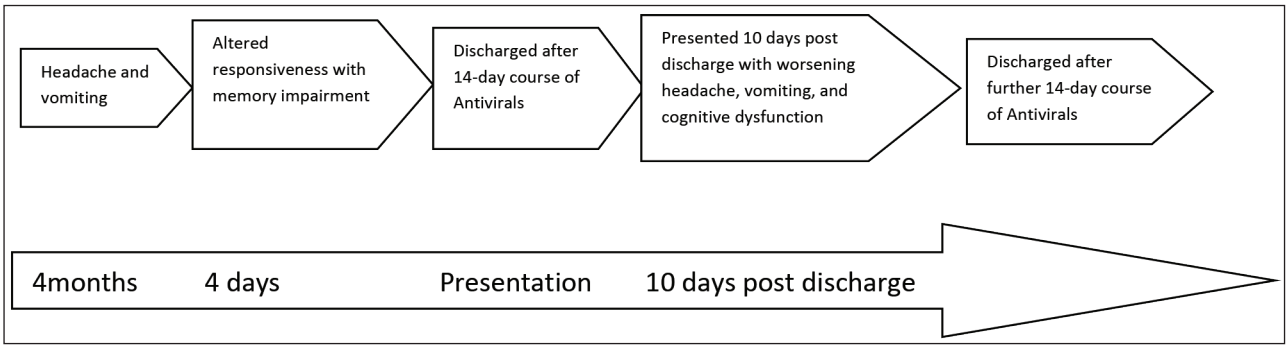
Case Report

An 18-year-old male with no previously known comorbidities presented to OPD with chief complaints of headache associated with nausea and occasional vomiting for the past 4 months. 4 days before admission he was noticed to have incoherent responsiveness and impaired short-term memory. On examination, he had intact comprehension and disorientation of time and place. Immediate recall and naming were impaired. No obvious motor/sensory deficit was noted. Local examination of genitalia showed painful vesicular lesions over the shaft of the penis. Routine blood investigations were unremarkable.

MRI brain (Figure 1A and 1B) showed confluent T2/FLAIR hyperintensity in the left medial temporal lobe, left insula, and left anterior cingulate gyrus. Imaging differentials considered at this stage were Viral (Herpetic) Encephalitis versus Autoimmune (NMDA Antibody associated)/paraneoplastic Encephalitis. EEG (Figure 2) showed evidence of generalized electrophysiological dysfunction maximum over the left frontotemporal region. LP-CSF (Figure 3) on Day 2 of admission showed TLC:



740 cells/cumm with differential count of Polymorph 65% and Lymphocyte 35%, Nil RBCs; Sugar: 75 mg/dl (corresponding RBS: 105 mg/dl) and protein level of 56 mg/dl. Cerebrospinal fluid (CSF) Biofire ME test showed a positive value of HSV-2. HIV 1 and 2 serology testing was negative. The patient was started on IV Acyclovir and antiseizure medicines. Taking into consideration the strong inflammatory response as evidenced by neutrophilic leukocytosis IV steroids were added to the treatment regimen followed by a tapering course of oral steroids over 14 days. Considering a remote possibility of superimposed bacterial infection, IV antibiotics were continued for 2 weeks. Our patient was given a modified dosage of IV acyclovir on account of worsening creatinine values during the hospital stay. After a 14-day course of IV Acyclovir patient had an improvement in his clinical symptoms with residual cognitive symptoms and mild diffuse headache. He was discharged on oral Acyclovir. 10 days after discharge, the patient had severe headache with nausea, vomiting, and reduced appetite with worsening cognitive function. He was readmitted and an MRI brain was repeated (Figure 1C and 1D) which showed large confluent T2/FLAIR hyperintensity in the left temporal lobe, insular cortex, and anterior cingulate gyrus with extensive curvilinear/gyral enhancement and an increase in extent/edema as compared to initial MRI brain ~30 days back. CSF NMDA antibody testing was negative. Absolute CD4 count was low: 403 cells/microL (Normal value: 424–1,509). A 28-day course of IV acyclovir was completed and after the patient had clinical improvement, he was discharged. At the time of discharge, the patient had a normal/acellular CSF report. On the last follow up, the patient had persistent, but improving short-term memory impairment with the resolution of all other deficits.

