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Case report

Ictal vomiting as an unusual presentation of herpes simplex encephalitis - Pathophysiological and therapeutic perspectives

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ABSTRACT

Introduction: Herpes Simplex Encephalitis (HSE) is a formidable neurological infection that is often challenging to diagnose owing to its diverse clinical manifestations. This case report details the clinical odyssey of a sixty-year-old female with diabetes, hypothyroidism, and hypertension, who presented with fever, vomiting, and evolving neurological symptoms.

Case Presentation: The patient's initial admission failed to yield a diagnosis, and her condition worsened, marked by behavioral changes, cognitive decline, and focal seizures. Neuroimaging revealed characteristic findings, confirming non-hemorrhagic herpetic encephalitis. Despite antiviral and antiepileptic therapy, persistent vomiting prompted further investigations, uncovering infrequent right temporal sharp waves on EEG, leading to a diagnosis of "ictus emiticus."

Conclusion: This case of Herpes Simplex Encephalitis (HSE) underscores the diverse clinical spectrum and challenges in management. The patient's atypical presentation underscores the importance of considering HSE in patients with fever and unexplained persistent vomiting for early diagnosis and better prognosis.

Diagnostic tools (neuroimaging, cerebrospinal fluid analysis, and electroencephalography) confirmed HSE involvement in the right temporal lobe, emphasizing the strong association between HSV encephalitis and seizures, which can be explained by various mechanisms.

Timely antiviral therapy and tailored antiepileptic strategies led to gradual clinical improvement, showcasing the potential of valproate beyond antiepileptic use.

This case prompts further exploration into HSE's pathophysiology and treatment. It emphasizes individualized patient care and vigilance for potential post-resolution sequelae, contributing to our evolving understanding of HSE.

Introduction

Acute viral central nervous system (CNS) infection is a significant etiological factor in acquired epilepsy [1,2], with Herpes Simplex Encephalitis (HSE) being the most prevalent subtype, primarily induced by Herpes Simplex Virus type 1 (HSV-1) [3,4]. The ingress of HSV-1 into the brain occurs through three distinct pathways, with a predilection for impacting the fronto-temporal regions. The first route involves migration from the primary oro-pharyngeal infection site via trigeminal or olfactory nerves. A secondary mechanism comprises the reactivation of the initial peripheral infection through the same neuronal pathways. The third pathway arises from the reactivation of latent HSV-1 within the brain [5]. This anatomical predisposition localizes HSV-1 in fronto-temporal regions, specifically affecting the medial part of the temporal lobes and the inferior part of the frontal lobes associated with the olfactory pathway, predominantly targeting the cerebral cortex [3,6,7]. This specific anatomical predilection elucidates the heightened occurrence of seizures during HSE.

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Focal seizures, followed by generalized seizures, constitute the primary seizure types associated with HSE [8]. Among these, a notable manifestation of focal seizures involves alterations in autonomic functions, often considered to hold localizing value [9,10]. This is particularly evident in temporal lobe epilepsies, where autonomic features frequently serve as the initial and overt components of a seizure, such as ictal vomiting [11–14]. The case we present here involves HSE, characterized by the development of seizures in the acute phase and persisting even after resolution, with ictal vomiting emerging as the predominant symptomatology. The subsequent sections provide an in-depth exploration of this case, offering a comprehensive analysis and discussion of the clinical, radiological, and therapeutic aspects encountered in managing this distinctive presentation of HSE.

Case presentation

A 60-year-old female with a known past medical history of type 2 diabetes mellitus, hypothyroidism, and long-standing hypertension presented to our hospital with a 3-week history of fever and recurrent vomiting. She had initially been admitted to another healthcare facility for one week with the same complaints. During that admission, she was diagnosed with a nonspecific viral infection. A routine workup was conducted, focusing on systemic and infectious causes. However, as there were no symptoms suggestive of central nervous system (CNS) involvement at the time, the workup did not specifically address CNS localization.

