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ORIGINAL COMMUNICATION

Predictors of outcome in HSV encephalitis

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Abstract This study aims to explore the clinical features, radiological findings, management and the factors influencing prognosis in PCR-confirmed herpes simplex virus encephalitis (HSE). This is a retrospective review of consecutive patients diagnosed with HSE at Mayo Clinic, Rochester, MN, between January 1995 and December 2013. Only HSE cases confirmed by PCR were included. Univariate and multivariate analysis was used to identify factors associated with good (modified Rankin Scale of 0–2) or poor outcome (mRS of 3–6) at hospital discharge and 1-year follow-up. We identified 45 patients with HSE. Median age was 66 (IQR 53.5–78) years. HSE was caused by HSV-1 in 33 cases and by HSV-2 in 9. Nearly half had seizures upon admission or during hospitalization. The most common regions involved on MRI were the temporal lobe in 35 (87.5 %), insula in 28 (70.0 %), frontal lobe in 27 (67.5 %) and thalamus in 11 (27.5 %) patients. MRI pattern was quite homogeneous with HSV-1 infection, but much more heterogeneous with HSV-2. Good outcome at discharge and at 6–12 months was seen in 16 (35.6 %) and 27 (65.9 %) patients, respectively. On multivariate analyses, older age ($p = 0.001$), coma ($p = 0.008$), restricted diffusion on MRI ($p = 0.005$) and acyclovir started after the first day of admission ($p = 0.050$) were associated with poor outcome at discharge. Older age, development of coma, presence of restricted diffusion on brain MRI and delay in the administration of acyclovir portend poor outcome in HSE. Conversely, presence of seizures, focal neurological deficits, EEG abnormalities and location or extension of FLAIR/T2 abnormalities did not influence functional outcome.

Keywords Encephalitis · Viral infections · Herpes simplex virus · Outcome · Imaging · DWI

Introduction

Herpes simplex virus encephalitis (HSE) is one of the most common causes of sporadic encephalitis with a global incidence of one to four cases per million people per year [1]. More than 90 % of the cases are caused by herpes simplex virus type 1 (HSV-1) and 7 % by herpes simplex virus type 2 (HSV-2) [2]. Before the development of antiviral therapy, HSE-related mortality and morbidity rates were around 70 % and 50 %, respectively [3]. Two major advances led to a frank improvement in outcomes: (1) two large randomized trials in the mid-1980s showing that intravenous acyclovir reduced the 6-month mortality rate to approximately 20 % [4, 5] and (2) introduction of HSV DNA amplification by PCR in the 1990s leading to earlier diagnosis of HSV encephalitis and hence, treatment [1, 6]. Yet, HSE remains a potentially fatal disease and neurological sequelae are still often present among survivors [7, 8].

Earlier studies looking into the factors associated with poor prognosis in HSE included patients diagnosed both clinically and with PCR [7, 9], had a small cohort of PCR-confirmed cases, or did not have a long-term follow-up [10–13]. The biggest study of PCR-confirmed HSV encephalitis cases ($n = 93$) was a multicenter study over a decade ago, but this study did not analyze associated imaging findings (particularly MRI) and electroencephalogram (EEG) changes [14, 15].

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In this study, we aimed to explore the clinical features, management, short- and long-term outcome and the factors influencing prognosis, with particular attention to radiological and EEG findings, in a cohort of PCR-confirmed HSE cases. We also explored the differences in the presentation, imaging, EEG findings and outcome between HSV-1 and HSV-2 cases.

Methods

Study design

We conducted a search for the following terms "HSV encephalitis", "herpes simplex encephalitis", "herpes simplex virus encephalitis", "herpes encephalitis" using our electronic data search system at the Mayo Clinic, Rochester, MN, between January 1995 and December 2013. All records were then manually reviewed and cases with a final diagnosis of HSV encephalitis were included in our final cohort.

Study definitions

Encephalitis was defined according to a recent international consensus statement as presentation with altered mental status (decreased or altered level of consciousness, lethargy or personality change) lasting more than 24 h, with at least three of the following associated manifestations: (1) fever $\geq$38 °C within 72 h before or after presentation, (2) generalized or partial seizures, (3) new onset of focal neurological findings, (4) cerebrospinal fluid (CSF) white blood cell count $\geq$5/mm^3, and (5) EEG abnormality [16]. HSV encephalitis was defined as encephalitis meeting the above criteria and the presence of HSV DNA in the CSF identified by PCR. Clinical outcome was graded using the modified Rankin Scale (mRS). Immunocompromised state was defined as patients diagnosed with AIDS, post-transplantation and receiving chemotherapy or chronic immunosuppressants. Coma was defined as a sum Glasgow Coma Scale score $\leq$8. Thrombocytopenia was defined as platelet count <150,000/mm^3. Seizures were defined clinically or by EEG. Status epilepticus (SE) was defined as continuous seizure activity lasting longer than 5 min or recurrent seizures without regaining consciousness between seizures for more than 5 min. Good outcome was defined as mRS score of 0–2 (patient capable of independent functioning). Post-encephalitic epilepsy was defined by the documentation of recurrent seizures after recovery from the acute episode of encephalitis that required the index hospitalization or the requirement of long-term antiepileptic drugs for >12 months [17].

Inclusion/exclusion criteria

Patients were included in our study if they (1) satisfied the above criteria for HSE encephalitis, (2) were admitted and treated at Mayo Clinic Hospital, and (3) were 18 years or older. Patients were excluded from our study if (1) HSV encephalitis was suspected clinically or radiologically without a positive PCR for HSV DNA, (2) HSV encephalitis was solely diagnosed based on a positive serum antibody, (3) had HSV meningitis only, (4) an alternative final diagnosis was identified, (5) were admitted elsewhere during the acute hospitalization.

Clinical parameters, procedures and investigations

All patients underwent a complete neurological examination performed by a neurologist upon admission, during hospitalization and at discharge. We collected the basic demographic data and information about any pre-existing health conditions from the patient records. During admission, details about the presenting signs/symptoms, duration of the symptoms, physical examination data like the GCS score, presence and type of seizures, focal neurological deficits, laboratory investigations and CSF profile were collected. The trends in the cell counts and CSF values, requirement for intensive care unit (ICU) and mechanical ventilation, and development of new onset seizures, SE or a focal neurological deficit were also recorded. The date of the positive HSV PCR, type of HSV, number of PCR tests done to reach the diagnosis and treatment administered were gathered. Functional status was assessed at discharge, and between 6 months and 1 year after discharge. We also checked for the presence of epilepsy at last follow-up in patients with a minimum follow-up of 12 months.

Radiological examination

Neuroimaging studies (CT and MRI scans) were performed within the first week of admission. The scans were independently reviewed and interpreted by a critical care neurologist (AAR) who was blinded to the clinical information of the patients. Findings recorded were the presence of FLAIR/T2 abnormalities, lateralization of changes, specific involvement of the temporal, frontal lobes, insula, thalamus or other areas of the brain, and presence of hemorrhage, mass effect (i.e., midline shift or regional tissue compression not limited to sulci effacement), contrast enhancement (leptomeningeal, parenchymal, or both) and cortical involvement. The presence of restricted diffusion using diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) was also collected.

