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Use of Clinical and Neuroimaging Characteristics to Distinguish Temporal Lobe Herpes Simplex Encephalitis From Its Mimics

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Background. We describe the spectrum of etiologies associated with temporal lobe (TL) encephalitis and identify clinical and radiologic features that distinguish herpes simplex encephalitis (HSE) from its mimics.

Methods. We reviewed all adult cases of encephalitis with TL abnormalities on magnetic resonance imaging (MRI) from the California Encephalitis Project. We evaluated the association between specific clinical and MRI characteristics and HSE compared with other causes of TL encephalitis and used multivariate logistic modeling to identify radiologic predictors of HSE.

Results. Of 251 cases of TL encephalitis, 43% had an infectious etiology compared with 16% with a noninfectious etiology. Of infectious etiologies, herpes simplex virus was the most commonly identified agent (n = 60), followed by tuberculosis (n = 8) and varicella zoster virus (n = 7). Of noninfectious etiologies, more than half (n = 21) were due to autoimmune disease. Patients with HSE were older (56.8 vs 50.2 years; $P = .012$), more likely to be white (53% vs 35%; $P = .013$), more likely to present acutely (88% vs 64%; $P = .001$) and with a fever (80% vs 49%; $P < .001$), and less likely to present with a rash (2% vs 15%; $P = .010$). In a multivariate model, bilateral TL involvement (odds ratio [OR], 0.38; 95% confidence interval [CI], .18–.79; $P = .010$) and lesions outside the TL, insula, or cingulate (OR, 0.37; 95% CI, .18–.74; $P = .005$) were associated with lower odds of HSE.

Conclusions. In addition to HSE, other infectious and noninfectious etiologies should be considered in the differential diagnosis for TL encephalitis, depending on the presentation. Specific clinical and imaging features may aid in distinguishing HSE from non-HSE causes of TL encephalitis.

Keywords. encephalitis; temporal lobe; herpes simplex; brain infection; magnetic resonance imaging.

Herpes simplex encephalitis (HSE), the most frequently identified cause of sporadic focal encephalitis worldwide [1, 2], is commonly associated with temporal lobe (TL) abnormalities on neuroimaging. However, mimics of HSE, including other infections and increasingly recognized autoimmune causes, have been described in cases of TL encephalitis. In a multicenter study of encephalopathy with TL involvement from 1989, one-third of patients with an identified etiology were diagnosed with an HSE mimic [3]. However, computed tomographic (CT) scans were unable to differentiate HSE from its mimics. Since then, magnetic resonance imaging (MRI) has become a widely used tool in resource-rich areas to evaluate encephalopathy and encephalitis. Given the higher sensitivity of brain MRI compared with CT in the detection of imaging abnormalities in HSE, specific MRI characteristics may be particularly useful for distinguishing HSE from other etiologies of TL encephalitis. For example, abnormalities on diffusion weighted imaging, indicative of ischemic injury, have been shown to be more sensitive than T2-weighted

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imaging, especially early in the course of infection, in the diagnosis of HSE in adults [4, 5] and may correlate with clinical response to treatment [6]. We examined cases referred to the California Encephalitis Project (CEP) with TL abnormalities to investigate the spectrum of etiologies associated with TL encephalitis and to identify specific clinical and radiologic features that distinguish HSE from its mimics.

METHODS

We performed a retrospective review of adult encephalitis cases with TL abnormalities on MRI in the CEP. Details of the design of the CEP have been published [7]. In brief, clinicians from >200 California hospitals referred potential cases to the CEP between 1998 and 2012. Referrals were made using a standardized case history form for epidemiologic, demographic, clinical, laboratory, and radiologic data. Those who met the CEP case definition for encephalitis (encephalopathy requiring hospitalization with ≥1 of the following: fever, seizure, focal neurologic findings, cerebrospinal fluid [CSF] pleocytosis, and/or electroencephalography or neuroimaging consistent with encephalitis) were enrolled. Core testing at the CEP included herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV), Epstein-Barr virus, human herpesvirus type 6, West Nile virus, and respiratory pathogens (influenza viruses, respiratory syncytial virus, adenoviruses, parainfluenza virus 1–4, human metapneumovirus, *Mycoplasma pneumoniae*). Testing for amoeba, fungi, and parasites was performed if exposure and travel history, clinical symptoms, and/or laboratory values suggested these infections. Infectious etiologies were classified as confirmed, probable, or possible based on a standardized algorithm [7, 8]. Noninfectious etiologies were identified through medical records and communication with referring physicians. Studies using CEP data are approved by the California Committee for the Protection of Human Subjects (project number 00-06-04).

