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ORIGINAL PAPER

Challenges in HSV encephalitis: normocellular CSF, unremarkable CCT, and atypical MRI findings

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Abstract

Purpose Herpes simplex virus (HSV) encephalitis continues to be the most common form of sporadic lethal encephalitis worldwide. The wide spectrum of clinical presentations and laboratory findings often poses a diagnostic challenge for physicians which might delay administration of life-saving therapy with acyclovir. Atypical presentations of HSV encephalitis have become increasingly prevalent with better diagnostic techniques and have not been well studied.

Methods We retrospectively evaluated all consecutive PCR-proven HSV encephalitis cases treated at the Hospital of the Ludwig-Maximilians-University in Munich, Germany from January 1, 2013 to February 28, 2018.

Results We included 18 patients with PCR-proven HSV encephalitis. The most common clinical features were altered mental status (77.8%), focal neurologic deficits (72.2%) and fever (72.2%). Remarkably, four of these patients (22.2%) had a normocellular cerebrospinal fluid (CSF) on admission. Electroencephalography and magnetic resonance imaging abnormalities were highly sensitive for HSV encephalitis independent of CSF cell count. Striking atypical findings on MRI were extensive global brain swelling and severe brainstem involvement in single patients. Of note, initial CT scans were normal in 11 out of 16 patients (68.8%). All patients were treated with acyclovir. Three patients still developed a clinical deterioration under therapy with acyclovir with one patient requiring decompressive craniotomy due to bilateral space-occupying temporal lobe hemorrhage. 94.4% of the patients survived but only 38.9% were discharged with a good clinical outcome (Glasgow Outcome Score = 5).

Conclusion Atypical presentations of HSV encephalitis seem to be more common than previously thought and physicians should apply a high level of clinical suspicion and a low threshold to initiate life-saving acyclovir therapy in suspected cases.

Keywords Herpes simplex virus (HSV) · Encephalitis · Foscarnet · Acyclovir · Neuroradiologic imaging · Normocellular

Background

Herpes simplex virus (HSV) is the most common pathogen in sporadic lethal encephalitis in immunocompetent patients worldwide affecting 1:250,000 to 1:1,000,000 inhabitants per year [1]. Thanks to more sensitive and more broadly available diagnostic techniques such as polymerase chain reaction (PCR) the incidence rates of HSV encephalitis have increased [2]. If left untreated, HSV encephalitis is associated with a mortality rate of up to 70% [3]. However, early initiation of acyclovir therapy has been shown to significantly reduce mortality. Despite treatment with acyclovir, the case-fatality rate of HSV encephalitis can be as high as 15% and only a minority of the survivors recovers completely [2, 4, 5].

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A diagnosis of HSV encephalitis is usually made by a positive PCR test which might not be available immediately in the emergency department. Therefore, clinicians often have to rely on clinical suspicion, basic cerebrospinal fluid (CSF) analysis (leukocyte count, protein, glucose) and imaging studies when deciding whether to start empiric acyclovir therapy in the emergency department [6]. However, while the typical signs and symptoms of HSV encephalitis such as altered mental status, epileptic seizures, behavioral changes as well as CSF pleocytosis have been well documented in the literature, each of these findings by itself lacks specificity [7]. In individual case series normal CSF samples on presentation have been reported [7–9].

Here, we provide an overview of 18 consecutive PCR-proven HSV encephalitis cases, highlight the extended spectrum of symptoms at clinical presentation, CSF findings, neuroradiologic imaging alterations, and clinical courses seen in adults with HSV encephalitis and point at potential pitfalls in the initial workup and throughout the course of the disease.

Methods

Inclusion criteria

For this retrospective cohort study, we identified and reviewed the charts of all adult (18 years of age or older) patients with PCR-proven HSV encephalitis who were treated at the Hospital of the Ludwig-Maximilians-University (LMU) Munich, a tertiary referral center in Germany from January 1, 2013 to February 28, 2018.