The patient was discharged after symptomatic treatment, but her condition deteriorated progressively following discharge. Within a few days, she developed behavioral changes, including irritability, mood disturbances, and difficulty concentrating. These symptoms evolved over the subsequent weeks into significant cognitive decline, manifesting as disorientation, memory impairment, and reduced ability to carry out daily activities.

On the day of admission to our hospital, her condition acutely worsened with the onset of abnormal, jerky movements involving the left side of her body. The episode lasted for several minutes and was followed by marked left-sided weakness, consistent with postictal paresis. There was no prior history of seizures or similar neurological events.

The family denied any recent travel, sick contacts, or exposure to environmental toxins. Additionally, there was no history of trauma, weight loss, night sweats, or use of immunosuppressive therapy. Before the onset of her current illness, her chronic conditions were reportedly well managed with her regular medications, though adherence became uncertain due to her cognitive decline.

Initial investigations, including a brain CT scan, showed right fronto-temporal hypodensity (Fig. 1), while CTA results were unremarkable. A subsequent brain MRI with contrast revealed an ill-defined, predominantly cortical abnormal signal affecting the right temporal lobe, right hippocampus, posterior portion of the right gyrus rectus, right insula, left hippocampus, and left fronto-parietal area. Patchy enhancement and mild linear lepto-meningeal enhancement were noted (Fig. 2a, b), consistent with non-hemorrhagic herpetic encephalitis rather than an ischemic pattern.

A lumbar puncture revealed marked pleocytosis with 500 leukocytes, predominantly lymphocytes (92 %), a protein level of 106 mg/dL, and normal glucose. HSV-1 PCR testing was positive (CSF sample sent to another hospital with a detection range of 10^a to 10^e copies/ml). Tests

