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ORIGINAL PAPER

Herpes simplex and varicella zoster CNS infections: clinical presentations, treatments and outcomes

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Abstract
Objectives To describe the clinical manifestations, cerebrospinal fluid (CSF) characteristics, imaging studies and prognostic factors of adverse clinical outcomes (ACO) among adults with herpes simplex virus (HSV) or varicella zoster virus (VZV) CNS infections.
Methods Retrospective review of adult patients with positive HSV or VZV polymerase chain reaction on CSF from an observational study of meningitis or encephalitis in Houston, TX (2004–2014), and New Orleans, LA (1999–2008).
Results Ninety-eight adults patients were identified; 25 had encephalitis [20 (20.4 %) HSV, 5 (5.1 %) VZV], and 73 had meningitis [60 (61.1 %) HSV and 13 (13.3 %) VZV]. HSV and VZV had similar presentations except for nausea ($P < 0.01$) and rash ($P < 0.001$). The CSF profile did not differ between HSV and VZV infection. Abnormal neuroimaging findings were found in 11.6 % (10/86) brain CTs and 21.3 % (16/75) brain MRIs. The EEG was abnormal in 57.9 % (11/19). Sixteen patients (16.3 %) had an ACO (10 HSV encephalitis, 3 VZV encephalitis and 3 VZV meningitis). Intravenous acyclovir administered within 48 h was protective against an ACO [OR 0.19 (0.04–0.80), $P = 0.02$). However, on logistic regression only Charlson comorbidity score >1 and an encephalitis presentation were independently associated with an ACO. The treatment for HSV meningitis was variable, and all patients had a good clinical outcome.
Conclusion Alpha herpes CNS infections due to HSV and VZV infections have similar clinical and laboratory manifestations. ACO was observed more frequently in those patients with comorbidities and an encephalitis presentation.

Keywords Herpes simplex virus · Varicella zoster virus · Meningitis · Encephalitis · Clinical outcome

Introduction

The Alphaherpesvirinae, a subfamily of Herpesviridae, includes both herpes simplex virus (HSV) and varicella zoster virus (VZV). Neurotropism, latency, and recurrent infection are unique characteristics of this group [1, 2]. In addition to recurrent mucocutaneous lesions, HSV and VZV contribute significantly to central nervous system (CNS) infections worldwide. The spectrum of HSV and VZV neurologic disease is broad, ranging from self-limiting aseptic meningitis to encephalitis causing permanent disability and death. Recurrent benign lymphocytic meningitis or Mollaret's syndrome associated with HSV infection has been often described [3]. A recent epidemiological study in the USA suggested that HSV was the most common identifiable cause of viral encephalitis (13.8 %) in hospitalized patients and accounted for 21.8 % of all encephalitis inpatient deaths. VZV accounted for 0.4 % of all encephalitis, and the mortality rate was similar to HSV encephalitis [4].

The detection of HSV or VZV by polymerase chain reaction (PCR) in the cerebrospinal fluid (CSF) is the current gold-standard diagnostic test because of its high

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sensitivity and specificity [5, 6]. Several antiviral medications are effective against HSV and VZV infections. The benefit of intravenous (IV) acyclovir has been well established in HSV encephalitis [7] and in the neonatal HSV infection [8], but data evaluating antiviral drugs for HSV meningitis are scattered and inconclusive [9, 10]. The data on antiviral therapy in VZV infections and outcome data on both HSV and VZV CNS infections are also limited to small case series.

We aimed to describe the clinical manifestations, CSF characteristics, imaging studies and prognostic factors of adverse clinical outcomes (ACO) of HSV and VZV central nervous system (CNS) infections in an adult population.