Exclusion criteria

Patients without clear signs of encephalitis [e.g. focal neurologic deficits, impaired level of consciousness or seizures, radiologic findings of encephalitis and/or temporal alterations on electroencephalography (EEG)] were excluded.

Study definitions

We considered patients to be immunosuppressed if they had either HIV/AIDS or any malignancy or had received a transplanted organ or were on immunosuppressive therapy.

A good clinical outcome was defined as a Glasgow Outcome Scale (GOS) of 5.

Ethics

The Medical Ethics Committee at the LMU Munich waived the necessity for informed consent to be obtained from each patient included due to the purely retrospective and observational study design (ID number: 18-225). Some details have been removed from the case descriptions to ensure patient anonymity.

Results

We identified 20 patients with PCR-proven HSV infection of the CSF. Two patients were excluded because they presented with signs and symptoms of meningitis but without any findings suggestive of encephalitis.

The most common presenting symptom was an altered mental status (77.8%) followed by focal neurologic deficits and fever (72.2% each). 12 of these patients were transferred to us from outside hospitals. A full characterization of our study population is shown in Table 1.

Normocellular CSF on admission

Of note, the initial CSF analysis yielded an unremarkable cell count in 4 out of our 18 patients (22.2%). Only a discrete elevation of CSF protein was noted in these patients. Out of these four patients, three patients were immunosuppressed: two patients suffered from a malignancy (non-small cell lung cancer, prostate cancer) and another patient was previously treated with prednisolone for acute exacerbation of chronic obstructive pulmonary disease. The latter one was additionally diagnosed to suffer from immunoglobulin (Ig) G 1–3 subclass deficiency.

3 of the 4 patients with an initially normocellular CSF received a repeated lumbar puncture 2–6 days after admission. All of them had an increase in CSF cell count on the repeated CSF analysis. Interestingly, all of these 4 patients already had a detectable HSV viral load in the CSF on admission (see supplementary material for more details).

Neuroradiologic imaging findings

MRI scans were performed 1–16 days after symptom onset (mean 5.5 days) in 17 patients and 94.1% were found to have pathologic MRI scan findings related to the HSV encephalitis. All MRI-positive patients had temporal lobe and most had insular involvement (Table 2). The lesion pattern was mostly asymmetrical, with bilateral temporal lobe involvement appearing in only 23.5% of the cases. Hemorrhagic transformation occurred in six patients in the course of the disease.

4 patients did not present with typical findings on the initial MRI scan: a male in his 50s presented clinically with acute onset of primarily brainstem deficits (diplopia, ataxia, nausea, and vomiting) that were preceded by fever and malaise for 1 week. While the CT scan on admission was normal, MRI 10 days after symptom onset (3 days after

Table 1 Patient characteristics

Characterization of study population ($n=18$)		
		Reference range
Age (mean, range)	54.7 (20–90)	
Male gender (n, %)	9 (50.0)	
Immunosuppression (n, %)	5 (27.8)	
Presenting symptoms (n, %)		
Altered mental status	14 (77.8)	
Fever	13 (72.2)	
Focal neurologic deficits	13 (72.2)	
Headache	7 (38.9)	
Seizure	4 (22.2)	
Abnormal initial CT findings (n, %)	5/16 (31.3)	
Abnormal initial MRI findings (n, %)	15/17 (88.2)	
Peripheral blood white cell count on admission (mean, range)	9.89 G/l (5.2–15.8)	4.00–10.40 G/l
C-reactive protein level on admission (mean, range)	0.38 mg/dl (0.1–1.4)	≤0.5 mg/dl
CSF studies on admission (mean, range)		
CSF cell count	131/µl (1–893)	≤5 /µl
CSF protein	67.8 mg/dl (10–123)	15–45 mg/dl
CSF/serum glucose ratio	0.54 (0.18–0.69)	
CSF viral load	618,536 Geq/ml (0–3,900,000)	
Abnormal EEG findings (n, %)	15/15 (100)	
Days to acyclovir initiation (mean, range)	1.1 (0–6)	

An initial CSF/serum glucose ratio and a quantitative HSV-I viral load in the CSF were not available for four patients. MRI and CT imaging studies as well as EEG had only been performed in 17, 16, and 15 patients, respectively.