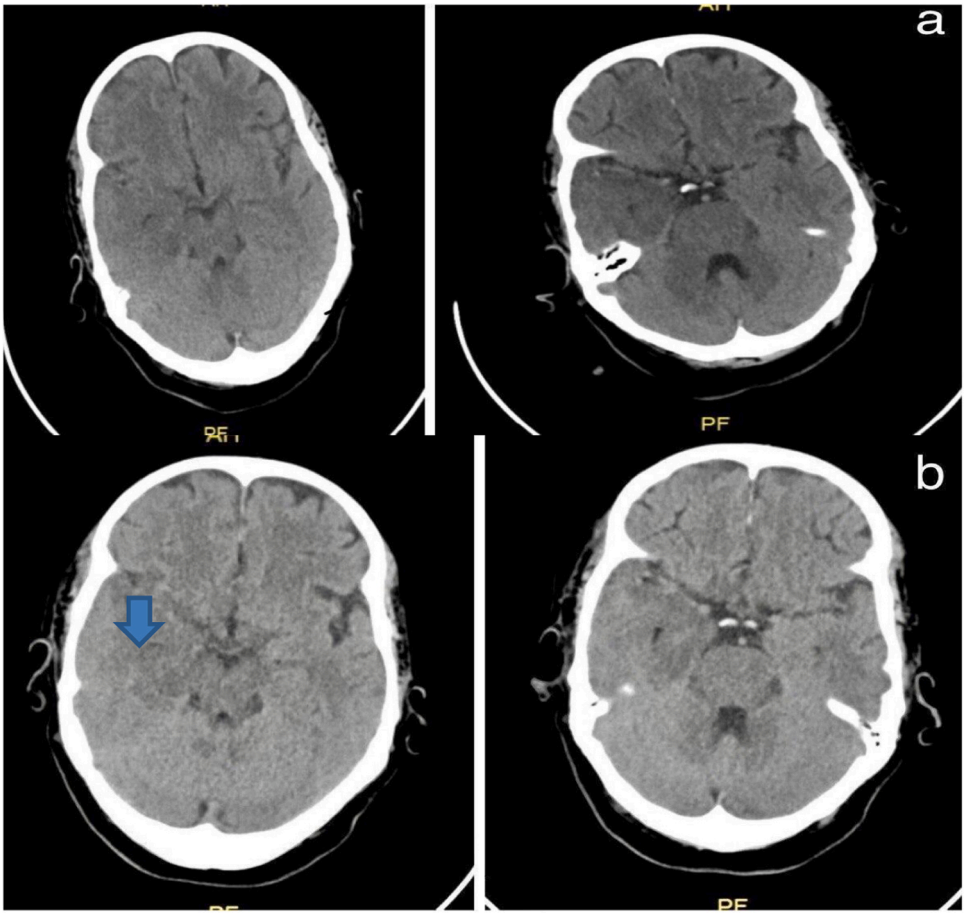

Fig. 1. Axial Brain CT show hypoattenuation (darkness) of the brain parenchyma; loss of gray matter-white matter differentiation in the right fronto-temporal area. (a) Post admission day-1 (b) post admission day-2.

