CASE REPORT

REVISED Case Report: Herpes simplex virus type 2 (HSV-2) meningo-encephalitis associated with traumatic brain injury – a case report from Lao PDR

[version 2; peer review: 2 approved]

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Abstract

Background

Neurological symptoms following head trauma are common; however, the cause may not always be obvious. In the absence of open wounds, fractures, or surgical interventions, infectious causes may not be considered, especially viral infections such as Herpes simplex, and investigations may not be targeted to investigate this possibility.

Case

A 39-year-old male presented with a severe headache, reduced consciousness, and confusion. Two days earlier, he had been discharged from the hospital, where he had been treated for traumatic brain injury with subarachnoid hemorrhage following a road traffic accident. Herpes simplex virus type 2 (HSV-2) was detected in the cerebrospinal fluid, confirming the diagnosis of viral meningoencephalitis. He was treated with oral aciclovir for two weeks and achieved full neurological recovery.

Open Peer Review

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Any reports and responses or comments on the article can be found at the end of the article.

Conclusions

This case highlights the risk of viral reactivation following trauma, particularly head injuries. Central nervous system infections, including viral infections, should be considered in cases of delayed deterioration following trauma, likely presenting with worsening headache, drowsiness and reduced cognitive state. The optimal treatment of herpes simplex virus (HSV) encephalitis may be challenging in resource-limited settings.

Plain language summary

Herpes simplex virus type 2 (HSV-2) is a common virus that many people are infected by. It causes genital and orolabial herpes (also known as cold sores). It can also rarely cause infections of the central nervous system. Once a person is infected, the virus remains in the body permanently. The infection is normally dormant, however, the virus can reactivate periodically, and cause recurrent symptoms. Re-activation may occur if the person is unwell or if the body is stressed. Sometimes, the cause for reactivation is not obvious. In this case, serious head trauma caused reactivation of HSV-2, and this led to an infection of the lining of the brain, and perhaps of the brain itself. HSV-2 infection of the brain is life-threatening, and requires intravenous medication - aciclovir. In low-resource settings, the diagnostic tests and treatments required for HSV-2 are not readily available, and they may be too expensive for many people to afford. Therefore, we must increase diagnostic capacity where needed, as well as access to life-saving medications.

Keywords

Herpes simplex virus, viral reactivation, meningitis, encephalitis, head injury, aciclovir, LMICs

This article is included in the Mahidol Oxford Tropical Medicine Research Unit (MORU) gateway.

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REVISED **Amendments from Version 1**

This revised version incorporates several improvements in response to the reviewers' comments.

We have given additional interpretation of the laboratory results, by explaining that leucocytosis and hyponatraemia are likely a consequence of inflammation and the syndrome of inappropriate ADH secretion secondadry to brain injury, with the possibility of bacterial co-infection also considered.

Additional detail is provided on the mechanisms of HSV reactivation, including loss of host-derived proteins that maintain viral latency, local immune dysfunction involving pro-inflammatory microglial activation, and systemic effects via sympathetic activation and glucocorticoid release. Relevant citations are added to support these new points. We acknowledge the difficulty in distinguishing between primary infection and reactivation on clinical grounds alone, and note that IgG serology can help distinguish between the two.

The background context has been strengthened by referencing other reported cases of CNS HSV reactivation following neurosurgery. These include major procedures (such as craniotomy and tumour excision) as well as more limited interventions (such as microvascular decompression of the trigeminal nerve).

Additional minor edits throughout the manuscript emphasise the focus on viral infection, in particular HSV reactivation. We have also emphasised viral reactivation following trauma specifically to the head, and in the absence of neurosurgery.

With regard to future work, we suggest more routine viral testing in the CSF following trauma, along with HSV IgG antibody titres where available, to generate observational data on the rates of infection and reactivation in comparable cases.

