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Herpes Simplex Virus type 2 encephalitis in critically ill adult: a retrospective analysis of EURECA and HERPETICS cohort studies

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Abstract

Background Herpes simplex virus type 1 (HSV-1) is the leading cause of sporadic infectious encephalitis. Although typically associated with benign meningitis, HSV-2 can also cause encephalitis in adults, a condition that remains poorly characterized in intensive care unit (ICU). We aimed to compare the characteristics, management, and outcomes of critically ill adult with HSV-2 and HSV-1 encephalitis.

Methods We performed a retrospective analysis of adults with herpes simplex encephalitis (HSE) admitted to the ICU in two large multicenter cohorts. Patients were classified according to cerebrospinal fluid (CSF) HSV genotype. The primary endpoint was unfavourable outcome at 3 months, defined as a modified Rankin Scale score 3-6.

Results Among 285 HSE patients, 17 (6%) had HSV-2 encephalitis (age 60 [53-67] years, female sex 58.8%). Although the proportion of immunocompromised status did not differ significantly between groups (29.4% vs 15.4%, p=0.13), HSV-2 cases had a significantly higher prevalence of HIV infection (17.6 vs 1.5%, p<0.01), less frequent brain MRI abnormalities (85.7% vs 97.7%, p=0.01) and similar CSF findings compared to HSV-1 cases. The duration of intravenous acyclovir treatment was shorter for HSV-2 cases (18 [4-21] days) versus 21[20-21] days, p=0.04). Unfavourable outcome occurred in 9/16 (56.3%) patients with HSV-2 encephalitis and in 175/236 (74.2%) patients with HSV-1 encephalitis (p=0.25).

Conclusion Encephalitis caused by HSV-2 represent a consistent proportion of severe HSE. Clinical presentation and outcomes and broadly comparable to those of HSV-1 cases, underscoring the importance of early recognition and standardized management of encephalitis caused by HSV, regardless of genotype.

Keywords Encephalitis, Herpes simplex virus type 2, Intensive Care.

Introduction

Herpes simplex encephalitis (HSE) is a severe condition affecting the central nervous system (CNS) and is associated with a poor prognosis even with early and appropriate treatment [1,2]. Herpes simplex virus type 1 (HSV-1) is the leading cause of sporadic infectious encephalitis, while HSV-2 is predominantly linked to benign meningitis [3]. Nevertheless, HSV-2 encephalitis does occur in adults and is often reported in immunocompromised patients, although this perception is not firmly supported by cohort-level data and may reflect historical assumptions rather than current epidemiology [4,5]. Moreover, few large-scale studies have directly compared HSV-1 and HSV-2 in the context of encephalitis, leaving important gaps in understanding potential differences in their clinical presentation, radiological features, and outcomes [6,7].

Over the past decades, advanced diagnostic tools, including multiplex polymerase chain reaction (mPCR) have led to the identification of several adult cases of HSV-2 encephalitis notably in immunocompetent adults, often highlighting atypical feature such as brainstem involvement or vasculitis [8–12]. Nonetheless, the available evidence remains very limited, as most publications consist of isolated case reports, resulting in a fragmented and potentially biased understanding of the condition.

Given these uncertainties, the present study aimed to provide a more comprehensive description of adult HSV-2 encephalitis by identifying cases across two large multicenter cohorts. We sought to directly compare HSV-2 and HSV-1 encephalitis to determine whether these two genotypes differ in their clinical presentation, radiological features, and outcomes. Immunocompromised status was a key focus of the analysis to evaluate the potential overrepresentation in this population.

Material and methods

This study is a retrospective analysis using collected data from two multicenter cohorts: HERPETICS [1] and EURECA [2]. All confirmed HSE cases included in the two cohorts, defined as patients fulfilling the International Encephalitis Consortium criteria for encephalitis [13] and having a positive HSV PCR in cerebrospinal fluid (CSF), were eligible for the study. HSV detection and genotyping relied exclusively on molecular methods, including simplex PCR, multiplex PCR, and, in earlier cases, particularly within the HERPETICS cohort, PCR assays that did not allow differentiation between

HSV-1 and HSV-2. Patients were classified as HSV-1 or HSV-2 encephalitis based on PCR results. All HSV-2 cases were reviewed by an intensivist (T.V.) prior to analysis to ensure diagnosis accuracy, and patients without definitive genotyping were excluded. The inclusion and exclusion criteria for each study are detailed in the Supplementary Material, along with the study flow chart (Supplementary Figure 1).

To assess cohort comparability and potential selection bias, additional analyses comparing HSV-1, HSV-2, and excluded HSV-untyped patients as well as HSV-2 patients among EURECA and HERPETICS cohorts were conducted; results are reported in Supplementary Tables 1 and 2.