Methods

Patient samples and case definitions

A case was defined as an adult patient (age $\geq$ 18 years) with symptoms of community-acquired CNS infection (fever, headache, stiff neck, altered mental status or focal neurologic symptoms), a CSF leukocyte count >5 cells/mm^3, and a positive CSF HSV or VZV PCR. Patients were identified from an observational study of meningitis and encephalitis in Houston, TX, from 2004 to 2014, and New Orleans, LA, from 1999 to 2008. This study was approved by the Institutional Review Board at University of Texas Medical School at Houston and at Tulane University in New Orleans. Encephalitis was defined using the International Encephalitis Consortium case definition [11]. Meningitis was defined by the presence of clinical symptoms of meningeal irritation (headache, stiff neck, nausea or vomiting) excluding encephalitis cases. HSV and VZV infection was confirmed by positive CSF PCR using Federal Drug & Administration (FDA)-approved assays. Comorbidity was assessed by the Charlson's comorbidity index [12]. Adverse clinical outcome (ACO) was assessed at time of discharge and determined with the Glasgow Outcome Scale from 1 to 4. In this scale, a score of 1 indicates death; 2 vegetative state (inability to interact with the environment); 3 severe disability (unable to live independently but follows commands); 4 moderate disability (unable to return to work or school but able to live independently); and 5 mild or no disability (able to return to work or school) [13].

Clinical data

Baseline patient characteristics were recorded at the time when the patient presented to the emergency department (ED). Demographic data (age, sex and race) and presenting symptoms (abnormal mental status, seizure, headache, acute focal deficit, stiff neck, nausea, photophobia, fever and rash) were retrieved from medical records. The laboratory data (CSF WBC, percentage of CSF lymphocytes, percentage of CSF granulocytes, red blood cells (RBC) in CSF, CSF protein, CSF glucose, serum WBC, serum glucose and serum creatinine) were reviewed. The relevant imaging studies, brain computed tomography scan (CT) and brain magnetic resonance imaging (MRI) were reviewed by board-certified neuroradiologists. Only intraparenchymal abnormalities were classified as an abnormal imaging study. Abnormal electroencephalography (EEG) was determined by the report of a board-certified neurologist. The duration from time of hospital arrival to lumbar puncture (LP) including CSF PCR requisition and detailed antiviral therapy during hospitalization and at discharge were reviewed.

Statistical method

Fisher's exact test, Chi-square test, and Student *t* test were used for binomial data, and ANOVA was conducted for continuous variable. All statistical tests were two-sided, and $P \leq 0.05$ was considered to be statistically significant. All statistical analyses were performed by using SPSS for MAC version 21.

Results

A total of 98 adults patients were identified; 80 (81.6 %) with positive CSF HSV PCR and 18 (18.4 %) with positive CSF VZV PCR; 25 had encephalitis [20 (20.4 %) HSV, 5 (5.1 %) VZV] and 73 had meningitis [60 (61.1 %) HSV and 13 (13.3 %) VZV].

Patients with HSV and VZV did not differ in age, sex or race. HSV and VZV had similar presentations except for nausea ($P < 0.01$) being more common with HSV and vesicular rash ($P < 0.001$) being more common with VZV. One patient with HSV meningitis had an ulcer consistent with herpes genitalis. Fifteen VZV cases had a dermatomal vesicular rash. VZV infection was associated more commonly with comorbidities ($P < 0.001$) and HIV infection ($P = 0.03$; see Table 1).

In this study, the interval of arrival time to lumbar puncture including PCR test requisition was broad (1–264 h) with a median duration of 23 h. The CSF profile did not differ between HSV and VZV infection (see Table 2). Of note, two patients had CSF PCR positive for both VZV and EBV. One patient with VZV encephalitis was found to also have positive anti-*N*-Methyl-D-aspartate (NMDA) receptor antibodies. Length of stay was longer in VZV infection than HSV infection (median of 8 days vs. 4 days; $P = 0.03$).

The data of each subgroup (HSV meningitis, HSV encephalitis, VZV meningitis and VZV encephalitis) are

Table 1 Baseline characteristics and outcome of 98 patients who have central nervous system infection caused by herpes simplex virus (HSV) or varicella zoster virus (VZV)