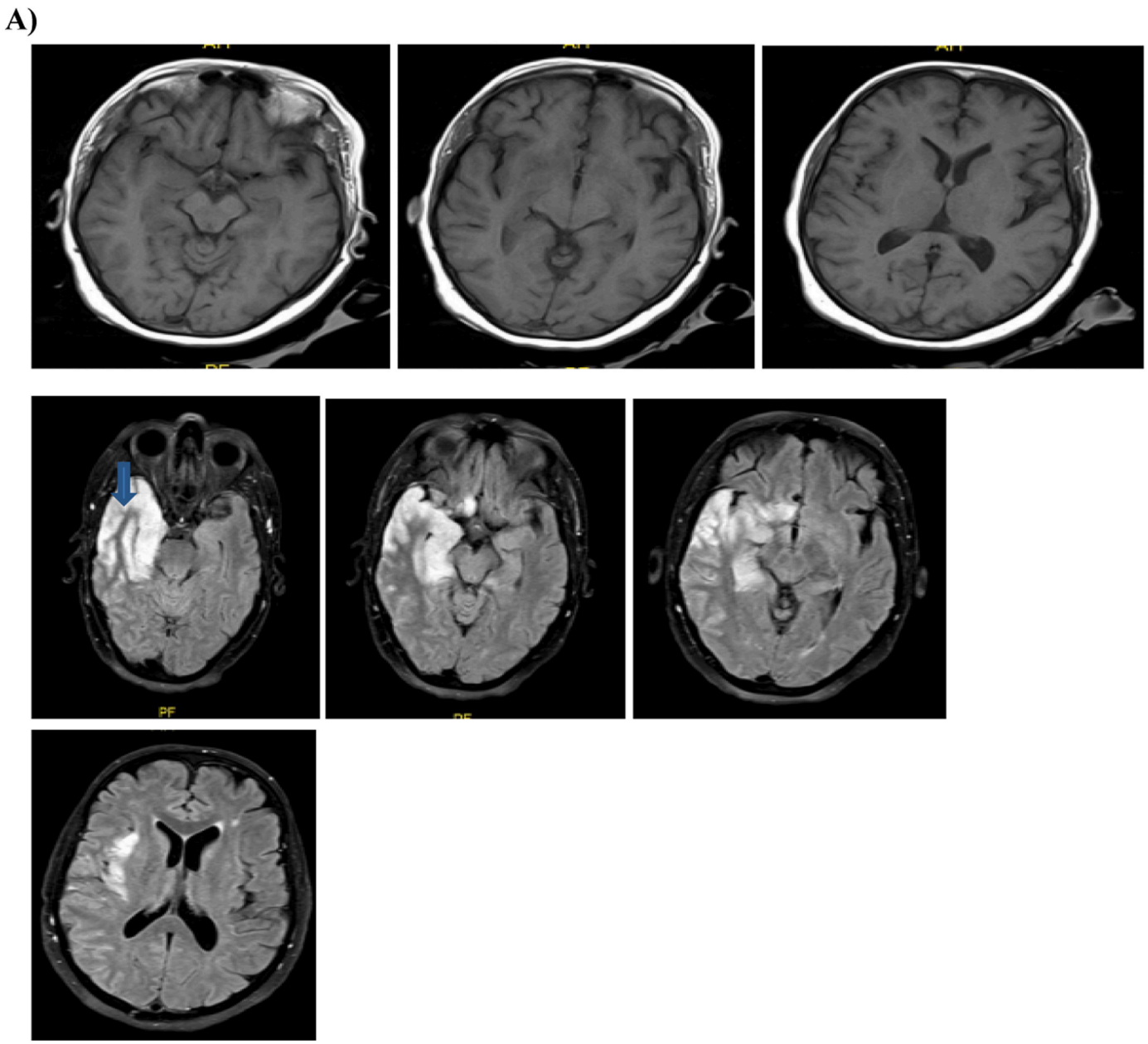

Fig. 2. a,b: Axial brain MRI show an ill-defined (predominantly cortical) area of abnormal signal intensity involving the right temporal lobe, right hippocampus, the posterior portion of right gyrus rectus and right insula, being hyperintense at both T2WI and FLAIR, hypo-intense at T1WI, with gyral swelling and diffusion restriction (prominent at insular region) with positive mass effect in the form of effacement of ipsilateral cortical sulci and sylvian fissure. Sparing of the right basal ganglia structures is seen. The left hippocampus also shows a subtle area of increased T2/FLAIR signal, with no diffusion restriction. Left fronto-parietal small white matter foci of abnormal signal being hyperintense at both T2 and FLAIR WI, isointense at T1WI, shows no diffusion restriction, no significant mass effect or perilesional edema. Post contrast study revealed subtle patchy enhancement of the involved region, associated with mild linear lepto-meningeal enhancement extending to the adjacent portions of the right parietal lobe.

for tuberculosis, Brucella, fungal cultures, and gram stain were negative. EEG findings showed Periodic Lateralized Epileptiform Discharges (PLEDs) in the right hemisphere (Fig. 3a).

After the initial diagnosis of herpes simplex encephalitis (HSE) was established, the patient was managed with a standard 21-day course of IV acyclovir alongside levetiracetam for seizure control. Gradual improvement was observed in her neurological symptoms, including left-sided weakness, cognitive impairment, and behavioral changes. However, the persistence of vomiting, despite initial improvement during treatment, warranted further investigation.

When the patient was readmitted two weeks after discharge with intractable vomiting, our clinical approach expanded to consider alternative aetiologies. A comprehensive evaluation was undertaken to rule out other causes of persistent vomiting. This included an upper gastrointestinal endoscopy, CT of the abdomen and pelvis, and a battery of laboratory tests, all of which returned unremarkable results. These findings effectively excluded gastrointestinal, metabolic, and systemic causes.

The persistence of symptoms in the absence of identifiable structural or systemic abnormalities raised the suspicion of ictal vomiting, a rare but recognized manifestation of epileptic activity localized to the temporal lobe. This hypothesis was supported by the patient's history of