Patients were considered immunocompromised if they had one of the following conditions: use of immunosuppressant drugs (including > 3 months of steroids), solid organ transplantation, solid tumour requiring chemotherapy in the last 5 years, hematologic malignancy (regardless of time since diagnosis and received treatments) or HIV infection. Detailed methods and definitions of relevant variables are provided in the Supplementary Material.

The primary endpoint was unfavourable outcome at 3 months following ICU admission, defined by a score of 3 to 6 on the modified Rankin scale (mRS), indicating moderate to severe disability or death.

Continuous variables are presented as median (interquartile range [IQR]) and categorical variables as number (percentage). Comparisons between HSV-2 and HSV-1 encephalitis were performed using the Chi-square test for categorical variables and the Mann–Whitney U test for continuous variables. Patients with missing data were excluded from analyses involving the corresponding variables. Associations between clinically relevant variables and unfavourable outcome were assessed using multivariable logistic regression. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) are reported in Supplementary Table 3.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software. A two-sided p-value < 0.05 was considered statistically significant.

Results

A total of 338 patients with HSE were eligible (HERPETICS n=285, EURECA n=53) for the study. We excluded 53 patients due to the lack of genotyping results leaving 285

patients for the main analysis. Of these, 17/285 (6.0%) HSE cases were due to HSV-2, (median age 60 years (interquartile range, 53–67), female sex (58.8%)). Baseline characteristics of patients are presented in Table 1.

Unfavourable outcome (mRS 3–6) occurred at comparable rates in HSV-2 and HSV-1 patients (56.3% [9/16], 95% confidence interval 29.9–80.2 vs. 74.2% [175/236], 95% CI 68.1–79.6; absolute difference 17.9%, p=0.25). Mortality was also similar between the two groups (18.8% [3/16], 95% CI 4.0–45.6 vs. 16.9% [40/236], 95% CI 12.4–22.4; p=0.85).

Immunocompromised status was observed in 5/17 HSV-2 encephalitis patients (29.4%) and 41/266 HSV-1 encephalitis patients (15.4%) (p=0.13). HIV infection was more frequent among HSV-2 patients (3/17, 17.6%) than in HSV-1 (4/266, 1.5%) cases (p<0.01). Details regarding immunocompromised status are available on Supplementary Table 4. Abnormal brain MRI findings were less frequent in HSV-2 cases (12/14, 85.7%), as compared to HSV-1 cases (217/222, 97.7%, p=0.01). Detailed description of MRI findings in HSV-2 cases is provided in Supplementary Table 5.

CSF analyses did not demonstrate a significant difference in leukocyte counts between HSV-2 and HSV-1 encephalitis cases (122 [38–263] cells/µL and 53 [14–181] cells/µL, respectively; p=0.18). CSF protein concentrations were also similar. Interestingly, 34 patients with HSV-1 encephalitis (13.1%) had no CSF pleocytosis, including 9 individuals who also had a normal protein concentration (<0.4 g/L). In comparison, only 1 patient with HSV-2 encephalitis (5.9%) had no CSF pleocytosis, although the CSF protein level was elevated. This difference was not statistically significant (p=0.39).

The rates of neurological and systemic complications during ICU stay, as well as their management, did not differ significantly between groups. We found no significant difference regarding acyclovir doses regimen among both groups (10 [10-10] mg/kg/8h versus 10 [10-11.4], p=0.11). Treatment duration was shorter among HSV-2 patients (18 [14-21] days) as compared to HSV-1 (21[20-21] days), p=0.04).

Table 1. Baseline characteristics and outcomes of patients with Herpes Simplex Encephalitis