Additional medical records for cases with incomplete data and/or unknown etiologies were requested from the referring hospital, including discharge summaries, neuroimaging reports, and neurology and infectious diseases notes. We reviewed demographics, clinical presentation, laboratory data, and brain MRI characteristics from the case history form and from requested medical records. We excluded cases in which TL abnormalities were chronic or normal variants, or when symptoms were present for >1 year. In addition to data gathered from imaging reports, brain MRIs at the time of admission (or the earliest available) for all HSE and VZV cases, plus 40 other randomly chosen non-HSE, non-VZV cases, were reviewed when available by a board-certified neurologist (F. C. C.) for evidence of (1) unilateral vs bilateral TL abnormalities; (2) abnormalities outside of the TL or limbic region (ie, insula or cingulate); (3) any restricted diffusion; (4) any intraparenchymal hemorrhage; and (5) any contrast enhancement.

We used χ^2, Student *t*, or Wilcoxon rank-sum tests to compare demographics, clinical variables, and MRI characteristics between HSE and non-HSE cases. For the final analyses, we constructed age- and sex-adjusted multivariate logistic regression models including all 5 MRI characteristics selected a priori to identify radiological predictors of HSE and non-HSE cases. *P* values were 2-sided with <.05 considered statistically significant. Statistical analyses were performed using Stata software, version 12.1 (StataCorp, College Station, Texas).

RESULTS

Etiologies of TL Encephalitis

Of 2001 adult encephalitis cases referred to the CEP from 1998 to 2012, we identified 251 with TL abnormalities who met entry criteria. Among the 251 cases, 108 and 40 were found to have an infectious and noninfectious etiology, respectively. In 103 cases, no etiology was identified (Table 1).

Of the 108 cases (43%) with an identified infectious cause of TL encephalitis, the most common etiologies were HSE (HSV-1 and -2), tuberculosis, and VZV. Fifteen other infectious etiologies were identified. Of these, 82% were considered to be either confirmed or probable etiologies. An additional 40 (16%) noninfectious diagnoses were made, of which more than half were of autoimmune etiology, including paraneoplastic disorders, central nervous system (CNS) vasculitis, anti–*N*-methyl-D-aspartate (NMDA) receptor (NMDAR) encephalitis, acute disseminated encephalomyelitis, systemic lupus erythematosus, and neurosarcoidosis (Table 1).

Comparison of Demographic and Clinical Features Between HSE and Non-HSE Cases

Demographic and clinical features of patients with TL encephalitis are detailed in Table 2. The mean age was 51.8 years (standard deviation, 17.9 years); 50% were women, and 50% were white. HSE cases were older and less likely to be a nonwhite race compared with all 3 comparator groups: (1) all other cases; (2) non-HSE infectious cases; and (3) autoimmune cases. HSE cases were less likely to be women compared with autoimmune cases. Compared with all 3 groups, HSE cases were more likely to present acutely and with a fever and less likely to present with a rash or ataxia, although the latter did not reach statistical significance. Compared with autoimmune cases, seizures and upper respiratory symptoms were more frequent among HSE cases, whereas psychotic symptoms and cranial nerve deficits were less common, although the latter did not reach statistical significance. Statistically significant differences observed in the CSF profile were higher white blood cell

Table 1. Identified Infectious and Noninfectious Etiologies of Temporal Lobe Encephalitis (N = 251)

Etiology	Cases, No. (% of Total)	Cases With Confirmed/ Probable Infectious Etiology, %
Infectious	108 (43)	82
Herpes simplex virus 1	57 (22.7)	91
Herpes simplex virus 2	3 (1.2)	100
Tuberculosis	8 (3.2)	88
Varicella zoster virus	7 (2.8)	71
Mycoplasma pneumoniae	5 (2.0)	20
Enterovirus	4 (1.6)	75
Balamuthia mandrillaris	4 (1.6)	100
Human herpesvirus 6	4 (1.6)	100
Creutzfeldt-Jakob disease	3 (1.2)	100
West Nile virus	2 (0.8)	100
Rocky Mountain spotted fever	2 (0.8)	50
Influenza	2 (0.8)	0
Other infectious[a]	7 (2.8)	57
Noninfectious	40 (16)	. . .
Glioma/lymphoma/other malignancy	9 (3.6)	. . .
Central nervous system vasculitis	6 (2.4)	. . .
Paraneoplastic	5 (2.0)	. . .
Toxic-metabolic	4 (1.6)	. . .
Vascular	4 (1.6)	. . .
NMDA receptor–associated limbic encephalitis	3 (1.2)	. . .
ADEM	3 (1.2)	. . .
Dementia	2 (0.8)	. . .
Other noninfectious[b]	4 (1.6)	. . .
No etiology identified	103 (41)	. . .