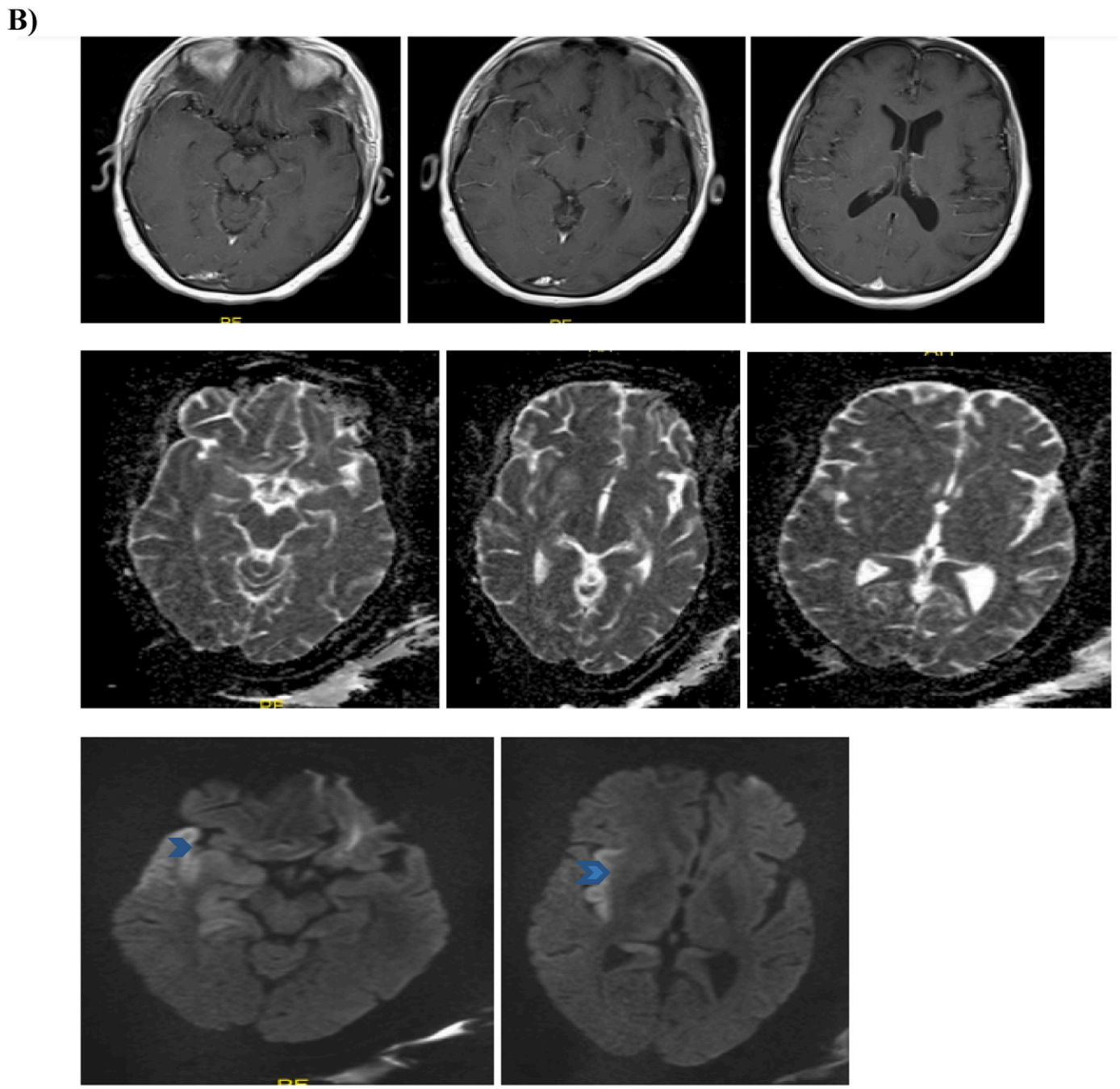

Fig. 2. (*continued*).

HSE, the prior EEG findings of PLEDs, and subsequent EEG evidence of infrequent right temporal sharp waves.

Given the possibility of ictal vomiting, her antiepileptic regimen was adjusted to include valproate alongside levetiracetam. The dramatic clinical response, with a rapid and sustained decrease in vomiting frequency, strongly supported the diagnosis of ictal vomiting. Follow-up EEGs showed the resolution of epileptic activity, corroborating the effectiveness of the modified treatment plan.

At follow-up, the patient demonstrated a favorable outcome. Her vomiting resolved completely, and there were no further episodes of generalized seizures. Motor power exhibited positive recovery, and the patient regained the ability to perform daily activities independently. While her cognitive function improved significantly, some residual cognitive impairment was noted during the three-month follow-up.

Discussion

Herpes Simplex Encephalitis (HSE), a severe neurological infection, poses diagnostic challenges due to its diverse clinical manifestations. The patient's initial three-week history of fever and repeated vomiting presented diagnostic complexities, leading to an initial discharge without a definitive diagnosis. The subsequent emergence of abnormal jerky movements and weakness on admission highlighted the intricate nature of the case. Conclusive evidence for HSE was derived from neuroimaging results and CSF analysis, with EEG findings playing a crucial role in confirming the epileptic nature of the symptoms.