	HSV-1 (N = 268)	HSV-2 (N = 17)	*p-value*
Demographic			
Age (years)	64 [53.3-72]	60 [53-66.5]	0.29
Female sex	124/268 (46.3)	10/17 (58.8)	0.31
Coexisting conditions			
Diabetes	37/266 (13.9)	2/17 (11.8)	0.80
Liver cirrhosis	5/266 (1.9)	1/17 (5.9)	0.27
End stage kidney disease requiring dialysis	3/268 (1.1)	1/17 (5.9)	0.11
Immunocompromised status	41/266 (15.4)	5/17 (29.4)	0.13
Including HIV	4/266 (1.5)	3/17 (17.6)	**< 0.01**
Reason for ICU admission			
Altered mental status	173/268 (64.6)	12/17 (70.6)	0.61
Seizure	92/268 (34.3)	4/17 (23.5)	0.36
Clinical characteristics			
Headache	78/217 (35.9)	4 /11(36.4)	0.98
Neck stiffness	14/218 (6.4)	1/11 (9.1)	0.72
Temperature (°C) [a]	38.7 [38.1-39.2]	38.8 [38.0-39.5]	0.89
Convulsive seizure	43/268 (16.0)	4/17 (23.5)	0.42
Convulsive status epilepticus	59/268 (22.0)	5/17 (29.4)	0.48
Focal sign	19/268 (7.1)	0/17 (0.0)	0.26
GCS < 8 indicating coma	92/254 (34.3)	5/17 (29.4)	0.57
SAPS II (points) [b]	42 [31-56]	33 [25-52]	0.58
Initial management			
Time between ICU admission and ACV (days) [c]	0 [-1-0]	0 [0-1]	0.19
Mechanical ventilation	184/267 (68.9)	11/17 (64.7)	0.56
Cerebrospinal fluid characteristics			
Leukocytes count (cells/µL) [d]	53 [14-181]	122 [38-263]	0.18
Lymphocyte percentage (%) [e]	87.4 [63.0-96.3]	84 [46-91]	0.23
Proteinorachia (g/L) [f]	0.7 [0.5-1.2]	0.8 [0.5-1.4]	0.92
Neuroimaging			
Abnormal MRI	217/222 (97.7)	12/14 (85.7)	**0.01**
Time from encephalitic symptoms to MRI (days) [g]	4 [2-9]	5 [2-9]	0.84
MRI brain lesion > 3 lobes	58/190 (30.5)	3/9 (33.3)	0.53
Intracranial haemorrhage	32/231 (13.9)	2/13 (15.4)	0.53
Outcome at 90 days			
mRS 0-2	66/236 (25.8)	7/16 (43.7)	0.12
mRS 3-6	175/236 (74.2)	9/16 (56.3)	0.12
Death	40/236 (16.9)	3/16 (18.8)	0.85

Data are expressed as median (IQR) or number (%), unless otherwise indicated. Number of patients may differ from the total cohort due to missing data for specific variables.

Abbreviations: HSV, herpes simplex virus; HIV, human immunodeficiency virus; GCS, Glasgow coma scale; SAPS II, simplified acute physiology score II; ICU, intensive care unit; ACV, acyclovir; MRI, magnetic resonance imaging; mRS, modified Rankin score.

[a] Determined in 255 HSV-1 and 15 HSV-2; [b] Determined in 237 HSV-1 and 15 HSV-2; [c] Determined in 261 HSV-1 and 15 HSV-2; [d] Determined in 259 HSV-1 and 17 HSV-2; [e] Determined in 168 HSV-1 and 15 HSV-2; [f] Determined in 236 HSV-1 and 16 HSV-2; [g] Determined in 195 HSV-1 and 13 HSV-2.

Discussion

HSV-2 encephalitis accounted for 6% of HSE cases in ICU, with clinical presentation and outcomes broadly comparable to HSV-1, underscoring that genotype alone should not alter clinical suspicion or management.

Clinical features and functional outcomes did not differ significantly from those diagnosed with HSV-1 encephalitis. Importantly, more than half of HSV-2 encephalitis experienced an unfavourable outcome in the form of persistent disability or death at 3 months. The mortality was 19% for HSV-2 encephalitis. Immunocompromised status did not differ between groups, except for a significantly higher prevalence of HIV-positive individuals in the HSV-2 group. Although clinical presentation and outcomes were similar across groups, patients with HSV-2 infection had fewer brain MRI abnormalities on admission and a shorter duration of acyclovir treatment during ICU stay.

Our study confirms that HSV-2 encephalitis, although infrequent, represents a consistent proportion of severe HSE cases, accounting for 6% in our cohort. Despite a 50% genetic homology between HSV-1 and HSV-2, the clinical presentation of HSV-2 encephalitis appears broadly similar to HSV-1 in our cohort. Accordingly, only multiplex PCR allows a rapid differentiation between these two genotypes. Nonetheless our cohort highlights a few distinctive features depending on the host condition.

Whereas HSE typically affects both sexes equally [14], we observed a non-significant higher proportion of female patients in the HSV-2 group, a finding consistent with previous data suggesting sex-related differences in HSV-2 acquisition [15].

Immunocompromised status appeared more frequent among HSV-2 patients, largely driven by a higher prevalence of HIV infection. However, given the very small number of HIV-positive cases, this observation must be interpreted with caution. It remains uncertain whether this association reflects the higher background prevalence of HSV-2 among people living with HIV or a true facilitation of neuroinvasion related to HIV-associated immunosuppression. HIV and HSV-2 are lifelong sexually transmitted infections that share overlapping risk factors and can reciprocally enhance viral replication through synergistic interactions. This epidemiological interplay makes it

difficult to distinguish coincidental co-infection from a causal contribution of HIV-induced immune dysfunction to the development of HSV-2 encephalitis [16,17]. This imbalance raises the possibility that outcome of HSV-2 encephalitis may be partly influenced by underlying immune status rather than reflecting a true genotype-specific effect. Therefore, post-hoc analyses were performed to assess the potential impact of immunocompromised status and HIV infection (Supplementary Table 3). These analyses did not suggest a significant independent association with unfavourable outcomes, but interpretation remains limited by the small number of HSV-2 cases and outcome events. Additionally detailed immunological data (including CD4 cell counts, HIV viral load, and treatment adherence) were not consistently available and the small number of patients further limited the assessment of potential confounding effects.