Abbreviations: ADEM, acute disseminated encephalomyelitis; NMDA, *N*-methyl-D-aspartate.

[a] Other infectious etiologies: syphilis, *Chlamydia pneumoniae*, coccidioidomycosis, *Nocardia*, adenovirus, human metapneumovirus, *Aspergillus*.

[b] Other noninfectious etiologies: systemic lupus erythematosus, neurosarcoidosis, and Hashimoto's steroid responsive encephalopathy.

(WBC) count, red blood cell count, and protein in HSE compared with all other cases (Table 3).

In a sensitivity analysis, we excluded cases presenting with symptoms of >1 month duration (n = 38), given the classically acute presentation of HSE. HSE cases were less likely to present with aphasia or mutism compared with autoimmune cases (34% vs 60%; $P = .086$), although this did not reach statistical significance. Additionally, the statistical trend toward HSE cases presenting less frequently with ataxia compared with all other cases (20% vs 30%; $P = .182$) and with non-HSE infectious cases (20% vs 33%; $P = .168$) was attenuated, as was the trend of HSE cases presenting less commonly with cranial nerve deficits compared with autoimmune cases (11% vs 25%; $P = .254$). Last, we no longer observed a statistically significant difference in mean CSF protein between HSE and other cases ($P = .11$). All other previously observed statistically significant differences in demographic and clinical features between HSE and non-HSE cases were preserved.

Comparison of Imaging Features Between HSE and Non-HSE Cases

Bilateral TL involvement and lesions outside the TL, insula, or cingulate were less common in HSE cases compared with all 3 comparator groups (Table 3). Compared with other infectious cases, hemorrhage was observed more frequently among HSE cases, although this did not reach statistical significance. No statistically significant difference in the frequency of enhancement or restricted diffusion was observed among the groups. In an age- and sex-adjusted multivariate model of all cases with TL abnormalities, bilateral TL involvement and lesions outside the TL, insula, or cingulate were predictive of lower odds of HSE (Table 4). Bilateral TL involvement also predicted lower odds of HSE compared with other infectious cases and autoimmune cases.

Sensitivity analyses after (1) inclusion of only confirmed and probable etiologies and (2) exclusion of cases with symptom duration of >1 month demonstrated preservation of the statistically significant associations between radiographic features and HSE cases observed in the full data set.

DISCUSSION

In a large statewide encephalitis cohort, we established that specific clinical and MRI characteristics may aid in distinguishing between HSE vs non-HSE cases of TL encephalitis. Both bilateral TL involvement and lesions outside the TL and limbic region lowered the odds of a diagnosis of HSE. Although bilateral TL abnormalities were once thought to be virtually pathognomonic for HSE [1], such findings can occur in the setting of numerous other diseases [9–13], which is consistent with our findings. In one review of 65 brain MRIs with bilateral TL hyperintensities [14], only 23% were due to HSE. Other diagnoses included mesial temporal sclerosis, gliomatosis cerebri, and MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes). While extratemporal involvement is well described in HSE, occurs in more than half of cases [15], and may even be present without TL abnormalities [16], we found that extratemporal involvement beyond the limbic regions (ie, insula and cingulate gyrus) was less common in HSE. Notably, extratemporal involvement in HSE is more likely to occur in pediatric [17–19] and immunocompromised populations [20], both of which were excluded in the current study. Additionally, although restricted diffusion may be the most sensitive MRI finding early in the course of HSE [4, 5, 21], our results did not support the