Table 2 Initial MRI characteristics

MRI finding	Number of patients (n, %)
Temporal lobe lesion	16 (94.1)
Insular lesions	12 (70.6)
Bilateral insular lesions	7 (41.2)
Frontobasal lesions	7 (41.2)
Bilateral frontobasal lesions	4 (23.5)
Bilateral temporal lobe lesions	4 (23.5)
Cingulate gyrus lesions	6 (35.3)
Other lesion locations	5 (29.4)
Diffusion restriction	11 (64.7)
Contrast enhancement	2 (11.8)

admission) revealed extensive T2-hyperintense lesions in the pons and cerebellum with a mild hemorrhagic component (Fig. 1a, b). Another patient was admitted after being found unconscious at home and being agitated and disoriented for less than 1 day. While the initial CT only showed two previously known cerebellar metastases from non-small cell lung cancer, the follow-up MRI (acquired 7 days after symptom onset) showed a generalized cortical swelling and diffusion restriction. Thus, the typical pattern of HSV encephalitis could not be identified and other differential diagnoses such as autoimmune encephalitis, status epilepticus and hypoxic brain injury were considered (Fig. 1c, d). One patient did not show any abnormalities at all while another patient had only a very small (5 mm diameter), unspecific T2-hyperintense lesion in the left temporal lobe. A follow-up MRI scan of the latter patient revealed that the lesion had progressed to a temporal lobe swelling typical for HSV encephalitis.

Clinical course and outcome

11 out of the 18 patients in our study required admission to the intensive care unit (ICU). One patient died and only 38.9% had a good clinical outcome (GOS = 5 at discharge). An overview of the clinical course and outcome is provided in Table 3.

Patients with a normocellular CSF tended to spent more time on the ICU (26.2 days vs. 11.7 days) than patients with a pleocytic CSF on admission. Possibly, this might be a result of a delay in the establishment of the diagnosis in comparison to those with elevated CSF cell counts on admission which was associated with a later initiation of therapy with acyclovir (2.5 days after admission vs. 0.7 days after admission).