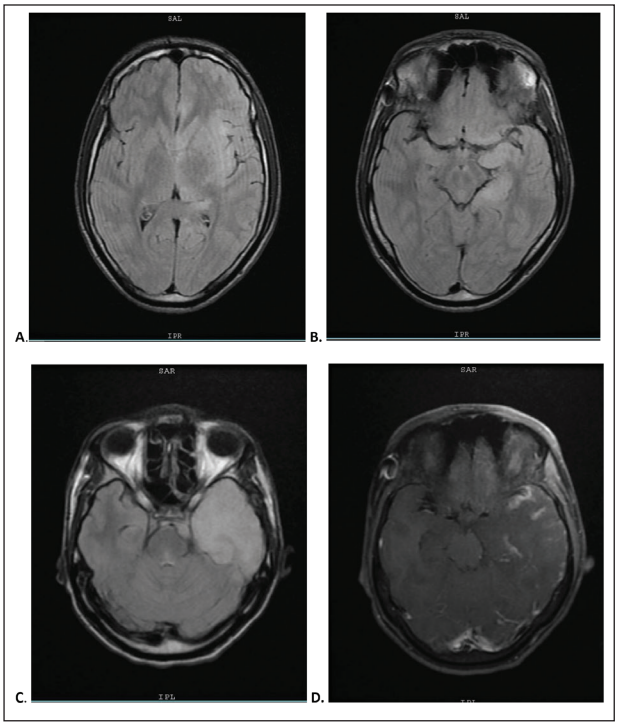


Figure 1. *MRI brain on 1st admission: A. Axial FLAIR image reveals ill-defined band-shaped hyperintensity along the left insular cortex. No basal ganglia involvement is demonstrated, B. Axial FLAIR image shows thick gyral hyperintensity predominantly along the left medial temporal lobe. Repeat MRI brain done after 2 months of illness: C. Axial FLAIR image reveals confluent hyperintensity in the region of the left temporal lobe involving both grey and white matter, D. Axial post gadolinium T1 image shows multifocal leptomeningeal and gyral enhancement in the region of the left temporal lobe. A mild associated mass effect is also seen.*

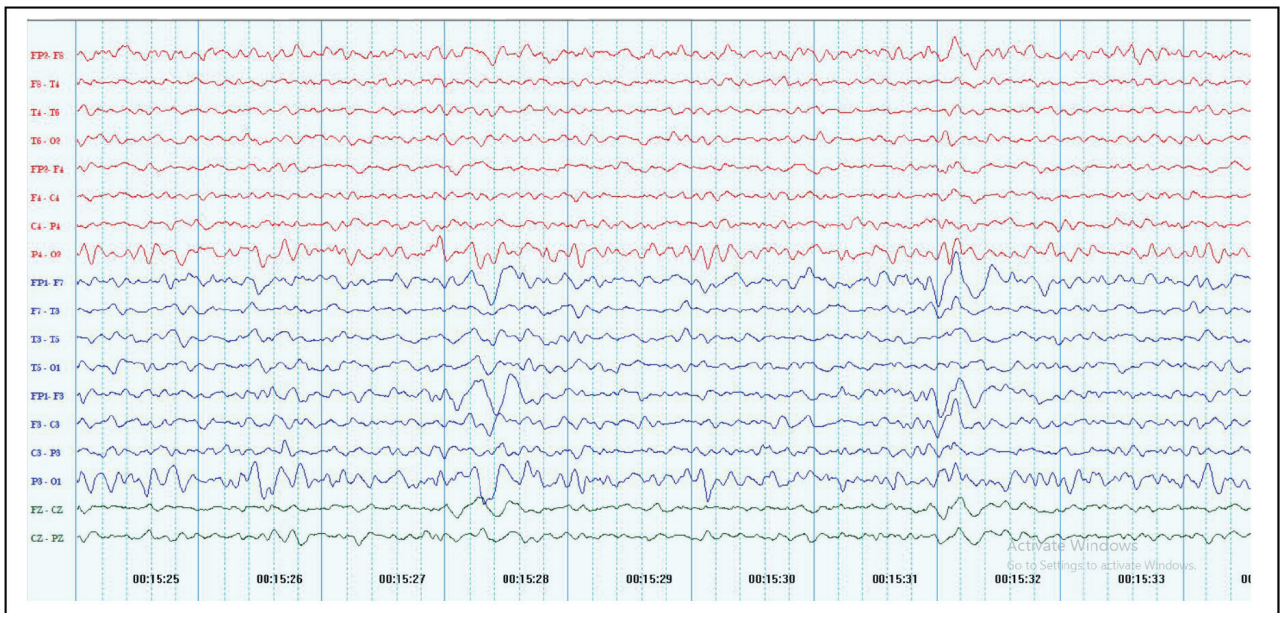


Figure 2. *EEG done at the sensitivity of 7 microvolt/mm with a low-frequency filter of 1Hz and high-Frequency filter of 70 Hz showed a background activity of 8 to 9 Hz, and, left frontal dominant generalized sharp and slow waves.*