EEG recordings

All the EEGs were performed using a 21-channel and employing 10–20 system of electrode placement, within 24 h of suspected encephalitis or seizures. Continuous EEG was reserved for patients who experienced continuous or frequent clinical or electrographic seizures. All the recordings were done in horizontal or vertical runs in bipolar montages and interpreted by an epileptologist with board certification in electroencephalography. The findings that were recorded included background activity, epileptiform discharges [focal sharp spike and wave, periodic lateralized epileptiform dischargers (PLEDs) and generalized periodic discharges (GPDs)] and the presence of focal slowing with the areas involved.

Statistical methods

For quantitative variables, data are presented as median (interquartile range) and for qualitative data as frequency (percentage). Patients were categorized into two groups of good and poor outcome based on their mRS at discharge and at 6–12 months. Univariate analyses were used to determine which variables were associated with poor outcome. Group differences for categorical data were assessed using the χ^2 test and Fisher's exact test as applicable while Mann–Whitney test was used to analyze continuous variables as they were not normally distributed. For the analyses, all the patients who presented with or developed thrombocytopenia, seizures, SE, or focal neurological deficits were grouped together as acute thrombocytopenia, acute seizures, SE and acute focal neurological deficits. A multivariate logistic regression analysis was performed to evaluate associations with outcome at discharge using different combinations of factors associated with outcome on univariate analysis, considering two variables at a time (to avoid over-fitting given the size of the population). Since the population size in the poor outcome group at 6–12 months was only 14, multivariate analyses could not be performed for this endpoint of delayed functional outcome. All statistical tests were two-sided and $p \leq 0.05$ was considered to be statistically significant. Statistical analyses were performed using the JMP 10.0.0 (SAS Institute Inc., Cary, NC, USA).

Results

We identified 239 patients in our initial search with the diagnosis of HSV encephalitis in the medical records. After excluding patients younger than 18 years old, patients without PCR confirmation of diagnosis, patients with a final alternative diagnosis, and patients admitted elsewhere during the acute hospitalization, our final cohort consisted of 45 PCR positive HSE cases. HSE was caused by HSV-1 in 33 and by HSV-2 in 9 cases. In three additional patients, the CSF PCR reports from 1990s mentioned that the PCR was positive for HSV, but did not report the type of HSV.

Clinical characteristics and presentation

The median age of our cohort was 66 (IQR 53.5–78) years with a female predominance (32, 71.1 %). The median duration of symptoms before hospital admission was 4 (IQR 1–7) days and 18 (40 %) patients were referred from other hospitals. Ten patients (22.2 %) were immunocompromised at admission and the cause was chemotherapy in 5 (50 %) patients and chronic steroids in 5 (50 %) patients. The most common symptoms at presentation were confusion in 41 cases (91.1 %), nausea/vomiting in 14 (31.1 %), focal deficits in 14 (31.1 %), focal seizures in 5 (11.1 %) and generalized seizures in 3 (6.7 %). Many patients had more than one symptom at presentation. Seventeen (37.8 %) patients developed seizures during hospitalization, of which 7 (15.6 %) were generalized and 11 (24.4 %) were focal. Eight patients (17.8 %) developed new focal deficits during the hospitalization. Status epilepticus was present in 4 (8.9 %) patients upon admission and it developed in 2 (4.4 %) during the hospitalization. Twenty-seven (60.0 %) patients were admitted to the ICU with a median duration of 3 (IQR 2–11) days and 16 (35.6 %) required mechanical ventilation for a median of 8 (IQR 2.3–17.3) days. Peripheral blood counts showed leukocytosis in 19 (42.2 %) patients at admission and in 25 (56.8 %) during hospitalization while thrombocytopenia was present in 9 (20.0 %) patients at admission and in 21 (47.7 %) during hospitalization. Detailed information on the demographics and clinical presentation of the entire HSE cohort, HSV-1 and HSV-2 viruses are presented in Table 1.

Laboratory findings

All the patients in our study had their CSF analyzed. The median CSF leukocyte count was 64 cells/mcL (range 1–2508) with seven patients having a count of less than 5 cells/mcL. The first PCR was positive for HSV in 41 patients after a median duration of 7 (IQR 3–10.5) days from symptom onset and 0 (IQR 0–3) days from the day of admission. HSE was diagnosed on the day of admission in 22 (48.8 %) patients and in 19 (42.2 %) patients after a median of 2 (IQR 1–5.3) days after admission. The repeat PCR test was positive in 4 (9 %) patients after a median duration of 12.5 (IQR 6.5–16.3) days from the onset of symptoms and 9.5 (IQR 4.5–14.5) days from the day of admission. Three of these patients showed CSF pleocytosis

Table 1 Demographics and clinical presentation of our cohort with HSV encephalitis categorized according to specific etiology

	All HSV cases ($n = 45$)[a]	HSV-1 ($n = 33$)	HSV-2 ($n = 9$)	p value
Age, years	66 (53.5–78)	67 (53.5–77.5)	66 (51.5–79)	0.987
Age > 65	25 (55.6)	18 (54.6)	6 (66.7)	0.511
Male gender	13 (28.9)	11 (33.3)	1 (11.1)	0.161
Immunocompromised	10 (22.2)	7 (21.2)	2 (22.2)	0.948
Duration of symptoms before hospitalization	4 (1–7)	4 (1–7)	2 (1–7)	0.494
Outside hospitalization	18 (40.0)	14 (42.4)	3 (33.3)	0.619
Clinical data				
Temperature	37.9 (37.2–38.8)	38 (37.2–38.6)	37.3 (37.1–37.9)	0.158
GCS[b]	14 (10–15)	14 (10.5–15)	10 (8–14)	0.182
Confusion[b]	41 (91.1)	31 (93.9)	7 (77.8)	0.181
Headache[b]	10 (22.2)	9 (27.3)	1 (11.1)	0.283
Photophobia[b]	2 (4.4)	1 (3.1)	1 (11.1)	0.359
Nausea/vomiting[b]	14 (31.1)	12 (36.4)	2 (22.2)	0.413
Seizures[c]	21 (46.7)	15 (45.5)	4 (44.4)	0.957
Generalized seizures[c]	10 (22.2)	6 (18.2)	2 (22.2)	0.784
Focal seizures[c]	13 (28.9)	11 (33.3)	2 (22.2)	0.513
Status epilepticus[c]	6 (13.3)	3 (9.1)	3 (33.3)	0.089
Focal deficits[c]	18 (40.0)	15 (45.5)	3 (33.3)	0.511
Acute thrombocytopenia[c]	21 (47.7)	14 (43.8)	4 (44.4)	0.971
ICU admission	27 (60.0)	20 (60.6)	5 (55.6)	0.784
Coma	15 (33.3)	9 (27.3)	4 (44.4)	0.334
Intubation/ventilation	16 (35.6)	10 (30.3)	4 (44.4)	0.432
Treatment				
Time to acyclovir	1 (1–3)	1 (1–2.5)	2 (1–2.5)	0.711
Acyclovir on day 1	23 (51.1)	19 (57.6)	4 (44.4)	0.484
Duration of acyclovir	21 (14–21)	21 (14–21)	21 (14–21)	0.627
Outcome				
Hospital stay	14 (8.8–23)	14 (9–23)	11 (3–25.5)	0.391
Hospital mortality	7 (15.6)	4 (12.1)	2 (22.2)	0.463
Good outcome at discharge	16 (35.6)	12 (36.4)	4 (44.4)	0.661
Good outcome at 6–12 months[d]	27 (65.9)	20 (68.9)	5 (55.6)	0.464
Epilepsy at last follow-up[e]	10 (45.5)	10 (55.6)	0 (0.0)	0.037