Table 2: Demographic and Clinical Characteristics by Etiology

	HSE Cases (n = 60)	All Non-HSE Cases (n = 191)	Other Non-HSE Infectious Cases (n = 48)	Autoimmune Cases (n = 21)
Mean age, y (SD)	56.8 (19.2)	**50.2[a] (17.2)**	**48.4[b] (18.6)**	**42.2[c] (15.8)**
Women (%)	30/60 (50)	95/191 (50)	22/48 (46)	**18/21[c] (86)**
Non-white race (%)	21/60 (35)	**102/191[a] (53)**	**29/48[b] (60)**	**12/21[c] (57)**
Symptoms for <1 wk before presentation (%)	51/58 (88)	**111/174[a] (64)**	**31/43[b] (72)**	**7/18[c] (39)**
Fever (%)	44/55 (80)	**90/180[a] (49)**	**23/44[b] (52)**	**10/19[c] (53)**
Neck stiffness (%)	17/53 (32)	39/183 (21)	14/47 (30)	6/20 (30)
Seizure (%)	30/55 (55)	104/184 (57)	23/46 (50)	**5/20[c] (25)**
Severe HA (%)	15/29 (52)	54/116 (47)	21/36 (58)	8/15 (53)
Impaired consciousness (%)	37/55 (67)	116/186 (62)	30/46 (65)	15/21 (71)
Confusion (%)	29/32 (91)	107/126 (85)	27/34 (79)	15/18 (83)
Aphasia/Mutism (%)	14/42 (33)	51/150 (34)	14/42 (33)	11/21 (52)
Hallucinations (%)	10/47 (21)	41/174 (24)	10/45 (22)	6/19 (32)
Psychosis (%)	2/38 (5)	16/143 (11)	4/39 (10)	**4/20[c] (20)**
Movement disorder (%)	2/7 (29)	6/47 (13)	2/9 (22)	1/8 (13)
Ataxi[a] (%)	8/44 (18)	**54/166[a] (33)**	**15/42[b] (36)**	**9/19[c] (47)**
Cranial nerve (%)	4/39 (10)	24/150 (16)	8/41 (20)	**5/18[c] (28)**
Rash (%)	1/52 (2)	**27/179[a] (15)**	**10/47[b] (21)**	**4/19[c] (21)**
URI symptoms (%)	11/53 (21)	27/175 (15)	9/44 (20)	**0/19[c] (0)**
GI symptoms (%)	19/52 (37)	**33/176[a] (19)**	12/46 (26)	5/20 (25)

Data are presented as No. (%) unless otherwise indicated. Boldface indicates statistically significant differences ($P < .10$) in demographics and clinical characteristics between HSE and other etiologies.

Abbreviations: GI, gastrointestinal; HA, headache; HSE, herpes simplex encephalitis; SD, standard deviation; URI, upper respiratory infection.

[a] HSE compared with non-HSE cases: mean age, $P = .012$; % nonwhite race, $P = .013$; % with <1 week of symptoms prior to presentation, $P = .001$; % with fever, $P \leq .001$; % with ataxia, $P = .064$; % with rash, $P = .010$; % with GI symptoms, $P = .007$.

[b] HSE compared with other infectious cases: mean age, $P = .024$; % nonwhite race, $P = .008$; % with <1 week duration of symptoms, $P = .003$; % with fever, $P = .044$; % with ataxia, $P = .066$; % with rash, $P = .002$.

[c] HSE compared with autoimmune cases: mean age, $P = .003$; % women, $P = .004$; % nonwhite race, $P = .076$; % with <1 week duration of symptoms, $P \leq .001$; % with fever, $P = .021$; % with seizure, $P = .023$; % with psychotic symptoms, $P = .080$; % with ataxia, $P = .017$; % with cranial nerve deficits, $P = .092$; % with rash, $P = .005$; % with URI symptoms, $P = .031$.

use of diffusion weighted imaging sequences to distinguish between HSE and other etiologies of TL encephalitis.

In the CEP, the largest cohort of encephalitis with TL involvement on MRI, HSE was the most commonly identified cause. However, a substantial number of cases were due to other infectious and noninfectious etiologies, including tuberculosis, VZV, malignancy, and vascular disease. Despite several decades between study periods and the advent of newer imaging modalities such as MRI, which is more sensitive than CT for the detection of HSE abnormalities, our results are broadly comparable to those of a multicenter study from 1973 to 1988 of HSE mimics by Whitley et al [3]. In that study, pediatric and adult patients with clinical findings suggestive of HSE (ie, encephalopathy plus evidence of TL involvement by electroencephalography or brain CT and/or technetium scan) underwent brain biopsy to establish a diagnosis. HSE was diagnosed in 45% of 432 patients, compared with 24% of 251 patients in the CEP cohort. An additional 22% of their patients were diagnosed with an entity other than HSE, compared with 35% of our cases. HSE mimics in the study included tuberculosis, malignancy, and vascular disease, in addition to other infectious (eg, bacterial and fungal abscesses, rickettsial infection, *Mycoplasma*, arboviruses) and noninfectious etiologies (eg, systemic lupus erythematosus), many of which were observed in our study. Although differences in demographic and epidemiologic risk factors between the 2 cohorts may have contributed to discrepancies in identified etiologies, increased awareness and knowledge of specific causes of encephalitis and improved diagnostics may also explain some diagnoses found in the CEP but not in the Whitley et al cohort, including anti-NMDAR encephalitis, *Balamuthia mandrillaris*, and VZV.