Studies indicate that seizures in HSE occur in the acute stage in approximately 75 % of cases [15], with unprovoked seizures in 40–65 % and Subsequent Epilepsy (SE) in 29 % [16,17], often proving intractable [18]. The risk of developing unprovoked seizures (postencephalitic

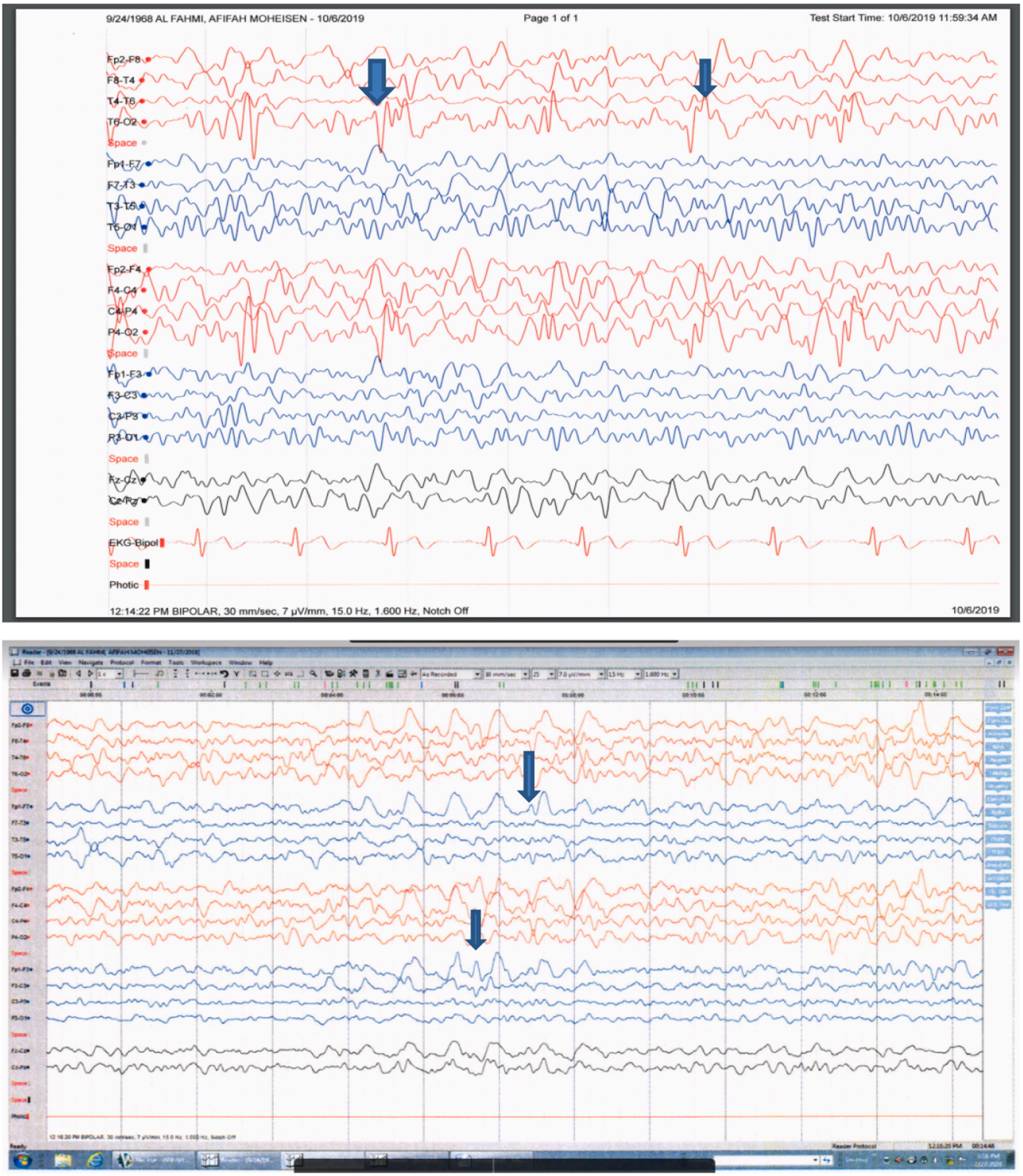

Fig. 3. **a:** EEG done at presentation showed PLEDS. **b**: EEG done 2 weeks later showed no more BLEDS but there is infrequent right temporal sharp waves.

epilepsy, PE) is notably higher for patients with encephalitis and early seizures (acute symptomatic seizures, ASS). This risk is most pronounced in the first five years post-encephalitis and remains elevated [2,19].