Data presented as n (%) or median (IQR)

[a] In three patients PCR report did not specify if HSV-1 or HSV-2. One patient was diagnosed in 1996 and two in 1998

[b] On admission

[c] On admission and during hospitalization

[d] Outcome at 6–12 months available in 41 patients

[e] Based on 22 patients (18 with HSV-1, 3 with HSV-2 and 1 with unknown HSV type) for whom this information was available

on their first CSF analyses with a count of 19, 89, 90 cells/mcL while one patient had a count of 2 cells/mcL. Two of these patients were diagnosed with HSV-2 and were immunocompromised because of chemotherapy. Positive serum HSV antibody was documented in only 2 (4.4 %) patients, but both of them also had a positive CSF PCR with HSV-1. Fifteen patients had acyclovir started before the PCR was checked. Among the four patients with initially negative PCR, two had acyclovir started before the CSF was obtained. The detailed CSF findings of the entire cohort are listed in Table 2.

Imaging findings

All patients except one underwent radiological testing, with CT scans in 42 (93.3 %) and MRI in 40 (88.9 %) patients.

Table 2 CSF and radiological findings of the cohort with HSV encephalitis categorized according to specific etiology

	All HSV cases ($n = 45$)[a]	HSV-1 ($n = 33$)	HSV-2 ($n = 9$)	p value
CSF findings				
CSF glucose (mg/dL)	61 (50.3–72)	61.5 (52.8–72)	39 (37–57.5)	0.011
CSF glucose/blood glucose	0.50 (0.44–0.57)	0.51 (0.45–0.57)	0.41 (0.38–0.62)	0.379
CSF protein (mg/dL)	75 (57.5–105)	76 (56.5–103)	71 (50.5–285)	0.509
CSF RBCs (n/mcL)	4 (2–54)	2 (2–34)	17 (8.5–531)	0.048
CSF leukocytes (n/mcL)	64 (12–191.5)	55 (16–153.5)	90 (13.5–708)	0.416
	64 (1–2508)[b]	55 (1–1199)[b]	90 (1–2508)[b]	
CSF neutrophils (%)	2 (0.3–13)	2 (0–7)	4 (1–36)	0.127
CSF lymphocytes (%)	74.5 (55.3–89.3)	74.5 (58.3–89.3)	83 (37.5–94.5)	0.815
CSF monocytes (%)	19 (7–29)	20 (10–30)	6 (3–24)	0.032
Radiological findings				
CT done	42 (93.3)	31 (93.9)	8 (88.9)	
MRI done	40 (88.9)	31 (93.9)	7 (77.8)	
FLAIR/T2	38 (95.0)	30 (96.8)	6 (85.7)	0.296
Right side	11 (28.9)	9 (30.0)	1 (16.7)	
Left side	11 (28.9)	8 (26.7)	3 (50.0)	
Bilateral	16 (42.1)	13 (43.3)	2 (33.3)	
Temporal lobe involvement	35 (87.5)	30 (96.8)	3 (42.9)	<0.001
Frontal lobe involvement	27 (67.5)	21 (67.7)	6 (85.7)	0.317
Insula	28 (70.0)	25 (80.7)	2 (28.6)	0.008
Thalamus	11 (27.5)	9 (29.1)	2 (28.6)	0.981
Hemorrhage	2 (5.0)	1 (3.2)	1 (14.3)	0.296
Mass effect	16 (40.0)	13 (41.9)	3 (42.9)	0.964
Restricted diffusion[c]	17 (50.0)	13 (48.2)	4 (57.1)	0.671
Contrast enhancement[d]	23 (69.7)	19 (70.4)	4 (80.0)	0.651
Leptomeningeal	1 (4.3)	1 (5.2)	0 (0.0)	
Parenchymal	17 (73.9)	14 (73.7)	3 (75.0)	
Both	5 (21.7)	4 (21.1)	1 (25.0)	
Cortical involvement	36 (90.0)	29 (93.6)	6 (85.7)	0.518
EEG findings				
EEG done	36 (80.0)	26 (78.8)	8 (88.9)	
Epileptic discharges present	26 (72.2)	23 (88.5)	2 (25.0)	<0.001
PLEDs	23 (88.5)	20 (87.0)	2 (100.0)	0.465
Focal slowing	21 (58.3)	18 (69.2)	2 (25.0)	0.026

Data presented as n (%) or median (IQR)

[a] In three patients PCR report did not specify if HSV-1 or HSV-2

[b] Data presented as median (range)

[c] Diffusion-weighted imaging (DWI) was done in 34 patients

[d] Contrast was administered to 33 patients

Our radiological data was collected preferentially from the MRI scans. MRI was done after a median duration of 2 (IQR 1–8.5) days from the day of admission. On MRI examination, 38 (95.0 %) patients showed FLAIR/T2 abnormalities, 17 (50.0 %) had restricted diffusion, 23 (69.7 %) had contrast enhancement and 36 (90.0 %) had cortical involvement. The most common regions involved were the temporal lobe in 35 (87.5 %) followed by insula in 28 (70.0 %), frontal lobe in 27 (67.5 %), thalamus in 11 (27.5 %) and parietal lobe in 2 (5.0 %) patients. Hemorrhage was present in 2 (5.0 %) while mass effect was seen in 16 (40.0 %) patients. As detailed in Table 2, patients with HSV-1 encephalitis had temporal and insular FLAIR signal abnormalities with cortical involvement in nearly all cases and significantly more frequent than HSV-2 cases. The typical radiological pattern of HSV-1 encephalitis (FLAIR sequence) is shown in Fig. 1 and the diffusion abnormalities on diffusion-weighted imaging (DWI)