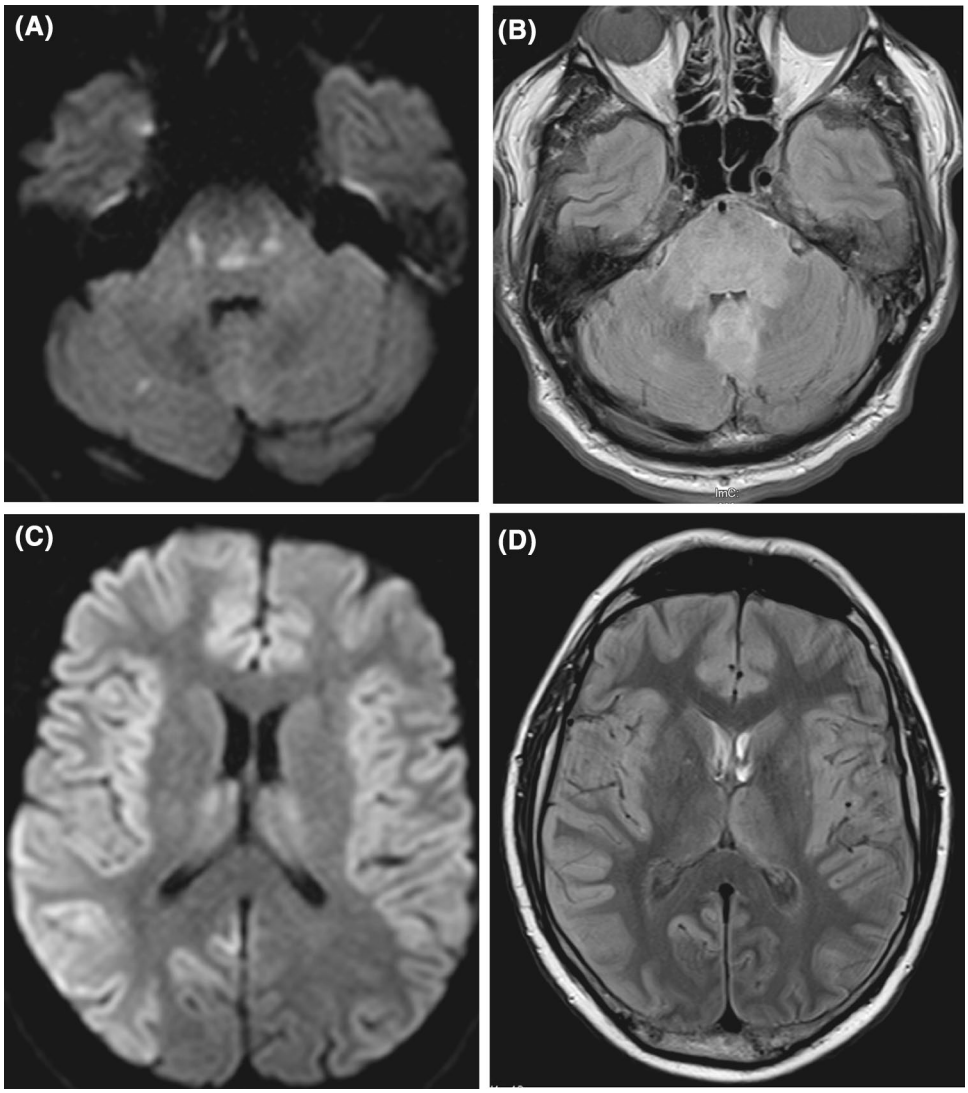

Fig. 1 Representative brain MRI acquired 4 days after symptom onset in a male patient in his 50s presenting predominantly with brainstem symptoms showing extensive pontine and cerebellar lesions on diffusion-weighted (**a**) and T2-weighted FLAIR sequences (**b**). Another patient presenting with a generalized tonic-clonic epileptic seizure developed generalized cortical swelling and extensive diffusion restrictions on MRI 6 days after admission. Representative diffusion-weighted (**c**) and T2-weighted FLAIR sequences (**d**) are shown

Table 3 Clinical course and outcome

Rate of ICU admission (*n*, %)	11 (61.1)
Days of ICU stay (mean, range)	24.5 (5–59)
Days of hospital stay (mean, range)	26.6 (7–59)
Mortality rate (*n*, %)	1 (5.6)
Good clinical outcome (Glasgow Outcome Score = 5 (*n*, %))	7 (38.9)

Despite early initiation of acyclovir therapy three patients in our study suffered a secondary deterioration. This is illustrated by the case of man in his 30s who had been treated with acyclovir for 8 days and showed a good clinical recovery initially. 8 days after admission, the patient developed a generalized tonic-clonic status epilepticus and anisocoria. Emergency CT scans revealed bilateral space-occupying temporal lobe hemorrhage that required decompressive hemicraniotomy (Fig. 2). Eventually the patient recovered but was left with significant neurocognitive deficits.

The other two patients who deteriorated under acyclovir therapy showed an increase in CSF cell count on repeated CSF analysis. In one patient, the HSV viral load increased even further on repeated PCR testing (2 days after therapy was begun) but sequencing of the isolated HSV CSF samples did not reveal any mutations associated with acyclovir resistance. The other patient developed space-occupying brainstem hemorrhage leading to compression of the ventricular system. All three patients who deteriorated while on acyclovir treatment were treated with fosacarnet in addition to acyclovir and subsequently recovered (see supplementary material for details).