A recent study on HSE patients with extensive follow-up revealed that risk factors for developing epilepsy following encephalitis include the presence of clinical seizures (ASSs) during acute illness (associated with an 8-fold risk increase to develop post-encephalitis epilepsy (PE)) and younger age but not CSF results, imaging, or EEG [20].

Mechanisms of epileptogenesis in HSE involve neuronal injury, modification of neural circuits, and the production of proinflammatory cytokines [21–23] leading to the activation of macrophages and microglia with subsequent production of interleukin (IL)-6 and tumor

necrosis factor (TNF)-α [24–26].

IL-6 and TNF-α disrupt the neuronal excitation/inhibition balance, increasing neuronal hyperexcitability [24,27,28] and may break down the blood-brain barrier, leading to cerebral edema which can trigger seizures [21,29,30].

SE can be sequelae of the acute symptomatic seizures due to the resultant functional and structural alterations of the brain, such as neuronal loss, neurogenesis, activation of microglia and astrocytes, gliosis, and neural circuit alteration [23,31].

Recent studies also suggest a potential association of CNS viral infection with subsequent autoimmune encephalitis (AE) [32–36], another cause of seizures and epilepsy. In a recent prospective study in a cohort of patients with HSE, 27 % of the cases developed AE associated with autoimmune responses against N-methyl-D-aspartate receptor and other neuronal surface proteins within 3 months after antiviral therapy [32].

Anatomically, temporal lobe involvement is common in HSE. In a retrospective study on imaging, temporal lobe involvement was in 60 % of patients, with pure temporal lobe involvement in 20 %, pure extra-temporal involvement in 15 %, and normal imaging in 25 % of the patients [37]. These anatomical preferences also share in the high seizure susceptibility. In our case, the right temporal lobe, right hippocampus, posterior portion of the right gyrus rectus and right insula, left hippocampus, and left fronto-parietal area were affected.

Interestingly, the focal seizures in our case manifested primarily as ictal vomiting, a rare clinical presentation thought to originate in the anterior part of the temporal lobe, the amygdala, or the insula [38], regions commonly involved in HSE [3,6,7], as was observed in our case, but, as of now, there are no studies to determine how frequently ictal vomiting occurs in HSE."

Ictal vomiting has been associated with the non-dominant hemisphere and has been considered a lateralizing sign [39]. However other cases have lateralized seizure onset to the dominant hemisphere [14,40]

Regarding diagnosis, in ictal vomiting/retching, interictal EEG can be normal and abundant movement artifacts may prevent the recognition of seizure onset [41,42]. But in our case, EEG showed infrequent right temporal sharp waves which disappeared after proper treatment.

Additionally, it is crucial to consider the impact of treatment strategies on the overall prognosis of patients with Herpes Simplex Encephalitis (HSE). The timely initiation of antiviral therapy, such as intravenous acyclovir, is a cornerstone in managing HSE, as it aims to inhibit viral replication and improve outcomes [43,44]. The effectiveness of antiviral treatment is underscored by the patient's gradual improvement in left-sided weakness, behavioral changes, and cognitive impairment, as observed in our case.

Recent studies have emphasized the role of immune modulators as potential adjuncts in the treatment of HSE. Immunotherapies, including corticosteroids and intravenous immunoglobulins, have shown promise in modulating the inflammatory response associated with HSE and potentially mitigating long-term neurological sequelae [45,46].