Apart from HIV infection, the prevalence of other immunocompromising conditions was comparable between groups (Supplementary Table 4), suggesting that immunocompromised status itself may play a limited role in the pathogenesis of encephalitis, and pointing instead to a shared pathogenic mechanism independent of the viral agent.

Consistent with clinical findings, brain MRI demonstrated comparable features across HSV groups, although some HSV-2 cases appeared to exhibit fewer abnormalities. Moreover, MRI consistently revealed a characteristic diagnostic pattern involving the temporo-fronto-insular regions (Supplementary Table 5), as previously reported in HSV-1 infection [18]. This observation contrast with earlier reports suggesting nonspecific white matter lesion, brain stem involvement or ischemic lesions mimicking Varicella Zoster Virus vasculopathy [6,8,10,19,20], which were not consistently observed in our cohort. Ultimately, this could support the hypothesis of a shared mechanism of neuroinvasion and neurovirulence in HSE involving similar anatomical route of viral entry with pronounced neurotropism for temporal, insular and frontal cortices likely due to similar molecular susceptibility [19–21]. Viral replication within neurons triggers lytic lesion with subsequent microglial inflammatory response contributing to neuroinflammation and tissue damage characterised by neuronal injury, cytotoxic oedema and necrosis reflected by typical asymmetric hyperintensities on MRI [18,22]. While the diagnosis is now facilitated by multiplex PCR, brain MRI is a valuable diagnostic tool, enabling early detection across all HSE, even when lumbar puncture is contraindicated, and aiding in distinguishing HSV-2 encephalitis from meningitis.

Finally, despite comparable outcomes across groups, the slightly shorter duration of antiviral treatment observed in HSV-2 encephalitis may suggest that its encephalitic potential remains underrecognized in clinical practice. Because HSV-2 infection is more commonly associated with meningitis and is often perceived as causing a milder neurological disease, clinicians may underestimate the severity of HSV-2 encephalitis and discontinue antiviral therapy prematurely. Alternatively, the shorter treatment course may reflect earlier clinical improvement prompting earlier discontinuation of acyclovir. Although HSV-2 patients exhibited lower SAPS II scores than HSV-1 cases, this difference was not statistically significant, and neither ICU length of stay nor overall hospital stay clearly supported one interpretation over the other. Overall, herpes simplex encephalitis—regardless of viral genotype—represents a distinct clinical entity from HSV-2 meningitis and warrants early recognition and an adequate duration of acyclovir treatment to optimise patient outcomes.

Data on adult HSV-2 encephalitis remain limited. Our study represents one of the largest adult cohorts reported to date, derived from a multicenter international collaboration with standardized 3-month outcome assessment. However, several limitations must be acknowledged. The rarity of HSV-2 encephalitis and the partly retrospective design introduce potential selection bias, random variability, and constraints on statistical analyses. Multivariate adjustments for confounders such as immunocompromised status, including HIV infection, did not reveal significant associations, and univariate comparisons should be interpreted with caution. Missing data for certain variables and heterogeneity further limit interpretation. For instance, the lower frequency of imaging abnormalities in HSV-2 cases should be interpreted cautiously, as detailed information on MRI sequences and center-specific protocols was unavailable and likely varied. Finally, 53 patients (15.6%) were excluded due to unavailable HSV genotyping, potentially introducing selection bias and affecting cohort representativeness.

These limitations reduce the robustness of our findings and may impact their interpretation and generalizability.

Conclusion

HSV-2 encephalitis, though rare, represents a consistent proportion of HSE in ICU patients and is associated with similarly unfavourable outcomes as HSV-1. Recognition of its encephalitic potential is crucial to avoid undertreatment. Standardized protocols for diagnosis and antiviral therapy should be applied regardless of genotype.

Declarations

Ethics approval and consent to participate

This secondary analysis was performed under the original ethics approvals of the HERPETICS and EURECA cohorts, and no additional informed consent was required from participants.

Consent for publication

Not applicable.

Availability of data and materials

The data supporting the findings of the study are available upon reasonable request after approval of a proposal from the corresponding author.

Competing interests

Authors declare no conflicts of interest.

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Authors' contributions

All authors as well as ENCEPHALITICA and EURECA study group members were involved in data acquisition. PJ, RS and TV participated in conception of study, methodology and design. NH performed statistical analysis. TV drafter the manuscript and developed figures. Study was supervised by RS and PJ. All authors reviewed, edited and provided final approval for the manuscript.

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