Unlike the Whitley et al study, most other studies of encephalitis have not focused specifically on TL cases. Over a 1-year period, a national multicenter study in France evaluated 253 cases of infectious encephalitis, defined as acute onset of illness; elevated CSF WBC count and/or protein; fever; and altered consciousness, seizures, or focal neurologic signs [22]. An infectious etiology was identified in 131 cases, of which 69% were due to a viral cause. The most common diagnoses were HSE (42%),

Table 3. Cerebrospinal Fluid and Imaging Characteristics, by Etiology

Characteristic	CSF WBC, Median (IQR)	CSF RBC, Median (IQR)	CSF Protein, Median (IQR)	CSF Glucose, Median (IQR)
CSF characteristics				
HSE cases (n = 60)	50 (22–76)	48 (12–77)	75 (48–105)	65 (54–74)
All non-HSE cases (n = 191)	**32 (2–65)[a]**	**33 (2–60)[a]**	**57 (41–96)[a]**	65 (54–82)
Other non-HSE infectious cases (n = 48)	32 (7–79)	38 (12–66)	66 (47–158)	61 (43–68)
Autoimmune cases (n = 21)	38 (22–79)	27 (1–74)	54 (33–118)	61 (49–73)

Characteristic	Bilateral Temporal Lobe, No. (%)	Lesions Outside of Temporal Lobe, Cingulate, or Insula, No. (%)	Restricted Diffusion, No. (%)	Hemorrhage, No. (%)	Enhancement, No. (%)
MRI characteristics					
HSE cases (n = 60)	12/56 (21)	17/56 (30)	16/56 (29)	5/56 (9)	22/56 (39)
All non-HSE cases (n = 191)	**70/153[b] (46)**	**89/158[b] (56)**	34/158 (22)	10/157 (6)	64/159 (40)
Other non-HSE infectious cases (n = 48)	**19/39[c] (49)**	**22/39[c] (56)**	13/39 (33)	**0/39[c] (0)**	19/41 (46)
Autoimmune cases (n = 21)	**10/19[d] (53)**	**12/20[d] (60)**	5/20 (25)	2/20 (10)	10/20 (50)

Boldface indicates a statistically significant difference in characteristic between HSE and other etiologies.

Abbreviations: CSF, cerebrospinal fluid; HSE, herpes simplex encephalitis; IQR, interquartile range; MRI, magnetic resonance imaging; RBC, red blood cell; TL, temporal lobe; WBC, white blood cell.

[a] HSE compared with non-HSE cases: CSF WBC count, $P = .003$; CSF RBC count, $P = .020$; CSF protein, $P = .043$.

[b] HSE compared with non-HSE cases: bilateral TL involvement, $P = .001$; lesions outside of TL, cingulate, or insula, $P = .001$.

[c] HSE compared with other infectious cases: bilateral TL involvement, $P = .005$; lesions outside of TL, cingulate, or insula, $P = .011$; presence of hemorrhage, $P = .055$.

[d] HSE compared with autoimmune cases: bilateral TL involvement, $P = .010$; lesions outside of TL, cingulate, or insula, $P = .019$.

VZV (15%), and tuberculosis (15%). Similarly, in a population-based, single-center study from 1999 to 2004 in Finland, 42 cases of encephalitis, defined as altered consciousness or personality, seizures, or focal neurologic signs plus CSF pleocytosis or radiologic and electroencephalographic findings consistent with encephalitis with no other apparent cause, were identified but an etiologic agent was found in only 36%, the majority of which were HSE (9.5%), VZV (9.5%), and tick-borne encephalitis (9.5%) [23]. In another study of 203 encephalitis patients recruited from 24 hospitals in England, nearly 19% were attributed to HSE, 5% to VZV, and 21% to autoimmune etiologies [2].