Clinical features	HSV infection $N = 80$ (%)	VZV infection $N = 18$ (%)	P values
Female	50 (62.5)	9 (50)	0.33
Age median (range in years)	40.5 (18–82)	46.5 (25–88)	0.55
Age >60 years	5 (27.8)	8 (10)	0.45
Caucasian race	39 (44.8)	10 (55.6)	0.60
Coexisting medical conditions			
Charlson's comorbidity index >1[a]	11 (13.8)	13 (72.2)	<0.001
HIV infection	5/74 (6.8)	4/14 (2.9)	0.03
Presenting symptoms			
Days ill (days)	2 (1–21)	3 (1–10)	0.23
Abnormal mental status[b]	20/80 (25)	5/18 (27.8)	0.96
Seizure	4/75 (5.3)	2/18 (11.1)	0.34
Headache	73/79 (92.4)	15/18 (83.3)	0.57
Acute focal deficit	11/69 (13.8)	2/17 (11.8)	0.83
Stiff neck	48/77 (62.3)	4/13 (30.8)	0.06
Nausea	54/76 (71.1)	5/16 (31.2)	<0.01
Photophobia	32/72 (44.4)	6/13 (46.1)	1.00
Fever	40/80 (50)	7/17 (41.2)	0.51
Rash	1/79 (1.3)	15/18 (83.3)	<0.001
Encephalitis	20/80 (25)	5/18 (27.8)	0.96
Outcome			
Median hospital length of stay (days)	4	8	0.03
Adverse clinical outcome[c]	10 (12.5)[d]	6 (33.3)[e]	0.07
Death	0	1	
Vegetative state	2	1	
Severe disability	7	1	
Moderate disability	1	3	

[a] Charlson's comorbidity index: predicting mortality by weighting comorbid conditions [11]

[b] Disorientation, extreme lethargy or Glasgow coma scale score <15

[c] Glasgow outcome scale 1–4 [13]

[d] All encephalitis; two with vegetative states (one discharged to hospice service and one with ventilator dependent), seven with severe disability (dependent requiring inpatient rehabilitation) and one moderate disability (expressive aphasia)

[e] Three encephalitis [one death (however, the cause of death was not felt to be associated with VZV infection because the patient was improved with IV acyclovir), one with vegetative state (also tested positive for NDMA in the CSF and had chronic abnormal jerking, tracheostomy) and one with severe disability (dependent requiring inpatient rehabilitation)] and three meningitis [all with moderate disability (one with keratitis, one with persistent facial droop and one with non-specific neurological deficit)]

reported in Table 3. HSV meningitis and HSV encephalitis did not differ in gender but the HSV encephalitis group was older, ($P < 0.001$). Caucasian race was also statistically different ($P = 0.01$). Also, more patients with comorbidities were in the HSV encephalitis group ($P < 0.001$) than HSV meningitis. In contrast, the clinical features and coexisting medical conditions did not differ between VZV meningitis and encephalitis. Presenting symptoms was different according to the encephalitis definition [11]. However, HSV meningitis presented with more headache and stiff neck compared to HSV encephalitis. There was no statistically difference in the CSF profile between HSV meningitis and encephalitis, but the CSF profile of VZV encephalitis revealed higher RBC ($P < 0.05$). As expected, more imaging findings were seen in HSV encephalitis. The median hospital stay was longer in the encephalitis group ($P < 0.001$ in HSV infection and $P < 0.05$ in VZV infection). ACO was significantly higher in HSV encephalitis but there was no difference in VZV infections.

The majority of the patients underwent neuroimaging. Brain CT scans were completed in 86 patients (87.7 %) with ten being abnormal. Of those, six patients had HSV encephalitis (2 with abnormal density in unilateral temporal/frontotemporal area, 1 with subacute infarct in the left insula cortex and 3 with non-specific findings), one HSV meningitis (increased density to the medial inferior left

Table 2 Laboratory data and imaging study of 98 patients who have central nervous system infection caused by herpes simplex virus (HSV) or varicella zoster virus (VZV)

	HSV infection; $N = 80$ Median (range)	VZV infection; $N = 18$ Median (range)	P values
CSF[a] analysis			
CSF WBC[b] (cells/mm^3)	265 (6–6400)	111.5 (9–3190)	0.48
CSF lymphocyte (%)	88.5 (2–100)	86 (51–99)	0.65
CSF granulocyte (%)	3 (0–94)	1 (0–25)	0.46
CSF RBC[c] (cells/mm^3)	15 (0–58,000)	18.5 (0–16,500)	0.83
CSF protein (mg/dL)	98.5 (18–445)	80 (40–360)	0.72
CSF glucose (mg/dL)	52 (35–169)	51 (38–112)	0.51