Finally, we have provided key recommendations by emphasising the importance of immediate intravenous aciclovir when viral encephalitis is suspected or suggested by CSF analysis

Any further responses from the reviewers can be found at the end of the article

Introduction

Herpes simplex virus (HSV) infections of the central nervous system (CNS) include overlapping but distinct syndromes of meningitis, meningoencephalitis, and encephalitis. They are among the most severe viral infections of the brain; untreated mortality is around 70% for HSV encephalitis, but this is reduced to 15% with timely treatment with intravenous aciclovir. Various other neurological manifestations of HSV infection have been described[1].

While meningitis and encephalitis are distinct clinical syndromes, their symptoms may overlap. For example, the cardinal features of meningitis (fever, headache, neck stiffness, and photophobia) may result in drowsiness, even without brain parenchymal involvement. In contrast, encephalitis requires altered consciousness including drowsiness, behavioral changes or coma, and focal neurological deficits may also be seen. While challenging, it is important to distinguish between these two syndromes because their treatment and prognosis differ. In particular, there is no convincing evidence that viral meningitis benefits from antiviral therapy, whereas encephalitis does.

HSV is the second most common cause of viral meningitis in adults after enterovirus[2] and is the most common cause of viral encephalitis in developed countries[3]. The aetiology of viral encephalitis in tropical countries differs considerably, with Japanese encephalitis virus and dengue virus infections being particularly common in children[4], despite being vaccine-preventable.

Most cases of encephalitis caused by HSV in adults and children are due to HSV type 1 (~90%). HSV-2 is more often seen in HSV encephalitis in neonates (due to its association with genital herpes) and in immunocompromised patients[5] and may be seen in meningitis in all patient groups.

Delays in diagnosis and difficulties in providing optimal care are responsible for much of the considerable mortality and morbidity associated with these infections[2,6,7], and this is particularly problematic when cerebrospinal fluid (CSF) analysis is not possible. For example, in Laos, lumbar puncture and CSF analysis are available only in Vientiane Capital, and microbiological analysis (including viral polymerase chain reaction (PCR)) is offered in a single hospital laboratory. A delay in aciclovir administration is a key modifiable risk factor for poor outcomes[8].

Not only is significant mortality seen early in HSV encephalitis, but significant long-term cognitive, psychiatric, and neurodevelopmental sequelae are also very common[9]. For example, 50% of survivors in a French cohort had moderate or severe disability as measured by the Glasgow Outcome Scale after 1 year[10], and the risk of epilepsy is significantly increased[11]. Such studies of HSV encephalitis outcomes have not been conducted in Laos, but a recent detailed study discovered that the health and financial sequelae of Japanese encephalitis in Laos and Vietnam are often catastrophic[12].

Both HSV-1 and HSV-2 infections are very common, although many people may not experience the classic presentation of orolabial or genital herpes. The seroprevalence of HSV-1 is usually reported as 60–90%, while the seroprevalence of HSV-2 in the general adult population of Europe is approximately 12%, similar to the seroprevalence in Asia[13,14]. HSV encephalitis is caused by viral reactivation in approximately 70% of cases. Thus, while HSV encephalitis is uncommon, a significant proportion of the population is at risk of an underlying infection.

Usual consensus is that symptoms of CNS infections caused by HSV are indistinguishable whether the infection is primary or a reactivation, although some have suggested that primary HSV infection may be associated with systemic symptoms of fever and malaise, and may be more acute and fulminant. Detecting HSV type-specific antibodies can distinguish between

these possibilities because most patients do not have a detectable IgG response at the time of first clinical presentation, but will have if symptoms are due to reactivation.

Although HSV meningitis and encephalitis are well-known syndromes, their association with head trauma has not been well described. Previous cases have reported HSV-1 encephalitis following both craniotomy for a traumatic acute subdural haematoma (proven to be reactivation because of positive HSV-1 IgG serology)[15] and resection of a meningioma[16], as well as various other post-neurosurgical cases summarised by Bhimani *et al.* HSV-2 encephalitis has been seen following a craniotomy and resection of a craniopharyngioma[17]. Surgeries may be comparatively minor, such as microvascular decompression of the trigeminal nerve[18].