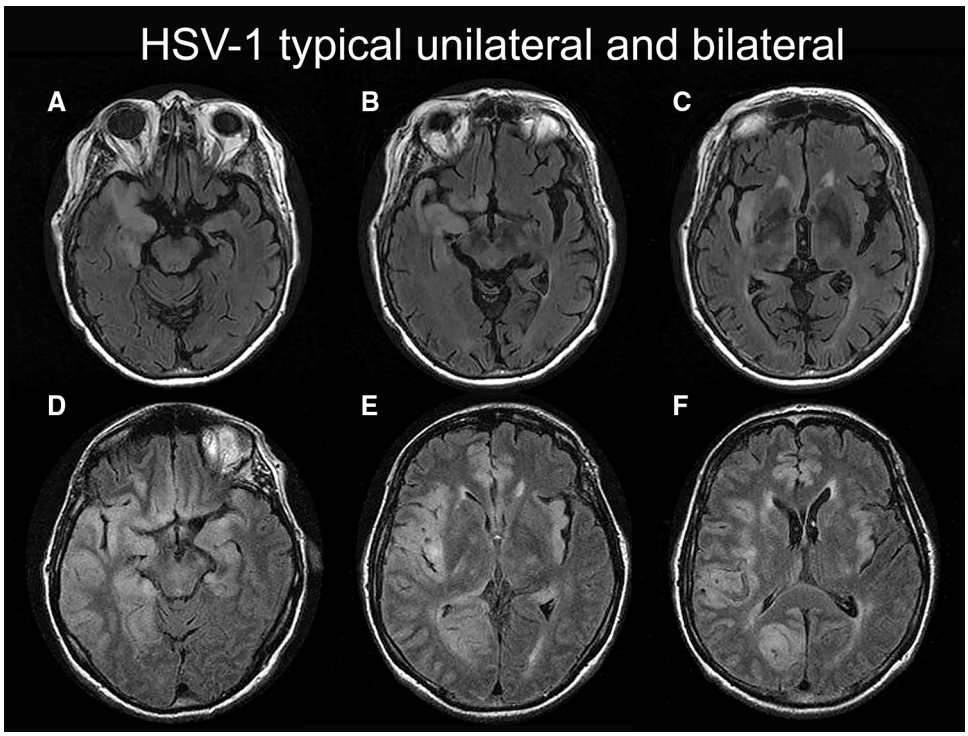

Fig. 1 Typical radiological pattern of HSV-1 encephalitis on MRI (FLAIR sequence). **a**–**c** Case with unilateral left temporal, insular and fronto-orbital involvement. **d**–**f** Case with extensive bilateral hemispheric involvement. Notice subtle posterior thalamic changes in images **c** and **e**

sequence are shown in Fig. 2. The MRI findings (FLAIR sequence) in HSV-2 encephalitis are shown in Fig. 3.

EEG findings

EEGs were done in 36 (80.0 %) patients (Table 2); 34 (94.4 %) patients showed slow background activity [theta in 7 (19.4 %) and delta in 27 (75.0 %)]. Interictal epileptiform discharges (IEDs) were seen in 26 (72.2 %) patients and they were unilateral in 21 (80.8 %) and bilateral in 5 (19.2 %) patients. Focal sharp wave and spikes were seen in 3 (11.5 %) patients, whereas PLEDs and GPDs were seen in 22 (84.6 %) and 1 (3.8 %) patient, respectively. Focal slowing was present in 21 (58.3 %) patients and the most common brain regions affected were the temporal lobe in 13 (61.9 %), an entire hemisphere in 4 (19.0 %), occipital in 3 (14.3 %) and frontal in 1 (4.7 %) patient. As shown in Table 2, epileptiform discharges were significantly more common in cases of HSV-1 encephalitis as compared to HSV-2.

Treatment and outcome

All patients were treated with intravenous acyclovir. The median time between hospital admission and initiation was 0 (IQR 0–2) days and 23 (51.1 %) patients received it on the first day of admission. Twenty-seven (60.0 %) patients received it for duration of 21 days and the median duration of therapy for the entire cohort was 21 (IQR 14–21) days. Good outcome at discharge was seen in 16 (35.6 %) patients. Among all the patients with good outcome at discharge ($n = 16$), only 4 patients (25.0 %) were treated between 1995 and 2004 while 75.0 % were treated in the second decade of our study ($p = 0.009$). Follow-up between 6 and 12 months after discharge was available for 41 patients and 27 (65.9 %) of them had a good outcome. Among the patients who were alive at discharge, 27 (79.4 %) had a good outcome at 6–12 months. We did not have follow-up information for four patients; at discharge two of these patients had a mRS of 3 and the other two had a mRS of 4. Twenty-two patients (48.8 %) had a follow-up of more than 12 months with a median follow-up of 65.3 (41.44–116.3) months. Post-encephalitic epilepsy was noted in 10 (45.5 %) of these patients.

Predictors of outcome

Univariate analysis was performed to determine the factors associated with outcome at discharge and at 6–12 months (Tables 3, 4). The outcome analyses for the cohort of HSV-1 patients at 6–12 months are presented in Table 5. Most of the variables associated with outcome at discharge and at 6–12 months were similar except for acute thrombocytopenia. On multivariate analyses, the factors associated with poor outcome were older age (unit odds ratio = 1.07; 95 % CI = 1.01–1.14, $p = 0.001$), coma (OR = 12.81; 95 % CI 1.57–285.31, $p = 0.008$), restricted diffusion on MRI (OR = 8.54; 95 % CI = 1.87–51.74, $p = 0.005$) and

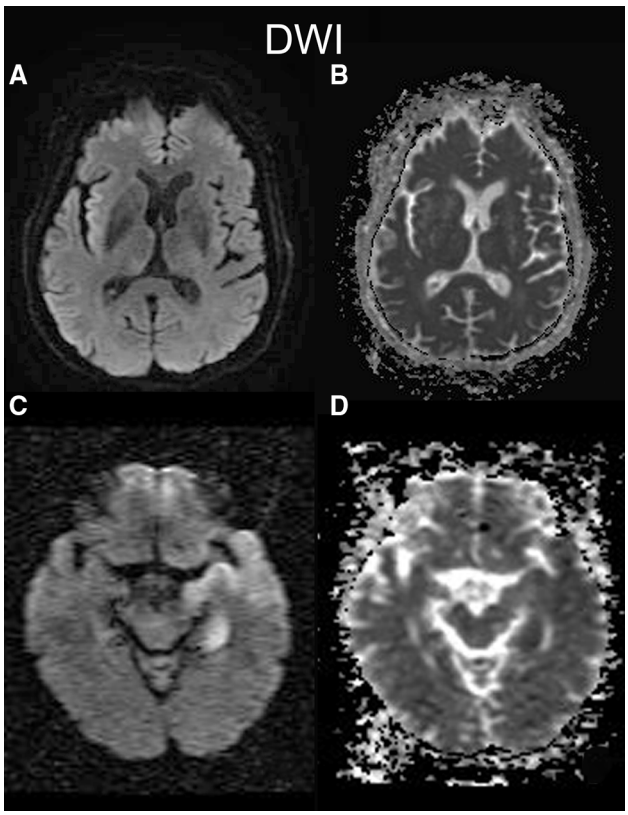

Fig. 2 Examples of two cases of HSV-1 encephalitis (**a**–**b** and **c**–**d**) with areas of restricted diffusion on diffusion-weighted imaging (DWI) sequence. **a** DWI abnormality affecting the right insular cortex. **b** Corresponding changes on the apparent diffusion coefficient (ADC) map. **c** DWI abnormality on the left temporal lobe. **d** Corresponding changes on the ADC map

acyclovir started after the first day of admission (OR = 5.13; 95 % CI = 1.08–21.45, $p = 0.050$).