[a] Cerebrospinal fluid

[b] White blood cells

[c] Red blood cells

temporal bone and left pterygoid region of uncertain etiology), and three VZV encephalitis (2 patients with non-specific findings and 1 with right frontal periventricular white matter low-density lesion). Brain MRIs were performed in 75 patients (76.5 %) with noted abnormal findings in 13 HSV encephalitis (5 with unilateral abnormality in temporal or frontotemporal area, 1 with bilateral frontotemporal abnormality, 1 with subacute infarct and early petechial hemorrhage in left insular cortex, and 6 with non-specific findings or data not available), one HSV meningitis (questionable minimal diffuse bifrontal lobe cortical T2 FLAIR hyper intensity) and one VZV meningitis (non-specific multiple small T2 FLAIR hyper intense foci in the subcortical and deep white matter). The EEG was abnormal in nine HSV encephalitis patients (3 with abnormal frontal and/or temporal waveform, 6 with non-specific abnormal patterns) and two VZV encephalitis patients (both with non-specific abnormal patterns). None of the meningitis patients had abnormal EEG.

The data for clinical outcome upon discharge were available in all patients (see Tables 1, 3). None of the HSV meningitis patients exhibited an ACO upon discharge. Sixteen patients (16.3 %) had an ACO including: 10 HSV encephalitis patients (two with vegetative states, seven with severe disability and one moderate disability) and six VZV patients. Of the six VZV patients, three had VZV encephalitis (one death, one with vegetative state and one with severe disability) and three VZV meningitis (one with keratitis, one with persistent facial droop and one with non-specific neurological deficit). ACO (see Table 4) were associated with age more than 65 years, comorbidities (Charlson's comorbidity index > 1), antiviral therapy administered in <48 h and an encephalitis presentation on bivariate analysis. However, on logistic regression, only comorbidities and an encephalitis presentation were associated with an ACO. Other parameters (gender, race and CSF profile) were not associated with ACO ($P > 0.05$).

Antiviral therapy was administered in 77 patients (78.6 %). Complete therapy details (type, administered route, duration and time of initiation) were available in 65 patients. The duration from the arrival time to treatment initiation (time to treatment) ranged from 1 to 128 h with median duration of 17 h. The median time to treatment in ACO group was different than those without ACO (37 vs. 15 h; $P = 0.03$). Antiviral therapy administered in <48 h was protective against an ACO [OR 0.19 (0.04–0.80), $P = 0.02$).

The treatment for HSV meningitis was highly variable (see Fig. 1). Detailed treatment data were available in 59 HSV meningitis patients. Eighteen (30 %) patients did not receive antivirals while hospitalized, but one patient received oral valacyclovir for 30 days at discharge. Thirty-seven patients (61.7 %) received initial IV acyclovir therapy (median duration 4 days; range 1–9 days) and four patients (6.7 %) received only oral therapy while hospitalized. The median duration of any antiviral treatment was 4 days with a range from 1 to 14 days during hospitalization. All patients with HSV meningitis had a good clinical outcome regardless of their therapy.

Discussion

To the best of our knowledge, our study is the most comprehensive review of alphaherpesviral CNS infections with HSV and VZV in adults from the USA. One prior epidemiological study (137 VZV, 72 HSV-1 and 32 HSV-2 CNS infections) reported the increasing incidence of alpha herpes viruses CNS infection with age and difference in HSV-2 CNS infection rates by gender; however, that study did not describe the clinical course. [14] Other reports are smaller [15, 16].

The presenting symptoms of HSV and VZV CNS infection were almost identical except for zoster rash, which

Table 3 Baseline characteristics, CSF analysis, imaging studies and outcome of 98 patients with alpha herpes CNS infection by subgroup