Our case report highlights CNS infection caused by HSV-2 reactivation after traumatic brain injury in the absence of surgery, and discusses the difficulties in managing this life-threatening infection in low-resource settings.

Case presentation

A 39-year-old male was admitted with severe headache, drowsiness, confusion, and reduced consciousness. There was no fever, vomiting, or seizures. He had been discharged from the hospital two days earlier following a road traffic accident that caused traumatic brain injury, and a CT scan showed subarachnoid hemorrhage. The admission had lasted nine days, after which he had largely recovered, and the new symptoms had emerged progressively since discharge.

The patient's medical history was otherwise unremarkable, although he was a cigarette smoker and regularly used amphetamines. His HIV test on admission was negative.

On admission, vital signs showed mild hypertension (149/96 mmHg) and tachycardia (heart rate, 188 beats per minute). Peripheral blood leucocyte count was elevated at 15.97 x 10^3 cells/μL (normal range 6.00–8.00 x 10^3/μl), with a neutrophilia (12.8 x10^3/μl) and a marked hyponatraemia of 125 mmol/L (normal range 136–145 mmol/L). His Glasgow Coma Scale score (GCS) was 14/15 (E3, V5, M6). The patient received fluid resuscitation and supplemental sodium chloride intravenously.

An initial review by the neurology team shortly after admission was normal, but on subsequent review the same day, the patient was found to have left hemiplegia (power 3/5 in the left arm), and his GCS had again dropped to 14 (E3, V5, M6), now with possible neck stiffness. Further treatment was initiated with ceftriaxone (2 g intravenously, twice daily), dexamethasone (8 mg orally, three times daily), and diazepam as empirical treatment for bacterial meningitis.

A repeat CT scan of the brain was performed, and the recurrence of intracranial hemorrhage and other acute abnormalities were excluded.

A lumbar puncture (LP) was performed the following afternoon (day 2 of admission), demonstrating a white cell count of 390/mm^3 (95% lymphocytes). The glucose level in the cerebrospinal fluid was 38 mg/dL (paired peripheral blood glucose was 145 mg/dL), protein was 72 mg/dL, the opening pressure was not measured, India ink stain for *Cryptococcus* spp. was negative, and rickettsial rapid diagnostic tests for murine (GenBio ImmunoDOT) and scrub typhus (IgM, InBios) were also negative. No organisms were seen on Gram staining, and no bacterial growth was observed on chocolate agar. A viral PCR panel was planned; however, the results were not immediately available.

On day 3 of admission, the patient was alert, with a GCS score of 15/15 and full power in all limbs, but with ongoing neck stiffness. Over the coming days, the persistent headache began to improve slowly.

On the sixth day of admission, HSV-2 was detected in the CSF by real-time PCR. Oral aciclovir 800 mg four times a day was added to treat HSV meningoencephalitis, and in the absence of MRI scanning, it was difficult to determine whether the patient had meningitis or encephalitis, although changes to consciousness or neurology were brief. No skin lesions suggestive of herpes were noted, and we were not able to ascertain whether the patient had a history of orolabial or genital herpes. Electrolytes were re-measured, and sodium levels were normal (136 mmol/L).

On day 10 of admission, the patient developed pedal oedema and diplegia, likely due to immobility and reduced albumin (3.0 g/dL; ref range 3.5–5.2 g/dL). By day 12, the patient had fully recovered, and ceftriaxone, oral aciclovir, and dexamethasone were discontinued. Repeat LP was not performed owing to financial constraints.

Discussion

The patient was diagnosed with HSV-2 meningoencephalitis. However, in retrospect, the clinical features were most consistent with meningitis. Indeed, the patient's neurological status rapidly normalized several days before administration of aciclovir, a clinical course that is not typical of untreated HSV encephalitis. The observed reduction in consciousness was minimal (the lowest GCS score recorded was 14/15), and meningitis associated with marked hyponatraemia was sufficient to explain this. The cause of hyponatraemia was not investigated but may reflect the syndrome of inappropriate ADH production due to intracranial pathology. Leucocytosis may represent an inflammatory response (increased neutrophil counts have been recorded following traumatic brain injury), or bacterial co-infection.

