Open Forum Infectious Diseases

MAJOR ARTICLE

Incidence, Duration, and Risk Factors Associated With Missed Opportunities to Diagnose Herpes Simplex Encephalitis: A Population-Based Longitudinal Study

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Background. Delays in diagnosing herpes simplex encephalitis (HSE) are associated with increased morbidity and mortality. The purpose of this paper is to determine the frequency and duration of diagnostic delays for HSE and risk factors for diagnostic delays.

Methods. Using data from the IBM Marketscan Databases, 2001–2017, we performed a retrospective cohort study of patients with HSE. We estimated the number of visits with HSE-related symptoms before diagnosis that would be expected to occur in the absence of delays and compared this estimate to the observed pattern of visits. Next, we used a simulation-based approach to compute the number of visits representing a delay, the number of missed diagnostic opportunities per case patient, and the duration of delays. We also investigated potential risk factors for delays.

Results. We identified 2667 patients diagnosed with HSE. We estimated 45.9% (95% confidence interval [CI], 43.6%–48.1%) of patients experienced at least 1 missed opportunity; 21.9% (95% CI, 17.3%–26.3%) of these patients had delays lasting >7 days. Risk factors for delays included being seen only in the emergency department, age <65, or a history of sinusitis or schizophrenia.

Conclusions. Many patients with HSE experience multiple missed diagnostic opportunities before diagnosis.

Keywords. delayed diagnosis; HSE; missed opportunities.

Herpes simplex encephalitis (HSE) is a common cause of sporadic viral encephalitis in the United States [1]. In the neonatal setting, HSE is often caused by herpes simplex virus (HSV)-2, but among children and adults, more than 90% of cases are caused by HSV-1 [2]. The incidence of HSE is estimated to be 1–4 per million population per year in the Western world [3–5]. However, unlike other causes of encephalitis, there is an effective treatment for HSE. The administration of acyclovir in appropriate doses dramatically decreases mortality, which is over 70% in the absence of therapy [6, 7]. It is unfortunate that, even with acyclovir treatment, long-lasting neurologic sequelae are common [8]. Optimal effectiveness of antiviral therapy is dependent upon prompt administration of acyclovir [9–11], which requires a timely diagnosis. In general, an etiologic diagnosis is often difficult to establish for viral encephalitis, and a substantial proportion of cases remain undiagnosed despite a thorough workup [12]. In contrast to other forms of viral encephalitis, HSE can be readily diagnosed with commercially available assays that use polymerase chain reaction (PCR) methodology to detect HSV deoxyribonucleic acid (DNA) in cerebrospinal fluid with high sensitivity and specificity [7].

In addition to tests designed to detect the presence of the virus, other testing approaches may aid in the diagnosis of the disease. For example, brain magnetic resonance imaging (MRI) tests are both sensitive and specific [7]. Moreover, specific electroencephalogram findings, although not pathognomonic, can be highly suggestive of HSE [7, 13, 14]. However, all of these diagnostic testing approaches rely on sufficient clinical suspicion. Although some signs and symptoms (eg, word-finding difficulties, or confusion and fever) are suggestive of HSE, they are not always present when HSE patients first present. Furthermore, many of the presenting signs and symptoms such as headache and confusion have many other, often more common, causes.

Delays in HSE diagnosis can lead to devastating clinical outcomes including major cognitive and neurologic deficits and increases in mortality [9, 15, 16]. Although the clinical manifestations of delayed treatment are well described, the overall incidence of diagnostic delays in different practice settings, and the average length of diagnostic delays, is not known. In addition, there are no precise estimates of the impact on clinical outcomes of varying lengths of delay. Thus, the purpose of this paper is to determine the incidence of diagnostic delays for

Received 1 June 2021; editorial decision 19 July 2021; accepted 25 July 2021.

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Open Forum Infectious Diseases®2021

https://doi.org/10.1093/ofid/ofab400

HSE. We also identify risk factors and outcomes associated with diagnostic delays.

METHODS

Data Source and Study Population

To identify cases of HSE, we used longitudinal commercial- and Medicare-supplemental-insurance claims from the IBM Marketscan Research Databases, 2001–2017. These databases represent more than 195 million commercially insured enrollees in the United States and contain claims from inpatient, outpatient, and emergency department (ED) visits along with outpatient prescription medications.

Patients with HSE were identified using the following diagnosis codes: 054.3 (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM]) and B00.4 (ICD-10-CM). To improve the accuracy of diagnosis codes, we also required an HSE diagnosis to be accompanied by procedure codes for a brain MRI or lumbar puncture within 2 days of the index diagnosis. We looked for signs and symptoms of HSE during healthcare visits before the index (initial) diagnosis and required that patients with HSE have at least 180 days of continuous enrollment before the index diagnosis.

Statistical Analysis

To identify diagnostic opportunities, we used an extension of the SPADE framework [17] by looking for signs and symptoms of HSE during healthcare visits in the time period before the index diagnosis where diagnostic opportunities are likely to occur. We began by identifying healthcare visits for "symptomatically similar diagnoses" (SSDs) that occur before the initial HSE diagnosis; SSDs are defined as symptoms, symptomatically similar diseases or syndromes, or testing/exam-based diagnoses that suggest infection was present. Examples of SSDs for HSE include fever, headache, neurologic symptoms, changes in mental status, and seizures. Supplementary Table 1 provides a complete list of all SSDs and corresponding ICD-9/10 codes considered.