	HSV meningitis $N = 60$	HSV encephalitis $N = 20$	*P* values	VZV meningitis $N = 13$	VZV encephalitis $N = 5$	*P* values
Clinical features						
Female	40 (66.7 %)	10 (50 %)	0.20	6 (46.2 %)	2 (40 %)	0.60
Age median (range in years)	36	55.5	<0.001	42	62	0.08
Age >60 years	1 (1.7 %)	7 (35 %)	<0.001	2 (15.4 %)	3 (60 %)	0.06
Caucasian race	24 (40 %)	15 (75 %)	0.01	7 (53.8 %)	1 (20 %)	0.20
Coexisting medical conditions						
Charlson's comorbidity index >1[a]	3 (5 %)	10 (50 %)	<0.001	8 (61.55)	3 (60 %)	0.95
HIV infection	3 (5 %)	2 (10 %)	0.59	4/10 (40.0 %)	0/4	0.25
Presenting symptoms						
Days ill (days)	2	2.5	0.03	3.5	3	0.62
Abnormal mental status[b]	0	20 (100 %)	<0.001	0	5 (100 %)	<0.001
Seizure	0	4 (20 %)	0.003	0	2 (40 %)	0.02
Headache	60 (100 %)	13 (65 %)	<0.001	13 (100 %)	2 (40 %)	0.04
Acute focal deficit	0	11 (55 %)	<0.001	2 (15.4 %)	0	0.33
Stiff neck	44/58 (75.9 %)	4 (20 %)	<0.001	4/11 (36.4 %)	0/2	1.00
Nausea	44/59 (74.6 %)	10 (50 %)	0.21	5/12 (41.7 %)	0/4	0.25
Photophobia	29/54 (50 %)	3 (15 %)	0.05	6/9 (46.2 %)	0/4	0.07
Fever	32 (53.3 %)	8 (40 %)	0.16	6/12 (50 %)	1 (20 %)	0.25
Rash	1 (1.7 %)	0	0.57	11 (84.6 %)	4 (80 %)	0.81
CSF[ca] analysis						
CSF WBC[db] (cells/mm^3)	325	265	0.69	150	68	0.39
CSF lymphocyte (%)	90	82	0.87	86	86	0.48
CSF granulocyte (%)	3	2.5	0.65	1	1	0.72
CSF RBC[ec] (cells/mm^3)	14	29	0.61	15	22	0.03
CSF protein (mg/dL)	99.5	82	0.72	81	79	0.47
CSF glucose (mg/dL)	52	55.5	0.73	73	62.2	0.05
Imaging studies[f]						
Abnormal CT findings	1/52 (1.9 %)	6/18 (33.3 %)	<0.001	0/12 (0 %)	3/4 (75 %)	0.07
Abnormal MRI findings	1/52 (1.9 %)	14/17 (70 %)	<0.001	1/4 (25 %)	1/2 (50 %)	0.33
Abnormal EEG	0/3 (0 %)	9/13 (45 %)	0.06	0/1	2/2 (100 %)	0.33
Outcome						
Median hospital length of stay (days)	3	11	<0.001	5	14	0.02
Adverse clinical outcome[cg]	0	10 (50 %)	<0.001	3/9 (335 %)	3 (60 %)	0.16
Death		0		01	10	
Vegetative state		2		01	10	
Severe disability		7		01	10	
Moderate disability		1		30	03	

[a] Charlson's comorbidity index: predicting mortality by weighting comorbid conditions [11]

[b] Disorientation, extreme lethargy or Glasgow coma scale score <15

[c] Glasgow outcome scale 1–4 [13]

[cd] Cerebrospinal fluid

[de] White blood cells

[fe] Red blood cells

[gf] For further details, please see result section in full text

[g] Glasgow outcome scale 1–4 [13]

Table 4 Bivariate analysis and logistic regression analysis of factors associated with adverse clinical outcomes (ACO)[a] in 98 patients who have central nervous system infection caused by alpha herpes viruses

Characteristic	Bivariate		Logistic regression	
	OR (95 % CI)	*P* values	OR (95 % CI)	*P* values
Charlson's score >1[b]	28.0 (6.8–114.2)	<0.001	14.6 (2.7–79.2)	<0.001
Encephalitis	25.3 (6.2–102.2)	<0.001	20.3 (3.8–106.7)	0.02
Age >65 years	11.7 (2.8–48.7)	<0.001	–	–
Antiviral therapy within 48 h	0.191 (0.04–0.798)	0.02	–	–

[a] Adverse clinical outcome was categorized as a Glasgow outcome scale 1–4 [13]

[b] Charlson's comorbidity index: predicting mortality by weighting co morbidity conditions [11]