Discussion

Herpes simplex virus encephalitis is commonly caused by HSV-1 and rarely by HSV-2. The causality of HSV-2 in cases of Herpes simplex virus-associated encephalitis is estimated to be less than 10% and is more commonly encountered in neonates and immunocompromised individuals [1,2]. Brain imaging was highly suggestive of Herpes Simplex Virus-associated encephalitis in our case with radiological findings being similar in HSV1 and HSV2 encephalitis [3]. Autoimmune/Paraneoplastic encephalitis was not favored due to asymmetric/unilateral involvement and lack of supporting clinical history like the history of malignancy. Acute ischemia was excluded due to the non-territorial distribution of signal abnormalities and lack of motor symptoms. Diffuse gliomas like gliomatosis cerebri may appear similar on MRI but were less likely due to non-contiguous involvement of brain parenchyma, sharp delineation at the level of insula-basal ganglia interface, and relatively rapid onset of symptoms. Another differential includes post-ictal status but this was excluded due to the absent history of seizure and involvement of typical anatomical locations of the brain. Progressive enhancement is a known evolutionary imaging feature of HSV-associated encephalitis as in the early stages contrast enhancement is usually absent. Gyriform, leptomeningeal, or patchy enhancement are usually seen after 1 week of symptom onset and may persist till disease resolution [3]. Marked CSF pleocytosis as described in our case has been described more commonly in pyogenic meningitis; rarely in viral meningitis like Mumps Virus, EEE virus, and LCMV [4]. Previously reported case series (Table 1) have established higher levels of leukocytosis in HSV-2-associated encephalitis compared to HSV-1 but with lymphocytic dominance [5–7]. An isolated case report from France about HSV-2 encephalitis in an immunocompetent adult showed CSF leukocytosis (459 cells/cumm; Lymphocytes: 97%) on Day 1 of admission and 1,300 cells/cumm (Lymphocytes 52%, monocytes 48%) on Day 3 of admission [8]. Our case is rendered unique by the presence of Marked Neutrophilic dominant leukocytosis. A review of published case series on Herpes Simplex Virus 2-associated encephalitis reported sequelae in the majority of recovered cases, similar to our case [5]. CD4 lymphocyte levels were low in our patient but did not qualify to meet the criteria for CD4 lymphocytopenia: defined as an Absolute CD4 count of less than 300 cells/cumm [9]. The need for prolonged IV antiviral therapy: 3 weeks or more, as in our case, also merits deliberation. This calls attention to prolonging treatment with IV Acyclovir in HSV-2 encephalitis if the patient is not having resolution