Next, we identified the "diagnostic-opportunity window"—the period of time before diagnosis when opportunities to diagnose patients with symptoms of HSE likely occur. Specifically, we identified the point τ-days before the index diagnosis where the number of SSD-associated visits each day significantly increases. We used the cumulative sum control chart (CUSUM) method to detect the day, τ, before diagnosis representing a change point in the frequency of SSD visits [18]. We then defined the period (1, τ) days before the index HSE diagnosis as the diagnostic-opportunity window.

Estimating Frequency and Duration of Diagnostic Delays

To estimate the frequency and duration of missed opportunities, we used an approach similar to Waxman et al [19], which has also been used to identify diagnostic delays associated with tuberculosis [20]. This approach begins by using a case-crossover-type approach to estimate the likely number of missed opportunities based on SSD-associated visits. First, the trend in SSD-related visits each day before the start of the diagnostic opportunity window (ie, before the disease is assumed to be present or diagnoseable) is estimated using a linear model. Next, this trend is extrapolated forward into the diagnostic opportunity window to compute the "expected" number of SSD-associated visits. Finally, the likely number of missed opportunities is estimated as the "excess" number of SSD-associated visits, defined as the difference between the "observed" and expected number of SSD-associated visits during the diagnostic opportunity window; we used a conservative approach in which the upper bound of the 95% one-sided prediction interval is used as the expected trend.

Next, after computing the likely number of missed opportunities each day, a bootstrapping approach is used to estimate the number of individuals that experienced a diagnostic delay, the number of missed opportunities per patient, and the duration of diagnostic delays. Specifically, this approach repeatedly resamples individuals with HSE, recomputes the expected number of missed opportunities (as described above), draws which visits represent a missed opportunity based on the expected number of missed opportunities each day, then computes how often individuals experience a missed opportunity and the duration of these delays. This procedure is repeated 25 000 times, and 95% bootstrap-based confidence intervals (CIs) are computed for each estimated value. This bootstrapping-based approach was used because not all SSD-associated visits during the missed opportunity window represent a diagnostic delay: some symptoms may be coincidental. By repeatedly drawing which visits represent a likely missed opportunity based on the expected level of SSD visits, we aim to more accurately estimate the number of missed opportunities and delay duration than by computing raw counts of such visits. Additional details on the entire estimation and bootstrapping procedures can be found in the Supplementary Material.

Estimating Risk Factors for a Diagnostic Delay

To evaluate risk factors for experiencing a potential diagnostic delay, we used a logistic regression model and assigned visits representing a potential missed opportunity—defined as an SSD-related visit in the diagnostic opportunity window—a value of 1 and the index diagnosis visit a value of 0. In addition, we considered patient age, sex, and treatment history for symptoms that might be confused with those of HSE. We evaluated whether a patient had a history of the following: migraines; chronic or recurrent sinusitis; schizophrenia and other psychiatric disorders; anxiety disorders; dementia or other cognitive disorders; mood disorders; and alcohol or substance abuse disorder during the 60–365 days before the index date. A complete list of the codes used to identify such events can be found in Supplementary Table 2. We also evaluated whether the patient was located in an

urban location (as defined by a metropolitan statistical area) and whether the visit occurred in an inpatient, emergency department, or outpatient setting. We treated all visits on the same day as a single visit representing a linked episode of care, and we created indicators for the various combinations of care that could be involved in a given day (eg, outpatient only, outpatient, and ED, etc). Finally, we performed variable selection using backwards elimination in conjunction with the Akaike Information Criterion (AIC). The demographic variables for sex and age were retained to evaluate whether differences existed between individuals based on sex or age. Wald confidence intervals (95%) were constructed using standard errors from the fitted logistic regression model.

Sensitivity Analyses

Not all signs and symptoms recorded during a clinic visit may be recorded by diagnostic codes in the insurance claim. For example, a patient may present with what appears to be a viral illness with fever and headache, but only the viral illness is recorded in the insurance claim. Thus, the potential SSD visits we identify may underestimate the true number of missed opportunities. We repeat all of our analyses to compute the frequency and duration of delays using all visits (with or without an SSD) as potential diagnostic opportunities.

Patient Consent

The data used in this study are deidentified, and studies of this nature are considered nonhuman-subjects research by our institutional review board.

RESULTS

From 2001 through 2017, we identified a total of 7095 individuals with an HSE diagnosis. Of these individuals, 2667 enrollees met all eligibility criteria: 5747 were enrolled for at least 180 days before the index HSE diagnosis and 2667 also had either a brain MRI or spinal tap within 2 days of index diagnosis. Table 1 presents (1) baseline criteria for the final study cohort and (2) the number of individuals in each group that had an SSD visit within the delay window.