CNS infections following head trauma may be suspected when there are physical injuries, because bacterial and fungal pathogens can be directly inoculated into the central nervous system – but viral infections are not typical. In the absence of fractures or penetrating wounds, infections are considered less likely. Consequently, the infectious aetiology of our

patient's re-presentation was unexpected, highlighting the importance of maintaining a broad differential diagnosis. Early lumbar puncture is important when safe to perform, but this is seldom achieved even in high-income settings[2]. Other possible infectious causes in this case include viruses and bacteria, including *Mycobacterium tuberculosis*, and fungi such as *Cryptococcus* spp. Differential diagnosis includes metabolic derangement (e.g., hyponatraemia, hypoglycaemia), toxins (including recreational drugs), and intracranial thrombosis.

In 1978, reactivation of HSV-1 following skin trauma was demonstrated in mice[19]. However, reactivation of herpes viruses, both HSV and Varicella zoster virus (VZV), following trauma is not frequently considered in clinical practice. Despite this, using a case-control study design of 16,771 cases, herpes zoster (shingles) was shown to be 3.4 times more common in patients who had experienced trauma in the previous 7 days (95% CI 2.8-4.2), and remarkably was 27.5 times more common (95% CI 5.4-140.3) if the injury was to the head[20]. In one case, a minor head injury was followed by a disseminated vesicular rash, most marked on the forehead, and the vesicle fluid tested positive for both VZV and HSV-1[21]. These cases of reactivation involve the skin, but viral reactivation leading to CNS infection is less commonly described but has occurred following neurosurgery[22]; thus, our case is an important reminder of this possibility.

HSV establishes life-long latency in sensory ganglia – which may be the trigeminal ganglion, or dorsal root ganglia. Multiple mechanisms by which some triggers may result in HSV reactivation from these sites are understood – including both local and systemic pathways. For example, host-derived proteins that maintain HSV latency may be depleted, including Nerve Growth Factor; this occurs when innervated tissue is damaged[22]. Other data describe local immune dysfunction following head injury, including pro-inflammatory microglial activation[23] as well as production of cytokines and other pro-inflammatory factors. This pro-inflammatory response with altered immune cell behavior converge to increase host susceptibility to reactivation. Even psychological and emotional stress have been implicated in viral reactivation, via activation of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis, causing release of catecholamines and glucocorticoids, respectively. Recent reviews provide further detailed explanations at the biochemical and molecular levels[22–24].

Clinical guidelines unambiguously mandate treatment with intravenous aciclovir 10 mg/kg three times a day for HSV encephalitis if initial CSF analysis suggests viral infection[25], although in our case, treatment was only started once a positive PCR result was obtained on day 6 of admission. The recommendation is usually for 14–21 days of intravenous therapy, stopping only when the repeat CSF analysis is negative for HSV by PCR. Given our patient's full clinical recovery and the costs associated with repeat lumbar punctures, he did not undergo repeat CSF analysis.

Achieving standards set by international guidelines may be aspirational in some settings, especially in low-income and middle-income countries. Intravenous aciclovir is not on the lists of essential medicines produced either in Laos or by the World Health Organization (https://iris.who.int/bitstream/handle/10665/371090/WHO-MHP-HPS-EML-2023.02-eng.pdf?sequence=1), and it is very rarely used in Laos. This situation is common in many LMICs[26]. Patients are instead treated with the oral formulation, which has a bioavailability of only 15–20%, and variable CSF penetration[27]. Consequently, clinical outcomes are likely to be much poorer than those in settings in which intravenous treatment is the standard of care. However, comparison of oral and intravenous aciclovir has not been studied in controlled trials, and these would likely be unethical to perform.

The oral prodrug of aciclovir, valaciclovir, has superior bioavailability and has been proposed as an option when intravenous aciclovir is unavailable. A 2011 study demonstrated that adequate CNS concentrations of aciclovir were achieved when valaciclovir (1 g) was administered three times daily[28]. However, the use of valaciclovir is far from settled, and a higher dosing regimen of 2 g three times a day or even four times a day has been proposed more recently, based on pharmacokinetic and pharmacodynamic considerations[27]. Valaciclovir is not available in Laos.