Furthermore, the recognition of ictus emeticus as a cause of intractable vomiting, supported by EEG findings, led to the addition of valproate to the treatment regimen, resulting in a dramatic response and a gradual decrease in vomiting frequency, highlights its potential beyond its antiepileptic properties. Valproate has been recognized for its neuroprotective effects, anti-inflammatory actions, and modulation of gamma-aminobutyric acid (GABA) neurotransmission, which may contribute to its efficacy in certain presentations of HSE [47,48].

It's important to note that while antiepileptic drugs (AEDs) play a pivotal role in seizure control; their selection should be tailored to the specific seizure phenotype. Narrow-spectrum AEDs, exemplified by carbamazepine, oxcarbazepine, phenytoin, and lacosamide, are deemed efficacious in diminishing the frequency of focal seizures. Conversely, broad-spectrum AEDs, including lamotrigine, levetiracetam, topiramate, valproate, and zonisamide, are conventionally employed for individuals manifesting either focal seizures or generalized seizures." [49–51]. This personalized approach to AED therapy ensures optimal management of seizures while minimizing potential adverse effects.

The integration of multimodal treatment approaches, including antiviral agents, immune modulators, and tailored antiepileptic strategies, reflects the evolving landscape of HSE management. As we continue to unravel the complexities of HSE pathophysiology, ongoing research and clinical trials may further refine treatment paradigms, ultimately enhancing outcomes for affected individuals.

Limitations and future considerations

Acknowledging the limitations of a single-case report, future research could explore the frequency of ictal vomiting in HSE cases and address any potential confounding factors affecting the generalizability of the findings.

Conclusion

In summary, this case of Herpes Simplex Encephalitis (HSE) highlights the importance of considering HSE in patients with fever and unexplained persistent vomiting, even in the absence of classical neurological signs. The persistence of symptoms post-treatment required a broad differential diagnosis to identify ictal vomiting as the underlying cause.

Neuroimaging, cerebrospinal fluid analysis, and electroencephalography confirmed HSE with right temporal lobe involvement, emphasizing the strong link between HSE and seizures. Excluding gastrointestinal and systemic causes was essential in guiding the diagnosis. Timely antiviral therapy with IV acyclovir and the addition of valproate for seizure control led to significant clinical improvement. Valproate also addressed ictal vomiting, demonstrating its potential beyond traditional seizure management.

This case underscores the need for further research into HSE's pathophysiology and treatment. It emphasizes individualized care and vigilance for post-resolution sequelae, contributing to a better understanding of HSE and its management.

List of Abbreviations

HSV: Herpes Simplex Virus.
HSV-1: Herpes simplex Virus Type 1.
HSE: Herpes Simplex Encephalitis.
CT: Computerized Tomography.
CTA: Computerized Tomography Angiography.
MRI: Magnetic Resonance Imaging.
TB: Tuberculosis.
EEG: Electroencephalogram.
CSF - Cerebrospinal Fluid
PCR - Polymerase Chain Reaction
IL-6 - Interleukin-6
TNF-α - Tumor Necrosis Factor-alpha
CNS - Central Nervous System
SE - Subsequent Epilepsy
ASS - Acute Symptomatic Seizures
PE - Postencephalitic Epilepsy
PLEDs - Periodic Lateralized Epileptiform Discharges
AEDs - Antiepileptic Drugs
AE: Autoimmune Encephalitis

Ethics approval and consent to participate

The study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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CRediT authorship contribution statement

Ahmed Waleed: Writing – review & editing, Supervision, Conceptualization. **Alghamdi abdulaziz:** Writing – review & editing, Supervision, Conceptualization. **Idris Abdelrahman:** Writing – review & editing, Supervision, Conceptualization. **Elshony Hosna:** Writing – review & editing, Writing – original draft, Visualization, Data curation, Conceptualization. **Almuhanna Rakan:** Writing – review & editing, Supervision, Conceptualization.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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Ethical approval

Ethics approval and consent to participate: The study was performed in accordance with the Declaration of Helsinki.

Consent

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

Consent for publication

N/A

Availability of data and material

The data used or analyzed during the current study are available from the corresponding author on reasonable request.

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