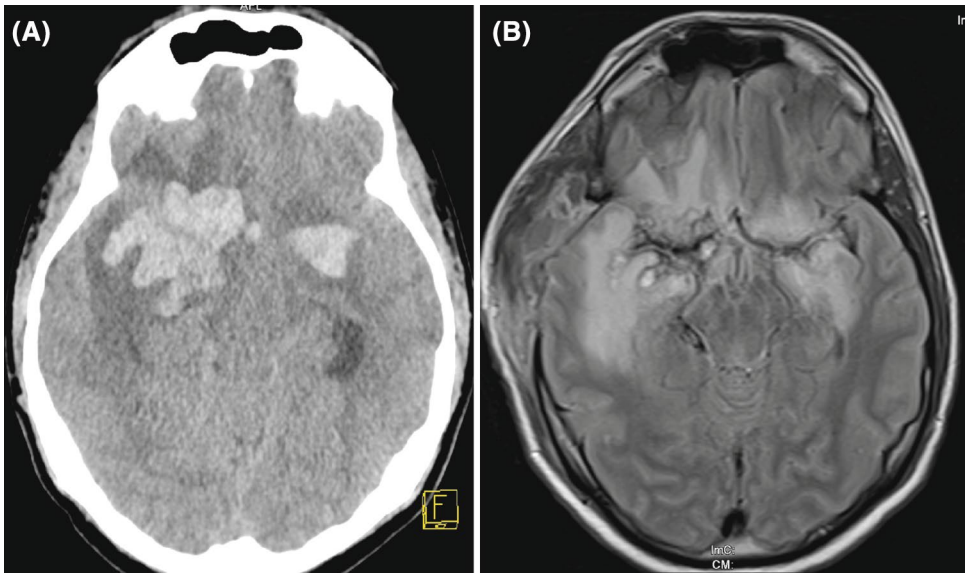

Fig. 2 Representative head CT **a** image after 8 days of acyclovir treatment revealed bilateral space-occupying temporal lobe hemorrhage. **b** Shows T2-weighted fluid-attenuated inversion recovery (FLAIR) sequences 10 days after decompressive right-sided hemicraniotomy

Discussion

In this retrospective study, we present 18 consecutive HSV encephalitis cases to highlight the diagnostic and management challenges that require a high level of suspicion from the treating physicians. The key findings in this study were (1) a subset of patients presented with a normocellular CSF on admission, (2) atypical MRI findings with (a) extensive global brain swelling in one and (b) severe brainstem involvement in another patient, and (3) clinical deterioration despite therapy with acyclovir in three patients.

While CSF studies in HSV encephalitis typically reveal a lymphocytic pleocytosis, a few recent studies have already described an initially normocellular CSF in up to 26.1% of patients [7–9]. Our data also underline the relevance of a normocellular CSF in the initial diagnostic workup of patients with herpes encephalitis. For 3 of our 4 patients with a normocellular CSF, symptom onset had been less than 3 days before the initial lumbar puncture was performed. Previous reports showed that this phenomenon can be encountered within the first 24–48 h after symptom onset [10]. However, 3/3 of these patients eventually developed a CSF pleocytosis on repeated CSF analysis. One patient with a normal CSF cell count on the first lumbar puncture (4 days after symptom onset), continued to have a very close to normal CSF cell count (6 cells/µl) on repeated lumbar puncture 2 days later, which is highly unusual. Noteworthy, this patient had been treated with prednisolone and was found to suffer from a previously unknown immunoglobulin (Ig) G 1–3 subclass deficiency during further workup. This has been linked to an increased risk for bacterial and viral respiratory tract infections [11] as well as recurrent bacterial meningoencephalitis [12, 13]. To our knowledge, no adult cases have so far been published associating HSV encephalitis with an IgG 1–3 subclass deficiency.

It is unclear why some patients present with normocellular CSF. Immunosuppression is one possible explanation [14]. Most importantly, patients with a normocellular CSF tend to receive acyclovir later than other patients, which could explain the poorer clinical prognosis of these patients. As HSV-PCR results are often not available immediately, physicians should, therefore, not be misled by a normal CSF cell count to exclude an infectious cause in patients presenting with an acute encephalopathy.