Despite these theoretical and practical concerns, oral aciclovir has some efficacy in the treatment of HSV encephalitis. Furthermore, a report of HSV encephalitis successfully treated with a 10-day course of oral aciclovir emphasized the 28-fold cost differential between intravenous and oral treatment[29], which is also a key consideration in the Lao context, where healthcare expenses are frequently catastrophic[12,30].

This study has some limitations. HSV encephalitis (especially HSV-1) typically involves the temporal lobes, and MRI is often performed to confirm the diagnosis; however, this was not performed in this case. Second, while we believe that the clinical presentation was due to viral reactivation, which is the most common scenario, we cannot exclude primary infection; measuring type-specific antibodies in the serum can be performed to clarify this point, but this test was not available and would not have altered clinical management. This dichotomy between primary infection and reactivation remains controversial[15] but high rates of latency would support reactivation as the more likely aetiology in this age group and clinical context.

Further studies should involve routine testing for viruses when CSF samples are available following trauma or neurosurgery to allow better estimation of the frequency of viral infection in these situations, along with measurement of IgG antibodies to differentiate primary infection from reactivation. Such studies would best be conducted in neurosurgical centres due to the high number of patients, and frequent CSF sampling in this group.

Conclusions

This case highlights the growing recognition that traumatic brain injury causes reactivation of herpes viruses, including reactivation in the central nervous system, and that infectious complications are important in the differential diagnosis of

neurological complications following traumatic brain injury. Furthermore, we highlight the lack of access to life-saving antiviral drugs in many countries along with the financial and practical challenges associated with managing these infections in many settings. The key lesson from this case is that treatment should be started as soon as herpes simplex encephalitis is considered. While valaciclovir is likely superior to oral aciclovir, intravenous aciclovir remains the treatment of choice.

Public and patient involvement

There was no formal patient or public involvement in the design or conduct of the study.

Ethic and consent

Written informed consent was obtained from the patient for the publication of this case report.

Data availability

No data are associated with this article.

Acknowledgments

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Open Peer Review

Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 18 December 2025

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✔ **Brent Stanfield**
Louisiana State University, Baton Rouge, USA

The updated manuscript is appropriate for publication.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I focus on preclinical herpesvirus vaccine development, herpesvirus molecular virology, and immunopathogenesis, aiming to translate findings into innovative therapeutic and prophylactic vaccines.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 18 December 2025

https://doi.org/10.21956/wellcomeopenres.28129.r141560

✔ **Franklyn Nkongho Egbe**
University of Liverpool, Liverpool, UK

The authors have satisfactorily responded to my comments. I have no further comments to make.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: HSV diagnosis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 21 November 2025

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Franklyn Nkongho Egbe
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Overall Summary

Thank you for inviting me to review this case report entitled “Herpes simplex virus type 2 (HSV-2) meningoencephalitis associated with traumatic brain injury – a case report from Lao PDR” by Vannachone and colleagues . The case report highlights a case of HSV infection - probably meningoencephalitis – likely caused by HSV-2 reactivation following traumatic brain injury (TBI) in a resource-limited setting with limited access to laboratory diagnosis of CNS infections and antivirals.

The case is a 39-year-old male patient discharged from the hospital after being treated for TBI following a road traffic accident. He was readmitted 9 days later with severe headache, drowsiness, confusion and reduced consciousness. After 6 days of unsuccessful empirical treatment for bacterial meningitis with ceftriaxone (2 g intravenously, twice daily), dexamethasone (8 mg orally, three times daily), and diazepam, HSV-2 was detected in his CSF by PCR. Oral aciclovir, 800 mg, was then added to his treatment regimen. The patient fully recovered by day 12, and treatment was discontinued. The authors suggested that HSV CNS infections should be considered in cases of delayed deterioration following TBI and further highlighted the challenges of optimal HSV infection treatment in resource-limited settings.