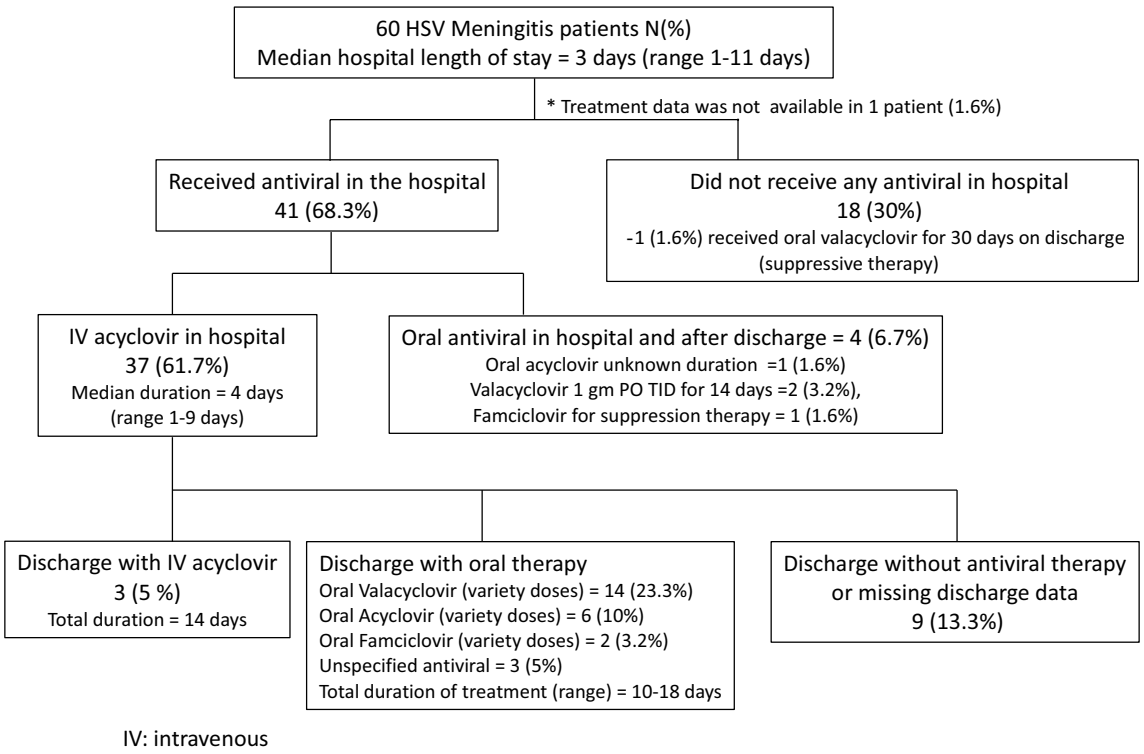

Fig. 1 Herpes simplex virus (HSV) meningitis treatment

was similar to the prior reports [16–18]. Cutaneous manifestations in HSV CNS infections are uncommon. In 1980s study, 8 % of patients with primary genital herpes infection were observed to have concurrent aseptic meningitis [19]. Cutaneous manifestations were found in only 4–7 % of patients in previously published reports of HSV CNS infection [9, 20]. In our series, one HSV meningitis patient and none of HSV encephalitis patients had concurrent genital HSV lesion. Seventeen percent of the VZV patients did not have concurrent vesicular rash consistent with previous reports of *Zoster sine herpete* [21]. Thus, CSF HSV and VZV PCR test should be sent routinely in patients with meningitis and encephalitis regardless whether skin manifestations are present.

The small subgroup analysis data (Table 3) must be interpreted cautiously as the sample size in each group was relatively small. As expected, patients with encephalitis had more abnormal mental status, seizures and abnormal neurological deficit as the standard definition to define encephalitis cases was used in this study [11]. Stiff neck and photophobia were more common in meningitis patients likely because meningitis patients were less delirious and able to report symptoms.

The CSF profiles were indistinguishable among alpha herpes CNS infections. One previous smaller study found differences in percentage of CSF monocyte count in VZV CNS infection [17], but this finding was not consistent with other reports [15, 16]. One of our patients with VZV infection had anti-NMDA receptor antibodies. Several prior reports have observed alpha herpes virus CNS infection preceding or occurring concurrently with the autoimmune anti-NMDA receptor encephalitis, [22–24]

suggesting an immunologic link [25]. Testing for the presence of anti-NMDA receptor antibodies could be considered if the patient does not improve after the antiviral treatment.

Despite evidence that routine brain imaging in patients with suspected CNS infection is not necessary unless patient is (1) >60 years, (2) immunocompromised, (3) has history of CNS disease, and (4) had seizure within 1 week, or (5) has symptoms of neurologic abnormalities [26], 61 patients (62 %) underwent a head CT scan without an indication. No significant intracranial abnormalities were found in those patients without an indication. Our study reassured the limited utility of neuroimaging study among patient without specific conditions.