Discussion

Our study of consecutive cases of PCR-confirmed HSV encephalitis, with detailed analyses of their radiologic and EEG changes, describes the presentation, management and short and long-term outcome of the disease and highlights the factors associated with functional recovery. The factors associated with poor outcome in our study were older age, development of coma, presence of restricted diffusion on brain MRI and delay in the administration of acyclovir. Presence of seizures, focal neurological deficits, EEG abnormalities and the presence or the extent of FLAIR/T2 abnormalities did not affect the outcome. The majority of patients with HSV encephalitis had a favorable outcome at 1 year.

Our study included a relatively sizable series of HSV-2 encephalitis cases. The prevalence of HSV-2 cases in our cohort was greater than previously reported [7, 14, 18] and allowed us to compare the HSV-1 and HSV-2 cases in terms of their clinical, radiological, and electroencephalographic characteristics. HSV-2 cases had a similar clinical presentation to HSV-1 cases, but lacked the distinctive MRI features of HSV-1 and had less epileptiform abnormalities on EEG.

The typical MRI abnormality in HSV-1 encephalitis was the presence of asymmetric FLAIR hyperintensity corresponding to edematous changes in the gray matter of the mesial temporal lobes, inferior frontal lobes and insula [19, 20]. In our study all the HSV-1 encephalitis patients except for one (with a poor quality MRI scan) showed these findings. Almost 97 % of them had FLAIR/T2 abnormalities, with temporal lobe and cortical involvement. Insula was affected in approximately 80 % of cases and frontal lobe in nearly 70 %. A previously less well described thalamic involvement was also noted in 29.1 % of HSV-1 cases ipsilateral to the dominant temporal lobe findings. Rarely changes in the parietal lobes were also seen. Only one patient with HSV-1 encephalitis did not have the typical MRI findings. This patient presented with a mild disease and the quality of the MRI was poor and difficult to interpret. Thus, the diagnosis of HSV-1 encephalitis is unlikely in the absence of these radiological findings on MRI. The MRI findings of HSV-2 cases tended to be much milder and inconsistent, with nearly 85 % of them showing FLAIR/T2 abnormalities and cortical involvement, 40 % of them with temporal lobe involvement and nearly a quarter with involvement of the insular regions. These patients were thought to be immunologically normal at the time of their encephalitis.

The most novel finding of our study is the recognition of an association between diffusion abnormalities and poor outcome at discharge and at 1 year. Restricted diffusion on MRI was present in more than two-thirds of the patients with HSE who experienced poor outcome. This radiological finding had been recently shown to predict outcome in a small cohort of neonatal HSE but had not been previously reported in adults [21]. Abnormalities in DWI are attributed to cytotoxic edema, and this has been shown to be the earliest change in HSE. It has also been found to be significantly better for lesion conspicuity in comparison to T2/FLAIR sequences for acute HSE (1–10 days), but not in chronic HSE [20]. No other abnormalities on MRI, including the extent of the inflammatory changes visualized on FLAIR sequences, specific affected regions, cortical involvement or contrast enhancement were associated with poor outcome. We have previously reported similar findings in a larger cohort of cases of acute encephalitis of various etiologies [22].

Delay in the initiation of acyclovir after admission has been shown to be associated with an unfavorable outcome

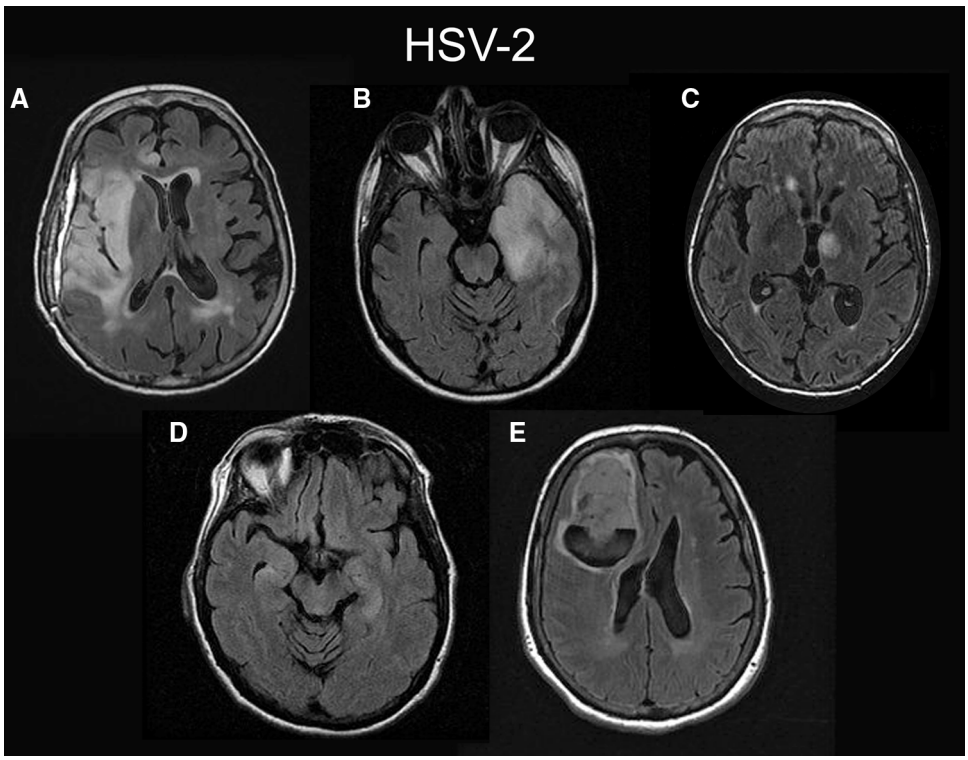

Fig. 3 Examples of various radiological manifestations seen in cases of HSV-2 encephalitis. All images are from FLAIR sequence. **a** Extensive hyperintensity involving the right temporal and frontal lobes. **b** Inflammatory changes restricted to the left temporal lobe. **c** Focal area of signal abnormality in the left thalamus. **d** Faint hyperintensity involving bilateral limbic structures and the inferior frontal cortex bilaterally. **e** Large right frontal hemorrhage; the patient's encephalopathy failed to improve after hematoma evacuation and actually progressed, EEG showed bilateral independent periodic epileptiform discharges and seizures, and PCR for HSV-2 was positive on her CSF

both at discharge and at 1 year, and longer delays have the most serious neurological consequences [7, 10, 12, 14]. In our study, delay in initiation of acyclovir was significantly associated with unfavorable outcome while 68.6 % of patients who received acyclovir on the first day of admission had a favorable outcome at discharge. The most common reasons for the delay in the initiation of therapy are the failure to consider HSE while awaiting the results of CSF analysis, relatively normal CSF findings with CSF white cell count $<10/mm^3$, chronic alcohol abuse, severe underlying disease and a delay in obtaining brain imaging following hospital admission [10, 23]. Unlike other prognostic factors associated with poor outcome, late initiation of acyclovir is easily modifiable. Our findings confirm the importance of starting acyclovir empirically in any patient with possible HSE while awaiting the results of the CSF PCR.