Overall Comments

The authors have provided a detailed description of the cases’ history and progression, the clinical examination and diagnostic tests used, and the treatment and clinical outcome.

However, they could add detailed information on the clinical features to guide other practitioners (see detailed comments below), and some recommendations for future research. Also, are there any clinical findings from his first admission (similar to those presented here) that could be included? e.g. it could be interesting to compare his first and second admissions' sodium levels and GCS scores.

Points to address to make the article scientifically sound
Abstract:
Background: Could the authors rephrase the background paragraph to focus more on the topic: HSV-2 CNS infections

*Text…Central nervous system infections should be considered in cases of **delayed deterioration** following trauma…*
Could the authors include some specific clinical picture of '*delayed deterioration*' from this case to guide other practitioners, e.g. severe headache, drowsiness, confusion, reduced consciousness, hyponatraemia and/or neurological deficits, as detailed in the case presentation?

Introduction:
- Could the authors describe previous case reports or studies on Traumatic brain injury and HSV infection? E.g. Bhimani et al 2024
- Could the authors add a brief review on CNS infection from HSV reactivation? e.g. what are the likely causes of HSV reactivation, and is TBI normally considered one of the causes? Could they provide information to enhance the reader's understanding of primary and reactivated HSV CNS infection?

Text :*Although HSV meningitis and encephalitis are well-known syndromes, their association with head trauma has not been described previously*
What about the case report by Bhimani et al 2024?

Text: ….This case report highlights the reactivation of HSV-2 after traumatic brain injury and discusses the difficulties in managing this life-threatening infection in low-resource settings….
Could the authors rephrase the objective to match their case report? E.g. … a case report of CNS infection caused by HSV-2 reactivation following TBI…?

Discussion:
Text…..although in our case, treatment was only started once a positive PCR result was obtained on day 6 of admission…
If there was clinical suspicion of meningoencephalitis from onset, why was aciclovir treatment delayed?

Conclusion
Text: …highlights the growing recognition that trauma can cause reactivation of herpes viruses, including reactivation in the central nervous system, and that infectious complications are important in the differential diagnosis of neurological complications following head trauma…
The authors could rephrase this to highlight that TBI could cause HSV-2 reactivation, leading to CNS infection, and thus should be considered in the differential diagnosis of neurological complications following TBI.

Could the authors suggest future studies to enhance our understanding of HSV infections caused by HSV reactivation following TBI?

References
1. Bhimani A, Cummins D, Kalagara R, Chennareddy S, et al.: A rare case of herpes simplex virus encephalitis from viral reactivation following surgically treated traumatic brain injury. *Brain Injury*.

2024; **38** (12): 1046-1051 Publisher Full Text

Is the background of the case's history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Partly

Is the case presented with sufficient detail to be useful for other practitioners?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: HSV diagnosis

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 01 Dec 2025

Souphaphone VANNACHONE

We thank the Reviewer for for their thoughtful comments on our article. We have attempted to address each of these, as described below.

Comment: 1. Are there any clinical findings from his first admission?
Response: Unfortunately, the medical records are no longer available, and therefore we are unable to provide blood test results from the initial admission.

Comment: 2. Rephrase the background paragraph to focus more on the topic: HSV-2 CNS infections
Response: We have now specifically emphasised the possibility of viral infections in the Abstract.

Comment: 3. Include some specific clinical picture of '*delayed deterioration*'.
Response: We have added the typical symptoms of worsening headache, drowsiness and reduced cognitive state in this paragraph.

Comment: 4. Describe previous case reports or studies on Traumatic brain injury and HSV infection? E.g. Bhimani et al 2024.
Response: Thank you highlighting this recent article, which we have now included.

Comment: 5. Add a brief review on CNS infection from HSV reactivation. e.g. what are the likely causes of HSV reactivation, and is TBI normally considered one of the causes?
Response: Details on the mechanisms of HSV reactivation are now provided, including loss of host-derived proteins that maintain viral latency, local immune dysfunction involving pro-inflammatory microglial activation, and systemic effects via sympathetic activation and glucocorticoid release. Citations are added to support this new information.