In our study, all patients had an abnormal EEG and only one patient had a normal MRI, which had been reported to have a sensitivity of about 80–95% for HSV encephalitis [15, 16]. Therefore, MRI and EEG studies should be done in patients with unclear encephalopathy or status epilepticus of unknown etiology, especially if CSF analysis including HSV PCR remains inconclusive [17]. Especially, MRI has been shown to be extremely helpful in establishing a diagnosis of HSV encephalitis [15].

While temporal lobe involvement is seen in over 90% of HSV encephalitis patients on the initial MRI [15], involvement of the brainstem and cerebellum is very rare [18–20]. A prompt initiation of acyclovir therapy and a high level of vigilance in these cases are of great importance as local cytotoxic edema and hemorrhage can lead to a compression of the ventricular system causing an increase in intracranial pressure and ultimately brain herniation.

A clinical deterioration despite prompt acyclovir treatment for HSV encephalitis should raise concern for a resistance to acyclovir, which has been reported especially in immunocompromised patients [21, 22]. However, the clinical relevance of acyclovir resistance is unclear. Here, three patients deteriorated despite acyclovir therapy. In one

patient, genotypic analysis of the HSV isolate did not reveal any mutations linked with acyclovir resistance. For the other two patients, testing could not be done as HSV PCR had either become negative or the HSV viral load had declined to a level that was too low to perform any testing for a resistance on repeated CSF analysis. The fact that HSV viral load in the CSF had substantially decreased argues against a resistance to acyclovir in these two patients. Nevertheless, the possibility of acyclovir resistance could not be excluded as the CSF viral load does not necessarily reflect the viral load in the brain parenchyma. Thus, we suggest to continue acyclovir and to consider adding foscarnet if a substantial deterioration under acyclovir therapy is encountered and positive HSV PCR results persist.

Small foci of hemorrhage within the temporal lobe are a well-known complication of HSV encephalitis but space-occupying intracerebral hemorrhage is very rare [23–25]. In the few case reports available, frank cerebral hemorrhage tended to occur during the second week of therapy. Potential explanations for this time course include the rupture of blood vessels due to HSV-induced vasculitis [24] and a peak in intracranial pressure by day 11–12 [23]. As in the patient presented here, decompressive hemicraniotomy can be a life-saving emergency procedure that has been successfully employed in HSV encephalitis patients after failure of conservative measures to reduce elevated intracranial pressure.

The greatest strength of our study was that we included all consecutive cases of PCR-proven HSV encephalitis treated in our hospital making it a representative sample of the broad spectrum of clinical and neuroradiological presentations of HSV encephalitis. However, our study has several limitations. Most importantly, we report data on a small number of patients which greatly reduced the power of our study and did not allow us to perform a statistical analysis. Our hospital serves as an academic referral center for Southern Bavaria and, therefore, especially difficult to treat patients were transferred to our hospital from small community hospitals. Thus, our patient population might not be fully representative of all HSV encephalitis cases as it reflected a collection of more severely affected patients than in other series.

Conclusions

HSV encephalitis can present with a wide variety of clinical, neuroradiologic and laboratory features requiring a high level of suspicion by the treating physician. Acyclovir therapy should be considered in all patients suspected of an acute encephalopathy based on a combination of clinical findings, laboratory studies, neuroradiologic imaging and EEG findings even without a CSF pleocytosis and before HSV-PCR results become available. In case of deterioration under therapy with acyclovir and repeatedly positive HSV PCR results, additional treatment with foscarnet can be considered.

Author contributorship JPB, UK, MP, HWP and MK designed the study, interpreted the data and wrote the first draft of the manuscript. KD, MP, HWP and MK were involved with clinical patient management. JPB, UK, MP, GP, HWP and MK interpreted the data and edited the manuscript. All authors reviewed and agreed on the final versions of the manuscript.

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Compliance with ethical standards

Conflict of interest Matthias Klein has received financial support from BioMerieux. The other authors declare no financial or other conflicts of interest.

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