The EEG is often abnormal in HSE, with the most prominent finding being the presence of PLEDs, slow background activity with a focal attenuation and electrographic seizures [16]. In our study, epileptic discharges and focal slowing were more common in HSV-1 encephalitis as compared to HSV-2. However, the presence of these abnormalities was not associated with short- or long-term outcome. On long-term follow-up, epilepsy occurred in HSV-1 cases with an incidence of 55.6 %, while this complication was not seen after HSV-2 infection in our cohort.

At discharge, 35.5 % of the patients had a favorable outcome and were capable of independent living and only 7 (15.6 %) patients died in the hospital. Among patients who survived the hospitalization, 79.4 % achieved a good outcome. These outcomes are better than in some previous studies, but comparable to other more recent reports [7, 12, 14]. The percentage of patients with a good outcome is slightly lower than in a recent trial that reported a good outcome in 90.2 % of cases (defined as no or minimal neuropsychological impairment by the Mattis Dementia Rating Scale at 12 months). However, the two cohorts cannot be directly compared. While our cohort included consecutive patients with all degrees of severity and immune status, that trial was restricted to immunocompetent subjects who had survived the acute hospitalization without severe deficits and were expected to survive for at least 90 days [24]. We also found that the outcomes in our cohort were significantly improved in the second decade of our study (2005–2013). This probably reflects the improving standards of care, prompter diagnosis and, most importantly, early administration of treatment.

The main limitations of our study are inherent to its retrospective design and the size of the cohort. Our hospital is a large referral center and more than a third of the patients included in this study were referred from other hospitals. Therefore, our findings might be affected by referral bias and might not be representative of the experience in other settings. Although we present short- and

Table 3 Variables associated with functional outcome at discharge: univariate analyses

	Unfavorable outcome ($n = 29$)	Favorable outcome ($n = 16$)	p value
Age	70 (57–80)	56 (50–67.5)	0.015
Age > 65	19 (65.5)	6 (37.5)	0.045
Male gender	8 (27.6)	5 (31.3)	0.796
Immunocompromised	9 (31.1)	1 (6.3)	0.039
Duration of symptoms before hospitalization	3 (1–7)	4.5 (1–8.5)	0.476
Outside hospitalization	13 (44.8)	5 (31.3)	0.369
Hospital stay	17 (12.5–24)	9.5 (6–13.5)	0.005
Temp on admission	38.1 (37.2–39)	37.6 (36.9–38.1)	0.032
GCS	12.5 (10–14.8)	14 (10–15)	0.202
Seizures	14 (48.3)	7 (43.8)	0.771
Generalized seizures	8 (27.6)	2 (12.5)	0.228
Focal seizures	8 (27.6)	5 (31.3)	0.796
Status epilepticus	4 (13.8)	2 (12.5)	0.902
Focal deficits	12 (41.4)	6 (37.5)	0.799
Coma	14 (48.3)	1 (6.3)	0.002
Acute thrombocytopenia	18 (64.3)	3 (18.8)	0.003
ICU	21 (72.4)	6 (37.5)	0.022
Intubation/ventilation	11 (37.9)	5 (31.3)	0.653
CSF findings			
CSF glucose (mg/dL)	61 (47.5–75.5)	58 (55–70)	0.833
CSF glucose/blood glucose	0.48 (0.44–0.56)	0.51 (0.40–0.57)	0.531
CSF protein (mg/dL)	70 (56.5–99.5)	79 (60–108.8)	0.421
CSF RBCs (n/mcL)	4 (1–62)	5.5 (2–23)	0.989
CSF leukocytes (n/mcL)	45 (7–108.5)	94.5 (28–274)	0.140
CSF neutrophils (%)	5 (1–31)	1.5 (0–3)	0.069
CSF lymphocytes (%)	72 (36–85.3)	81.5 (65.5–93.8)	0.103
MRI findings ($n = 40$)			
FLAIR/T2	24 (96.0)	14 (93.3)	0.712
Bilateral involvement	11 (44.0)	7 (46.7)	0.869
Temporal lobe involvement	22 (88.0)	13 (86.7)	0.902
Frontal lobe involvement	18 (72.0)	9 (60.0)	0.435
Insula	18 (72.0)	10 (66.7)	0.723
Hemorrhage	1 (4.0)	1 (6.7)	0.712
Mass effect	11 (44.0)	5 (33.3)	0.503
Restricted diffusion	13 (68.4)	4 (26.7)	0.014
Contrast enhancement	15 (71.4)	9 (60.0)	0.475
Cortical involvement	22 (88.0)	14 (93.3)	0.576
Thalamic involvement	7 (28.0)	4 (26.7)	0.927
EEG ($n = 36$)			
Discharges present	19 (76.0)	7 (63.6)	0.452
PLEDs	17 (89.5)	6 (85.7)	0.794
Focal slowing	15 (60.0)	6 (54.6)	0.760
Viral type			
HSV 1	21 (80.8)	12 (75.0)	0.660
HSV 2	5 (19.2)	4 (25.0)	0.660
Treatment and outcome			
Time to acyclovir	2 (1–3.3)	1 (1–19)	0.049
Acyclovir on day 1	12 (41.4)	11 (68.8)	0.050
Good outcome at 6–12 months[a]	11 (44.0)	16 (100.0)	<0.001
Epilepsy at last follow-up[b]	7 (70.0)	3 (25.0)	0.032

Data presented as n (%) or median (IQR)

[a] Outcome at 6–12 months available in 41 patients

[b] Based on 22 patients for whom this information was available

Table 4 Variables associated with functional outcome for all patients at 6–12 months: univariate analyses