Recognition of immune-mediated disorders of the CNS is rapidly increasing. The ability to distinguish autoimmune etiologies from HSE and other infectious causes of TL encephalitis using clinical and radiologic characteristics is highly relevant to patient care. The heterogeneous nature of immune-mediated

Table 4. Magnetic Resonance Imaging Characteristics Associated With Herpes Simplex Encephalitis in Multivariate Logistic Regression, Final Models[a]

	Model 1: HSE Compared With All Non-HSE Cases (n = 209)		Model 2: HSE Compared With Other Infectious Cases (n = 90)		Model 3: HSE Compared With Autoimmune Cases (n = 75)	
Characteristic	OR (95% CI) (Total No. With MRI Characteristic)	*P* Value	OR (95% CI) (Total Number With MRI Characteristic)	*P* Value	OR (95% CI) (Total No. With MRI Characteristic)	*P* Value
Bilateral TL	0.38 (.18–.79) (n = 82)	.010	0.30 (.11–.82) (n = 31)	.019	0.24 (.06–.94) (n = 22)	.040
Lesions outside of TL, cingulate, or insula	0.37 (.18–.74) (n = 106)	.005	0.41 (.16–1.05) (n = 39)	.064	0.36 (.10–1.35) (n = 29)	.13
Restricted diffusion	1.62 (.75–3.50) (n = 50)	.22	0.67 (.24–1.85) (n = 29)	.44	0.81 (.17–3.85) (n = 21)	.79
Hemorrhage	1.51 (.44–5.13) (n = 15)	.51	. . .	. . .	8.95 (.23–348.65) (n = 7)	.24
Enhancement	0.98 (.49–1.94) (n = 86)	.95	0.56 (.21–1.52) (n = 41)	.26	0.47 (.12–1.81) (n = 32)	.27

Abbreviations: CI, confidence interval; HSE, herpes simplex encephalitis; MRI, magnetic resonance imaging; OR, odds ratio; TL, temporal lobe.

[a] Adjusted for age, sex, and all variables listed in the table.

causes of encephalitis, however, renders it difficult to compare them as a group with HSE and other infectious causes of TL encephalitis. Even within the neuronal surface antibody syndromes, which include anti-NMDAR and anti–voltage-gated potassium channel (VGKC) encephalitis, the clinical manifestations and radiologic findings can vary widely depending on the antibody involved [24]. Furthermore, other immune-mediated causes of encephalitis, such as Hashimoto encephalopathy or neurosarcoidosis, may present, clinically and radiologically, quite differently from one another. We found that patients with HSE were more likely to present acutely and with fever and less likely to present with psychotic symptoms compared with autoimmune cases, which has been reported in other studies comparing HSE to autoimmune cases [25]. We also observed an association between HSE and seizures at the time of presentation. In a single-center study comparing clinical and radiological characteristics between 12 HSE and 10 autoimmune limbic encephalitis cases, seizures were more common in autoimmune encephalitis, although this did not reach statistical significance [25]. The higher frequency of seizures in autoimmune cases observed in their study may have been due to a narrower case definition of autoimmune disease, in which only patients with confirmed antineuronal antibodies or paraneoplastic disease were included. In another review of anti-VGKC encephalitis patients, all 42 had seizures during their clinical course, most at presentation [26].

We observed an association between the absence of lesions outside the limbic region and HSE compared with autoimmune cases. In the aforementioned single-center study, although lesions outside of the limbic region were not specifically commented upon, absence of basal ganglia involvement on imaging distinguished HSE from autoimmune etiologies [25]. In that study and in ours, bilateral TL involvement was more common in the autoimmune group (83% vs 58%), although this did not reach statistical significance in their small sample. Furthermore, bilateral TL abnormalities in autoimmune disease may develop on subsequent imaging. In a review of 42 patients with anti-VGKC encephalitis, 79% had mesial TL abnormalities at some point during their clinical course [26]. The majority of these abnormalities, including enlargement of the amygdala or hippocampus with associated T2 hyperintensity, were present at presentation. However, almost 30% of cases that initially had either unilateral or no TL involvement progressed to bilateral involvement on follow-up imaging. Comparable to the MRI findings in autoimmune cases from our study, <30% had evidence of contrast enhancement, >40% had restricted diffusion, and none had hemorrhage. However, unlike our findings, extratemporal abnormalities on MRI were uncommon (n = 2). In comparison, in a cohort of >400 patients with anti-NMDAR encephalitis, 50% had normal brain MRIs, whereas the other half had abnormal T2 or fluid-attenuated inversion recovery signal hyperintensity, including in the medial TL, insula, cerebellum, cerebral cortex, basal ganglia, or brainstem [27].