Comment: 6. Could they provide information to enhance the reader's understanding of primary and reactivated HSV CNS infection?
Response: The difficulty in distinguishing between primary infection and reactivation on clinical grounds alone is stated explicity, adding that IgG antibody testing can distinguish between the two possibilities.

Comment: 7. Rephrase the objective to match their case report? E.g. … a case report of CNS infection caused by HSV-2 reactivation following TBI…?
Response: We have re-focused this sentence by re-phrasing it as suggested: “Our case report highlights CNS infection caused by HSV-2 reactivation after traumatic brain injury in the absence of surgery and discusses the difficulties in managing this life-threatening infection in low-resource settings.”

Comment: 8. Why was aciclovir treatment delayed?
Response: Viral infection was not anticipated, although we recognise a lymphocytic CSF should have raised clinical suspicion sooner. In addition, aciclovir is very expensive in Laos and empiric prescription is uncommon.

Comment: 9. Rephrase this to highlight that TBI could cause HSV-2 reactivation,
Response: We have re-written the text to emphasise that traumatic brain injury specifically may cause reactivation as follows: “This case highlights the growing recognition that traumatic brain injury causes reactivation of herpes viruses, including reactivation in the central nervous system, and that infectious complications are important in the differential diagnosis of neurological complications following traumatic brain injury.”

Comment: 10. Suggest future studies to enhance our understanding of HSV infections caused by HSV reactivation following TBI.
Response: We have suggested an observational study in the first instance whereby CSF is routinely tested for viruses, and serum HSV IgG titres measured. Neurosurgical centres are likely to have suitable patient numbers and expertise.

Competing Interests: No competing interests were disclosed.

Reviewer Report 05 December 2024

https://doi.org/10.21956/wellcomeopenres.25022.r112708

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Brent Stanfield
Louisiana State University, Baton Rouge, USA

The article, titled *"Herpes simplex virus type 2 (HSV-2) meningoencephalitis associated with traumatic brain injury – a case report from Lao PDR,"* describes a compelling case of a 39-year-old male who experienced neurological symptoms, including severe headache and altered consciousness, following traumatic brain injury (TBI). After a road traffic accident resulting in subarachnoid hemorrhage, the patient initially recovered but later presented with symptoms indicative of meningoencephalitis. Diagnostic testing ultimately revealed HSV-2 in the cerebrospinal fluid (CSF), confirming viral meningoencephalitis. Treated with oral acyclovir, the patient achieved full neurological recovery. This case report offers valuable insights into the rare association between TBI and HSV-2 reactivation and highlights the challenges of diagnosing and treating such cases in resource-limited settings.

The background of the patient's history and progression is described in reasonable detail. However, some aspects could benefit from further clarification. The authors provide a thorough account of the initial trauma and subsequent hospital admission, but the timeline of events following discharge could be expanded to better illustrate the progression of symptoms. For instance, specifying whether the neurological symptoms emerged gradually or suddenly after discharge would enhance the understanding of how HSV-2 reactivation was triggered by trauma. This information would be particularly useful for practitioners who might encounter similar cases.

Details of the physical examinations, diagnostic tests, treatments, and outcomes are generally comprehensive. The authors describe the patient's clinical presentation, initial diagnostic workup, and the decision to treat empirically for bacterial meningitis while awaiting viral PCR results. The diagnostic process, including CSF analysis and PCR confirmation of HSV-2, is well-documented. However, there are opportunities to strengthen the discussion around the treatment decisions. The authors note the use of oral acyclovir due to resource limitations but do not sufficiently elaborate on the clinical implications of using oral rather than intravenous acyclovir, which is the standard of care for HSV meningoencephalitis. This omission leaves the reader questioning how these constraints may have influenced the patient's recovery trajectory and whether alternative antiviral therapies, such as valacyclovir, were considered or feasible in this setting. Additionally, further context regarding the significance of the elevated leukocyte count and hyponatremia observed in the patient would provide a more nuanced understanding of the clinical findings.