While treatment for HSV encephalitis is recommended [27, 28], the treatment for HSV meningitis is controversial. A randomized control trial did not suggest a benefit of valacyclovir in the prevention of recurrent HSV meningitis [29]. Although most HSV meningitis patients did well after their infection, complications have been reported [10, 30, 31] of note, and the definition of meningitis in each report was slightly different raising possibility of patients with myelitis or neuritis having been enrolled [10]. In our study, none of the HSV meningitis patients had abnormal neurological deficits or significant complications at discharge. None of the immunocompetent patients had a complication regardless of the treatment regimens upon discharge (Fig. 1). Our data were similar to a previous smaller study with 49 HSV-2 meningitis patients that treatment had no impact among immunocompetent group [32, 33]. Although the benefit of antiviral treatment in immunocompetent patients is not established, most patients received antiviral therapy in our study, similar to previous reports [32, 33].

Prior studies have suggested that immunocompromised patients may benefit from antiviral treatment for HSV meningitis, reducing post-infection complications [10, 34, 35]. In our series, only three patients had comorbidities (two with HIV infection and one with Wegener granulomatosis receiving chronic steroid therapy). All received antiviral treatment and did well upon discharge. Once antiviral treatment is considered, the risk and benefit must be carefully weighed. The intravenous infusion of acyclovir is known to cause acute renal injury and there is also the risk of the central line infection [9]. Oral valacyclovir could be an alternative option as it has excellent CSF concentration and has been used successfully used in HSV encephalitis in case series [36].

Because alpha herpes viruses are one of the most common causes of CNS infections, the prediction of ACO would aid the clinicians in planning for appropriate treatment and guiding discussions about prognosis. Overall, ACOs were associated with age older than 65 years, more comorbidities (a Charlson's comorbidity score > 1), and antiviral therapy <48 h and with the presentation of encephalitis on bivariate analysis. Independent prognostic factors after multivariable logistic regression analyses revealed that a Charlson's score >1 and an encephalitis presentation were associated with ACO ($P < 0.05$). The median time to treatment in ACO group was different from those without ACO (37 vs. 15 h; $P = 0.03$). Antiviral therapy administered in <48 h was protective against an ACO [OR 0.19 (0.04–0.80), $P = 0.02$), but it was not significant on logistic regression analysis. Previous data mostly described unfavorable outcome of herpes encephalitis associated with delayed antiviral therapy [7, 37, 38]. The data specific to all types of alpha herpes CNS infection are still lacking. A recent retrospective cohort study of 438 patients with HSV meningoencephalitis revealed that the outcome predictors were age, GCS and the elapsed time period between onset of symptoms and treatment. Although this study was large, they used the common terminology of "meningoencephalitis" (did not subclassified into meningitis vs. encephalitis), and the comorbidities were not explored in this study [37]. Our study included extensive patient-level data from the admission to discharge. The course of hospitalization and investigations were well described. We used standard definitions for encephalitis and avoided the overlapping terminology of "meningoencephalitis." This may explain why we did not observe any complication among HSV meningitis patients.

Our study has some limitations. First, as the study was retrospective, we were not able to retrieve follow up data. Such data would be important targets for future studies to learn about benefit of HSV meningitis treatment, especially in immunocompetent hosts. In addition, our cohort did not include other CNS infections such as myelitis and neuritis. The data of specific type of HSV (1 vs. 2) were not available. This would be interesting information as the epidemiology of HSV infection is changing (e.g., HSV1 is now more prevalent in genital HSV infection) [39].

In conclusion, we described the clinical manifestations, CSF characteristics, imaging studies and prognostic factors of adverse clinical outcomes (ACO) of HSV and VZV central nervous system (CNS) infections in an adult population. Several interesting observations are notable. First, based on the similarity of HSV and VZV CNS infections, we strongly support testing both HSV and VZV PCR in any patient who presents with aseptic meningitis or encephalitis regardless of skin manifestations. Second, the yield of neuroimaging was low among HSV meningitis population in our study. Unless there are specific indications, unnecessary imaging could be avoided. Third, the factors associated with ACO include Charlson's comorbidity index more than one and the presentation of encephalitis. Lastly, our

data supported that HSV meningitis treatment regimens are diverse, but overall outcome is good.

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Compliance with ethical standards

Conflict of interest All the authors declare that they have not conflict of interest.

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