Our study has several limitations. First, the timing of imaging in relation to the course of illness has potential implications on our results. A large portion of imaging available in the CEP is from early in the hospital course, when patients are first admitted and evaluated. As a result, the reviewed imaging may have missed imaging characteristics that develop as illness progresses. We may not have detected an association between bilateral TL involvement and HSE, for example, because bilateral abnormalities are more typical of subacute infection and occur later in the illness when scans are less likely to be repeated. Similarly, the lack of a significant association between HSE and hemorrhage, observed in only 9% of HSE cases, may have been due to the timing of imaging. (An alternative explanation is that bilateral TL involvement and hemorrhage in HSE are both less common now due to early antiviral therapy). For this same reason, we may not have seen an association between HSE and contrast enhancement, as it often lags behind symptom onset. In practice, however, clinicians often rely on neuroimaging obtained early in the hospital course to make crucial diagnostic and treatment decisions. We did not have information regarding the region of the TL involved (eg, isolated mesial temporal involvement vs diffuse TL), which may distinguish between HSE and autoimmune disease [25]. Additionally, potential variation in the strength of the MRI scanner over the study period or among hospitals may have affected our evaluation. We were not able to determine etiologies for all TL encephalitis cases. Incomplete classification of the etiology, if it was more likely to have occurred in non-HSE cases leading to differential misclassification, may have led to bias. For example, a proportion of cases in the cohort occurred before the discovery of immune-mediated encephalitis and prior to routine clinical testing for associated antibodies. Furthermore, we were unable to systematically test for autoimmune or paraneoplastic antibodies in the full cohort. However, if cases of anti-NMDAR and VGKC encephalitis often demonstrate MRI abnormalities outside the TL or bilateral TL involvement, as prior studies indicate, then incomplete classification of these immune-mediated etiologies would have attenuated our findings. Finally, CEP is not a population-based study and is likely biased toward patients who are severely ill and more diagnostically challenging.

In the largest cohort of TL encephalitis with available MRI data, we demonstrated that specific clinical and MRI characteristics may aid in distinguishing HSE vs non-HSE cases. As the sensitivity of CSF HSV polymerase chain reaction (PCR) is imperfect [18, 19, 28, 29], particularly early in the course of HSE, clinicians evaluating TL encephalitis patients who present with these characteristics yet have a negative PCR result for CSF HSV should maintain a high index of suspicion for HSE and strongly consider a repeat lumbar puncture. Although HSE was the most common diagnosis in the cohort, we identified several other

infectious and noninfectious etiologies of TL encephalitis. Bilateral TL involvement, contrary to previous reports, was actually associated with lower odds of HSE, as were lesions outside of the TL and limbic region. Use of these imaging characteristics, in combination with the clinical history, epidemiologic risk factors, and laboratory testing, may improve our ability to differentiate between etiologies of TL encephalitis. Possible next steps include assessing the performance of these MRI characteristics in an unselected prospective cohort to determine their predictive value and evaluating MRI characteristics on serial brain imaging, obtained from the time of presentation to after a diagnosis is reached, to identify features that may enhance our ability to distinguish HSE from other causes of TL encephalitis.