	Unfavorable outcome (14)	Favorable outcome (27)	*p* value
Age	75 (63.8–81.5)	57 (50–69)	0.007
Age > 65	11 (78.6)	11 (40.7)	0.018
Male gender	3 (21.4)	8 (29.6)	0.569
Immunocompromised	6 (42.9)	3 (11.1)	0.023
Duration of symptoms before hospitalization	2.5 (1–7.8)	5 (1–7)	0.411
Outside hospitalization	4 (28.6)	11 (40.7)	0.439
Hospital stay	15.5 (12.8–23.8)	12 (8–25)	0.107
Temperature on admission	38.1 (37.2–39.2)	37.9 (37.1–38.8)	0.179
GCS	14 (10–15)	14 (10.5–15)	0.869
Seizures	7 (50.0)	14 (51.9)	0.910
Generalized seizures	4 (28.6)	6 (22.2)	0.656
Focal seizures	4 (28.6)	9 (33.3)	0.755
Status epilepticus	3 (21.4)	3 (11.1)	0.386
Focal deficits	4 (28.6)	12 (44.4)	0.318
Coma	9 (64.3)	4 (14.8)	0.001
Acute thrombocytopenia	9 (64.3)	9 (34.6)	0.071
ICU	11 (78.6)	13 (48.2)	0.051
Intubation/ventilation	5 (35.7)	8 (29.6)	0.693
CSF findings			
CSF glucose (mg/dL)	61.5 (41.3–78)	59 (50.8–70.5)	0.955
CSF glucose/blood glucose	0.48 (0.44–0.60)	0.50 (0.41–0.56)	0.893
CSF protein (mg/dL)	72 (58.3–113.3)	74 (57–105)	0.902
CSF RBCs (n/mcL)	2 (1–64.5)	4 (2–25)	0.522
CSF nucleated cells (n/mcL)	50 (2.8–96.8)	80 (26–259)	0.111
CSF PMN leukocytes (%)	5 (1–18.5)	2 (0–7)	0.279
CSF lymphocytes (%)	76 (46–84)	72 (58.3–91.3)	0.561
MRI ($n = 36$)			
FLAIR/T2	11 (100.0)	23 (92.0)	0.219
Bilateral involvement	6 (54.6)	11 (44.0)	0.559
Temporal lobe involvement	9 (81.8)	22 (88.0)	0.628
Frontal lobe involvement	7 (63.6)	16 (64.0)	0.983
Insula	7 (63.6)	17 (68.0)	0.799
Hemorrhage	1 (9.1)	1 (4.0)	0.554
Mass effect	6 (54.6)	8 (32.0)	0.204
Restricted diffusion	7 (77.8)	9 (39.1)	0.045
Contrast enhancement	6 (66.7)	14 (70.0)	0.858
Cortical involvement	10 (90.9)	23 (88.0)	0.795
Thalamic involvement	2 (18.2)	7 (28.0)	0.522
EEG ($n = 32$)			
Discharges present	9 (75.0)	14 (70.0)	0.759
PLEDs	9 (100.0)	12 (85.7)	0.147
Focal slowing	8 (66.7)	10 (50.0)	0.354
Viral type			
HSV 1	9 (69.2)	20 (80.0)	0.465
HSV 2	4 (30.8)	5 (20.0)	0.465
Treatment and secondary epilepsy			
Time to acyclovir	2.5 (1–5)	1 (1–2)	0.040
Acyclovir on day 1	5 (35.7)	16 (59.3)	0.151
Epilepsy at last follow-up[a]	1 (50.0)	9 (45.0)	0.893

Data presented as *n* (%) or median (IQR)

[a] Based on 22 patients for whom this information was available

Table 5 Variables associated with functional outcome at 6–12 months for HSV-1 encephalitis patients only: univariate analyses

	Unfavorable outcome (9)	Favorable outcome (20)	*p* value
Age	77 (65–84)	57 (50.3–68.8)	0.015
Age > 65	7 (77.8)	8 (40.0)	0.046
Male gender	2 (22.2)	7 (35.0)	0.483
Immunocompromised	3 (33.3)	3 (15.0)	0.273
Duration of symptoms before hospitalization	3 (1–10.5)	5 (1.3–8.5)	0.553
Outside hospitalization	3 (33.3)	8 (40.0)	0.731
Hospital stay	15 (12.5–20)	11 (7.3–21.8)	0.163
Temperature on admission	38.5 (37.6–39.2)	37.9 (37–38.5)	0.109
GCS	13 (10.8–15)	14 (12–15)	0.617
Seizures	4 (44.4)	11 (55.5)	0.599
Generalized seizures	2 (22.2)	4 (20.0)	0.892
Focal seizures	3 (33.3)	8 (40.0)	0.731
Status epilepticus	1 (11.1)	2 (10.0)	0.928
Focal deficits	3 (33.3)	10 (50.0)	0.399
Coma	5 (55.6)	2 (10.0)	0.009
Acute thrombocytopenia	5 (55.6)	6 (31.6)	0.226
ICU	7 (77.8)	10 (50.0)	0.149
Intubation/ventilation	2 (22.2)	5 (25.0)	0.871
CSF findings			
CSF glucose (mg/dL)	62 (52.5–78)	60 (51–70)	0.445
CSF glucose/blood glucose	0.52 (0.47–0.60)	0.51 (0.44–0.56)	0.396
CSF protein (mg/dL)	68 (57.5–92)	75 (56.3–105)	0.724
CSF RBCs (n/mcL)	2 (1–41.3)	3 (2–12.3)	0.409
CSF nucleated cells (n/mcL)	45 (4–97)	84 (28 –232)	0.098
CSF PMN leukocytes (%)	5 (0.5–29.3)	1 (0–3)	0.158
CSF lymphocytes (%)	78 (24.8–84.5)	71 (65–91)	0.559
MRI ($n = 27$)			
FLAIR/T2	7 (100.0)	19 (95.0)	0.434
Bilateral involvement	5 (71.4)	8 (40.0)	0.148
Temporal lobe involvement	7 (100.0)	19 (95.0)	0.434
Frontal lobe involvement	4 (57.1)	13 (65.0)	0.713
Insula	5 (71.4)	16 (80.0)	0.645
Hemorrhage	0 (0.0)	1 (5.0)	0.435
Mass effect	4 (57.1)	7 (35.0)	0.308
Restricted diffusion	5 (83.3)	7 (36.8)	0.041
Contrast enhancement	3 (60.0)	13 (72.2)	0.605
Cortical involvement	6 (85.7)	19 (95.0)	0.448
Thalamus involvement	2 (28.6)	5 (25.0)	0.854
EEG ($n = 22$)			
Epileptiform discharges	6 (85.7)	14 (93.3)	0.575
PLEDs	6 (100.0)	12 (85.7)	0.218
Focal slowing	6 (85.7)	9 (60.0)	0.207
Treatment and secondary epilepsy			
Time to acyclovir	3 (1–4.5)	1 (1–2)	0.125
Acyclovir on day 1	4 (44.4)	13 (65.0)	0.303
Epilepsy at last follow-up[a]	1 (50.0)	9 (56.3)	0.867

Data presented as *n* (%) or median (IQR)

[a] Based on 18 patients for whom this information was available

long-term functional outcome, we were not able to assess neuropsychiatric outcomes. The size of our cohort was not sufficiently large to allow a multivariable analysis for variables associated with functional outcome strictly among HSV-1 cases. Since there were only 10 patients who had epilepsy at last follow-up, we could not analyze the factors predicting the development of this complication.

Conclusion

Our study of a consecutive series of patients with PCR-confirmed HSE indicate that the outcomes of HSE have improved over time and are now generally good, irrespective of clinical presentation or the extension of radiographic involvement. Younger age, preservation of consciousness, earlier treatment and absence of DWI abnormalities portend a favorable outcome. Conversely, presence of restricted diffusion on MRI should be considered a marker of unfavorable prognosis. Treatment with acyclovir should be initiated immediately in any suspected case and aggressive treatment should be pursued in patients with severe presentation because good functional recovery is possible.