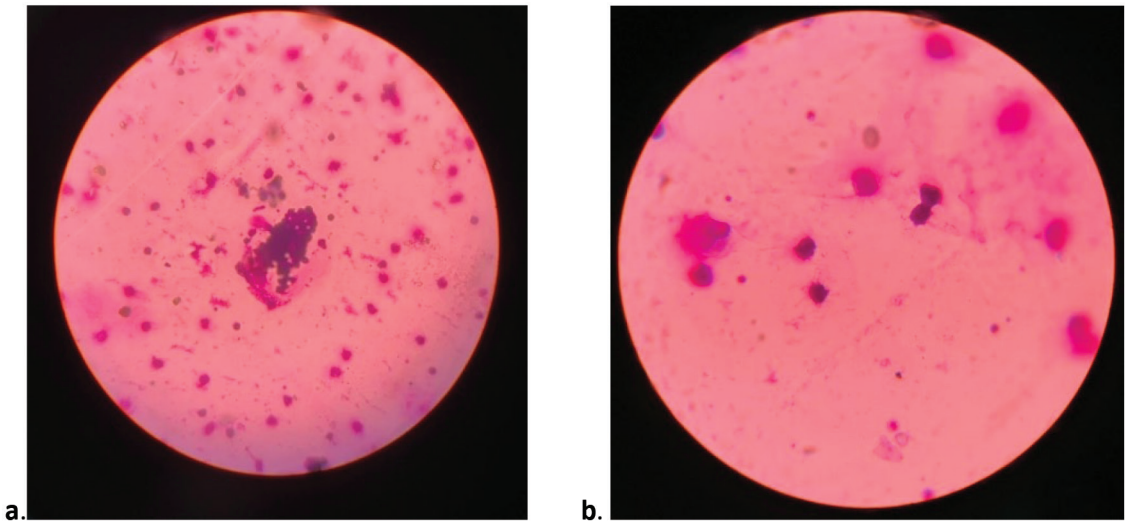


Figure 3. *(a,b) CSF cytology depicting viable and degenerated neutrophilic cells infiltrate. (100 X, Giemsa Staining).*

Table 1. *Comparison of CSF findings of HSV-2-associated encephalitis across various reported case series.*

S. NO	STUDY (DURATION); NUMBER OF PATIENTS OF HSV-2 ENCEPHALITIS/ MENINGITIS	CSF TLC CELLS/ CUMM: MEDIAN(IQR)	CSF LYMPHOCYTE PERCENTAGE: MEDIAN(IQR)	CSF PROTEIN (MG/DL): MEDIAN(IQR)	CSF GLUCOSE (MG/DL): MEDIAN(IQR)
1	Lee et al. [5] (2010–2018); *n* = 27	264 (88–450)	88 (82–93)	88 (63.6–122.7)	54 (45–62)
2	Ihekwaba et al. [6] (2003–2007); *n* = 8	240 (180–2,200)	100 (80–100)	120.5 (61.1–370.4)	N A
3	Omland et al. [7] (1999-2003); *n* = 41	Mean: 392 Range:2–1,174	Mean: 95 Range: 81–100	Mean: 127 Range: 36–273	Mean: 55.3 Range: 25.2–81
4	Present case	740	35	56	75

of symptoms or acellularity in CSF. The persistent cognitive deficit of short-term memory impairment serves to highlight the expected neurological sequelae of temporal lobe encephalitis and may serve as a window for further neurorehabilitation interventions.

Conclusion

This case serves to highlight the clinical heterogeneity of HSV-associated encephalitis. Rarely, in younger adults, HSV-2 can cause Encephalitis and should be considered as a differential diagnosis. Meticulous examination of external genitalia can help in strengthening the diagnosis. HSV-2-associated encephalitis is associated with a fierce inflammatory response: profound leukocytosis and elevated protein levels. To the best of the author`s knowledge, prominent neutrophilic leukocytosis (740 cells/cumm; Neutrophils 65% and Lymphocyte 35%) as in our case has not been reported previously in HSV-2-associated encephalitis. This case also provides insight into the continuation of IV antiviral therapy (Acyclovir) till the resolution of symptoms or till a repeat CSF shows the resolution of infection as per PCR-based assay/acellularity in CSF.

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What is new?

Marked Neutrophilic dominant leucocytosis can be a presenting feature of HSV-2 associated encephalitis and treatment with IV acyclovir may need to be prolonged beyond 3 weeks in certain cases, who continue to remain symptomatic/have a persistent hypercellular response on LP CSF.

List of Abbreviations

CD4	Cluster of differentiation 4
CSF Biofire ME test	Film Array Multiplex PCR-based Meningoencephalitis panel
EEE virus	Eastern equine encephalitis virus
EEG	Electroencephalogram
FLAIR	Fluid attenuated inversion recovery
HIV	Human Immunodeficiency Virus
HSV	Herpes simplex virus
IV	Intravenous
LCMV	Lymphocytic choriomeningitis virus
LP-CSF	Lumbar puncture-cerebrospinal fluid
MRI	Magnetic resonance imaging
NMDA	N-Methyl D-aspartate
PCR	Polymerase Chain reaction
RBS	Random blood sugar
T2	Transverse relaxation time
TLC	Total leucocyte count

Conflicts of interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

Funding

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Consent for publication

Written consent was obtained from the patient.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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Summary of case

1	Patient (gender, age)	18/M
2	Final diagnosis	HHV 2 associated encephalitis
3	Symptoms	Headache, nausea, vomiting
4	Medications	Acyclovir, anti epileptics, steroids
5	Clinical procedure	Iv and oral
6	Specialty	Neurology