Notes

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References

1. Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis **2008**; 47:303–27.
2. Granerod J, Ambrose HE, Davies NW, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis **2010**; 10:835–44.
3. Whitley RJ, Cobbs CG, Alford CA, et al. Diseases that mimic herpes simplex encephalitis. Diagnosis, presentation, and outcome. NIAD Collaborative Antiviral Study Group. JAMA **1989**; 262:234–9.
4. McCabe K, Tyler K, Tanabe J. Diffusion-weighted MRI abnormalities as a clue to the diagnosis of herpes simplex encephalitis. Neurology **2003**; 61:1015–6.
5. Küker W, Nägele T, Schmidt F, Heckl S, Herrlinger U. Diffusion-weighted MRI in herpes simplex encephalitis: a report of three cases. Neuroradiology **2004**; 46:122–5.
6. Duckworth JL, Hawley JS, Riedy G, Landau ME. Magnetic resonance restricted diffusion resolution correlates with clinical improvement and response to treatment in herpes simplex encephalitis. Neurocrit Care **2005**; 3:251–3.
7. Glaser CA, Gilliam S, Schnurr D, et al. In search of encephalitis etiologies: diagnostic challenges in the California Encephalitis Project, 1998–2000. Clin Infect Dis **2003**; 36:731–42.
8. Glaser CA, Honarmand S, Anderson LJ, et al. Beyond viruses: clinical profiles and etiologies associated with encephalitis. Clin Infect Dis **2006**; 43:1565–77.
9. Jeong YM, Hwang HY, Kim HS. MRI of neurosyphilis presenting as mesiotemporal abnormalities: a case report. Korean J Radiol **2009**; 10:310.
10. Wong SH, Smith DW, Fallon MJ, Kermode AG. Murray valley encephalitis mimicking herpes simplex encephalitis. J Clin Neurosci **2005**; 12:822–4.
11. Hasegawa T, Kanno S, Kato M, Fujihara K, Shiga Y, Itoyama Y. Neuro-Behçet's disease presenting initially as mesiotemporal lesions mimicking herpes simplex encephalitis. Eur J Neurol **2005**; 12:661–2.
12. Jung K-Y, Chung C-S, Park K-W. Bilateral medial temporal lesions in Japanese encephalitis. Neurology **2007**; 68:1319.
13. Saunderson RB, Chan RC. Mesiotemporal changes on magnetic resonance imaging in neurosyphilis. Intern Med J **2012**; 42:1057–63.
14. Sureka J, Jakkani R. Clinico-radiological spectrum of bilateral temporal lobe hyperintensity: a retrospective review. Br J Radiol **2012**; 85: e782–92.
15. Wasay M, Mekan SF, Khelaeni B, et al. Extra temporal involvement in herpes simplex encephalitis. Eur J Neurol **2005**; 12:475–9.
16. Taylor SW, Lee DH, Jackson AC. Herpes simplex encephalitis presenting with exclusively frontal lobe involvement. J Neurovirol **2007**; 13:477–81.
17. De Tiège X, Héron B, Lebon P, Ponsot G, Rozenberg F. Limits of early diagnosis of herpes simplex encephalitis in children: a retrospective study of 38 cases. Clin Infect Dis **2003**; 36:1335–9.
18. Schleede L, Bueter W, Baumgartner-Sigl S, et al. Pediatric herpes simplex virus encephalitis: a retrospective multicenter experience. J Child Neurol **2013**; 28:321–31.
19. To TM, Soldatos A, Sheriff H, et al. Insights into pediatric herpes simplex encephalitis from a cohort of 21 children from the California Encephalitis Project, 1998–2011. Pediatr Infect Dis J **2014**; 33:1287–8.
20. Tan IL, McArthur JC, Venkatesan A, Nath A. Atypical manifestations and poor outcome of herpes simplex encephalitis in the immunocompromised. Neurology **2012**; 79:2125–32.
21. Obeid M, Franklin J, Shrestha S, Johnson L, Quattromani F, Hurst D. Diffusion-weighted imaging findings on MRI as the sole radiographic findings in a child with proven herpes simplex encephalitis. Pediatr Radiol **2007**; 37:1159–62.
22. Mailles A, Stahl JP. Infectious encephalitis in France in 2007: a national prospective study. Clin Infect Dis **2009**; 49:1838–47.
23. Kupila L, Vuorinen T, Vainionpää R, Hukkanen V, Marttila RJ, Kotilainen P. Etiology of aseptic meningitis and encephalitis in an adult population. Neurology **2006**; 66:75–80.
24. Ramanathan S, Mohammad SS, Brilot F, Dale RC. Autoimmune encephalitis: Recent updates and emerging challenges. J Clin Neurosci **2013**; 21:722–30.
25. Oyanguren B, Sánchez V, González FJ, et al. Limbic encephalitis: a clinical-radiological comparison between herpetic and autoimmune etiologies. Eur J Neurol **2013**; 20:1566–70.
26. Kotsenas AL, Watson RE, Pittock SJ, et al. MRI findings in autoimmune voltage-gated potassium channel complex encephalitis with seizures: one potential etiology for mesial temporal sclerosis. Am J Neuroradiol **2014**; 35:84–9.
27. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol **2011**; 10: 63–74.
28. Weil AA, Glaser CA, Amad Z, Forghani B. Patients with suspected herpes simplex encephalitis: rethinking an initial negative polymerase chain reaction result. Clin Infect Dis **2002**; 34:1154–7.
29. Puchhammer-Stöckl E, Presterl E, Croÿ C, et al. Screening for possible failure of herpes simplex virus PCR in cerebrospinal fluid for the diagnosis of herpes simplex encephalitis. J Med Virol **2001**; 64:531–6.