Compliance with ethical standards

The study was approved by the Mayo Clinic Institutional Review Board and all patients or their representatives signed a consent form allowing their participation in the study. The research has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Cinque P, Cleator GM, Weber T, Monteyne P, Sindic CJ, van Loon AM (1996) The role of laboratory investigation in the diagnosis and management of patients with suspected herpes simplex encephalitis: a consensus report. The EU Concerted Action on Virus Meningitis and Encephalitis. J Neurol Neurosurg Psychiatry 61(4):339–345
2. Aurelius E, Johansson B, Skoldenberg B, Forsgren M (1993) Encephalitis in immunocompetent patients due to herpes simplex virus type 1 or 2 as determined by type-specific polymerase chain reaction and antibody assays of cerebrospinal fluid. J Med Virol 39(3):179–186
3. Whitley RJ, Soong SJ, Dolin R, Galasso GJ, Ch'ien LT, Alford CA (1977) Adenine arabinoside therapy of biopsy-proved herpes simplex encephalitis. National Institute of Allergy and Infectious Diseases collaborative antiviral study. N Engl J Med 297(6):289–294. doi:10.1056/NEJM197708112970601
4. Skoldenberg B, Forsgren M, Alestig K, Bergstrom T, Burman L, Dahlqvist E, Forkman A, Fryden A, Lovgren K, Norlin K et al (1984) Acyclovir versus vidarabine in herpes simplex encephalitis. Randomised multicentre study in consecutive Swedish patients. Lancet 2(8405):707–711
5. Whitley RJ, Alford CA, Hirsch MS, Schooley RT, Luby JP, Aoki FY, Hanley D, Nahmias AJ, Soong SJ (1986) Vidarabine versus acyclovir therapy in herpes simplex encephalitis. N Engl J Med 314(3):144–149. doi:10.1056/NEJM198601163140303
6. Aurelius E, Johansson B, Skoldenberg B, Staland A, Forsgren M (1991) Rapid diagnosis of herpes simplex encephalitis by nested polymerase chain reaction assay of cerebrospinal fluid. Lancet 337(8735):189–192
7. Sili U, Kaya A, Mert A (2014) Herpes simplex virus encephalitis: clinical manifestations, diagnosis and outcome in 106 adult patients. J Clin Virol 60(2):112–118. doi:10.1016/j.jcv.2014.03.010
8. Stahl JP, Mailles A, De Broucker T (2012) Herpes simplex encephalitis and management of acyclovir in encephalitis patients in France. Epidemiol Infect 140(2):372–381. doi:10.1017/S0950268811000483
9. Sheybani F, Arabikhan HR, Naderi HR (2013) Herpes simplex encephalitis (HSE) and its outcome in the Patients who were Admitted to a Tertiary Care Hospital in Mashhad, Iran, over a 10-year Period. J Clin Diagn Res 7(8):1626–1628. doi:10.7860/JCDR/2013/5661.3221
10. Hughes PS, Jackson AC (2012) Delays in initiation of acyclovir therapy in herpes simplex encephalitis. Can J Neurol Sci 39(5):644–648
11. Kapur N, Barker S, Burrows EH, Ellison D, Brice J, Illis LS, Scholey K, Colbourn C, Wilson B, Loates M (1994) Herpes simplex encephalitis: long term magnetic resonance imaging and neuropsychological profile. J Neurol Neurosurg Psychiatry 57(11):1334–1342
12. McGrath N, Anderson NE, Croxson MC, Powell KF (1997) Herpes simplex encephalitis treated with acyclovir: diagnosis and long term outcome. J Neurol Neurosurg Psychiatry 63(3):321–326
13. Pleumpanupat P, Danchaivijitr N, Danchaivijitr C (2009) Retrospective study of patients with herpes simplex encephalitis and positive CSF PCR. J Med Assoc Thai 92(Suppl 2):S95–100
14. Raschilas F, Wolff M, Delatour F, Chaffaut C, De Broucker T, Chevret S, Lebon P, Canton P, Rozenberg F (2002) Outcome of and prognostic factors for herpes simplex encephalitis in adult patients: results of a multicenter study. Clin Infect Dis 35(3):254–260. doi:10.1086/341405
15. Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, Hartman BJ, Kaplan SL, Scheld WM, Whitley RJ (2008) The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 47(3):303–327. doi:10.1086/589747
16. Venkatesan A, Tunkel AR, Bloch KC, Lauring AS, Sejvar J, Bitnun A, Stahl JP, Mailles A, Drebot M, Rupprecht CE, Yoder J, Cope JR, Wilson MR, Whitley RJ, Sullivan J, Granerod J, Jones C, Eastwood K, Ward KN, Durrheim DN, Solbrig MV, Guo-Dong L, Glaser CA (2013) Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis 57(8):1114–1128. doi:10.1093/cid/cit458
17. Singh TD, Fugate JE, Hocker SE, Rabinstein AA (2015) Postencephalitic epilepsy: clinical characteristics and predictors. Epilepsia 56(1):133–138. doi:10.1111/epi.12879
18. Chow FC, Glaser CA, Sheriff H, Xia D, Messenger S, Whitley R, Venkatesan A (2015) Use of clinical and neuroimaging characteristics to distinguish temporal lobe herpes simplex encephalitis from its mimics. Clin Infect Dis 60(9):1377–1383. doi:10.1093/cid/civ051
19. Misra UK, Kalita J, Phadke RV, Wadwekar V, Boruah DK, Srivastava A, Maurya PK, Bhattacharyya A (2010) Usefulness of various MRI sequences in the diagnosis of viral encephalitis. Acta Trop 116(3):206–211. doi:10.1016/j.actatropica.2010.08.007

20. Sawlani V (2009) Diffusion-weighted imaging and apparent diffusion coefficient evaluation of herpes simplex encephalitis and Japanese encephalitis. J Neurol Sci 287(1–2):221–226. doi:10.1016/j.jns.2009.07.010
21. Okanishi T, Yamamoto H, Hosokawa T, Ando N, Nagayama Y, Hashimoto Y, Maihara T, Goto T, Kubota T, Kawaguchi C, Yoshida H, Sugiura K, Itomi S, Ohno K, Takanashi J, Hayakawa M, Otsubo H, Okumura A (2015) Diffusion-weighted MRI for early diagnosis of neonatal herpes simplex encephalitis. Brain Dev 37(4):423–431. doi:10.1016/j.braindev.2014.07.006
22. Singh TD, Fugate JE, Rabinstein AA (2015) The spectrum of acute encephalitis: causes, management, and predictors of outcome. Neurology 84(4):359–366. doi:10.1212/WNL.0000000000001190
23. Poissy J, Wolff M, Dewilde A, Rozenberg F, Raschilas F, Blas M, Georges H, Chaffaut C, Yazdanpanah Y (2009) Factors associated with delay to acyclovir administration in 184 patients with herpes simplex virus encephalitis. Clin Microbiol Infect 15(6):560–564. doi:10.1111/j.1469-0691.2009.02735.x
24. Gnann JW Jr, Skoldenberg B, Hart J, Aurelius E, Schliamser S, Studahl M, Eriksson BM, Hanley D, Aoki F, Jackson AC, Griffiths P, Miedzinski L, Hanfelt-Goade D, Hinthorn D, Ahlm C, Aksamit A, Cruz-Flores S, Dale I, Cloud G, Jester P, Whitley RJ (2015) Herpes simplex encephalitis: lack of clinical benefit of long-term valacyclovir therapy. Clin Infect Dis. doi:10.1093/cid/civ369