The discussion of the findings is thought-provoking and highlights the novelty of the case, particularly the link between TBI and HSV reactivation. The authors effectively emphasize the importance of maintaining a broad differential diagnosis when neurological symptoms develop following trauma. They also draw attention to the diagnostic and therapeutic challenges posed by resource limitations in low-income settings. Nevertheless, the discussion would benefit from a deeper exploration of the mechanisms by which trauma may trigger HSV-2 reactivation. While the authors briefly touch on immune dysregulation as a potential factor, they could enhance their argument by integrating evidence from existing literature or animal models that demonstrate the

pathways leading to viral reactivation after trauma. Such an expansion would strengthen the scientific foundation of the case report and its broader implications for understanding HSV pathogenesis.

The report is presented with sufficient detail to be useful to other practitioners, particularly those working in resource-limited environments. It provides actionable insights into the diagnostic approach and treatment options for similar cases. However, the article would be even more practical if it included a concise summary of lessons learned or key recommendations. For example, a brief reflection on how clinicians can navigate the challenges of limited diagnostic tools and treatments would make the report more accessible and relevant to a global audience.

To ensure the article is scientifically sound, the authors should address several key points. They should clarify the timeline of symptom progression to provide a clearer picture of the case's trajectory. The rationale for choosing oral acyclovir should be discussed in greater detail, along with a reflection on how this decision aligns with international treatment guidelines and its implications for patient outcomes. Expanding the discussion on the mechanisms of HSV-2 reactivation would also enhance the scientific rigor of the report. Lastly, summarizing actionable insights for practitioners would improve the utility of the case report.

In summary, the article is a valuable contribution to the literature, shedding light on an unusual but clinically significant association between TBI and HSV-2 reactivation. While it is largely well-written and informative, addressing the points above will strengthen its clarity, scientific depth, and practical relevance. With these revisions, the report will serve as an excellent resource for clinicians and researchers alike.

Is the background of the case's history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Partly

Is the case presented with sufficient detail to be useful for other practitioners?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I focus on preclinical herpesvirus vaccine development, herpesvirus molecular virology, and immunopathogenesis, aiming to translate findings into innovative therapeutic and prophylactic vaccines.

I confirm that I have read this submission and believe that I have an appropriate level of

expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 01 Dec 2025

Souphaphone VANNACHONE

We are grateful to the Reviewer for their careful reading of our manuscript. We have endeavoured to answer all suggestions, which we agree strengthen our article, and we provide a point-by-point response.
Comment: 1. The timeline of events following discharge could be expanded.
Response: The readmission was only 2 days after discharge, so not a significant timeframe for complex new symptomatology to evolve. We have emphasised the gradual worsening of symptoms, which were non-specific.

Comment: 2. Elaborate on the clinical implications of using oral rather than intravenous acyclovir … was valacyclovir considered or feasible? The text states that intravenous aciclovir is the only recommended option for herpes simplex encephalitis.
Response: We have stated that use of oral aciclovir may lead to worse outcomes due to pharmacokinetic parameters; and we have added that this has not been studied in trials. We have described the likely inferior role of valacyclovir, and we have explained that valacyclovir is not available in Laos.

Comment: 3. Significance of the elevated leukocyte count and hyponatremia.
Response: The updated text explains that these may have various causes, but following brain injury, may be due to inflammation and SIADH – although bacterial co-infection and hypovolaemia remain possible.

Comment: 4. The mechanisms by which trauma may trigger HSV-2 reactivation.
Response: Details on the mechanisms of HSV reactivation are provided, including loss of host-derived proteins that maintain viral latency, local immune dysfunction involving pro-inflammatory microglial activation, and systemic effects via sympathetic activation and glucocorticoid release. Citations are added to support this new information.

Comment: 5. A concise summary of lessons learned or key recommendations.
Response: We have provided the key lesson that immediate intravenous aciclovir is required when viral encephalitis is suspected clinically or suggested by CSF analysis.

Competing Interests: No competing interests were disclosed.