Of the case patients we identified, 2497 (93.6%) patients had at least 1 healthcare visit in the 180 days before their index HSE diagnosis. Of these patients, 641 (24.0%) had at least 1 inpatient visit, 1182 (44.3%) had at least 1 ED visit, and 2461 (92.3%) had at least 1 outpatient visit. Focusing on SSD-related visits, we found that 1839 (69.0%) patients had at least 1 SSD visit in the 180 days before their index HSE diagnosis.

Figure 1 depicts the pattern of SSD-related visits that occurred in the 180-day period before the index HSE diagnosis. There is a dramatic increase in SSD-related visits that occur approximately 4 weeks before the index diagnosis date. Appendix Figures 1 and 2 depict similar patterns broken down by different categories of individual SSD diagnoses and healthcare settings.

Table 1. Demographic Data

Variable	Total Patients (% of Patients)	Patients With Symptomatically Similar Diagnoses in Delay Window (% of Patients in Group)
Age at Diagnosis		
<18	134 (5.0%)	89 (66.4%)
18–35	298 (11.2%)	157 (52.7%)
36–45	301 (11.3%)	172 (57.1%)
46–55	499 (18.7%)	260 (52.1%)
56–65	645 (24.2%)	354 (54.9%)
>65	790 (29.6%)	385 (48.7%)
Sex		
Male	1245 (46.7%)	646 (51.9%)
Female	1422 (53.3%)	771 (54.2%)
Enrollment Time Before Index (Years)		
Mean	3.9	4.0
Median	2.9	3.0
Range	0.5–16.9	0.5–16.9
Count ≤1.5 years	696 (26.1%)	356 (51.1%)
Count ≤2 years	696 (26.1%)	485 (51.7%)
Count ≤3 years	939 (35.2%)	717 (52.3%)
Count >3 years	1372 (51.4%)	700 (54.1%)
Region		
Rural	486 (18.2%)	279 (57.4%)
Urban	2164 (81.1%)	1130 (52.2%)
Missing	17 (0.6%)	8 (47.1%)

The pattern of SSD visits appears to be fairly stable across settings and SSD categories, with a very gradual linear increase from 180 days to approximately 4 weeks before the index diagnosis. Our CUSUM change point detection approach also identified 4 weeks (28 days) before the index diagnosis as the upper bound τ for the diagnostic opportunity window.

Figure 2 depicts the expected trend line in the number of SSD-associated visits and the corresponding number of diagnostic opportunities, based on our detected change point. Across all patients, 2119 (79.5%) patients had a visit for any reason, and 1417 (53.1%) patients had at least 1 SSD-related visit between 28 days and 1 day before their index diagnosis. There were 4191 SSD visits that occurred during the 28-day diagnostic opportunity window; these represent "potential" missed opportunities. Based on our simulation analysis, we estimated that 2729 visits (CI, 2457–3018 [58.6%–72.0%]), or 65.1% of the potential missed opportunities, represented a true missed opportunity; the remaining SSD visits are consistent with expected trends before the diagnostic opportunity window and are considered coincidental. We also estimated that approximately 182 (CI, 151–214) missed opportunities occurred in inpatient settings, 1764 (CI, 1594–1941) occurred in outpatient settings, and 784 (CI, 712–863) occurred in ED settings. A list of the top 10 diagnoses occurring within the delay window can be found in Supplementary Table 4. The frequencies of these diagnoses were similar at the beginning and end of the diagnostic opportunity window.

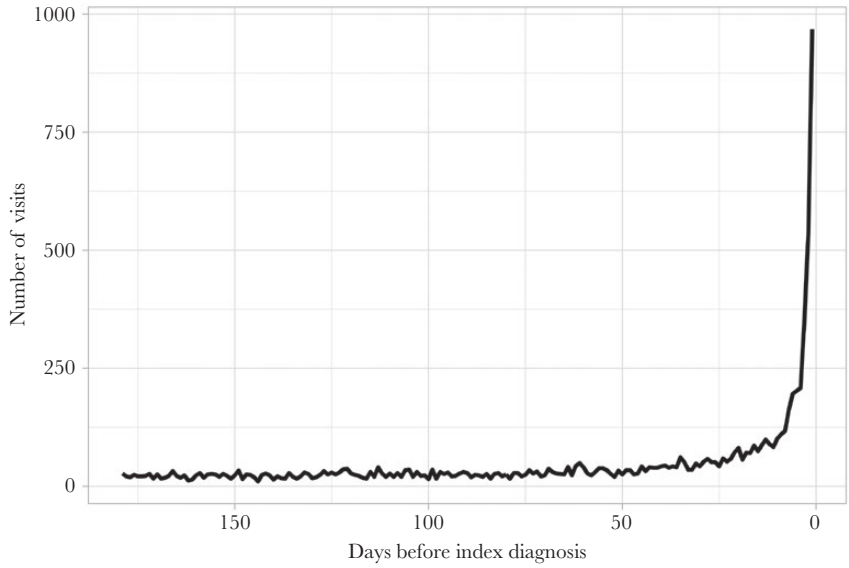

Figure 1. Spike in symptomatically similar diagnoses-related visits before index diagnosis.

Table 2 presents the estimated number of missed opportunities that each patient experienced based on the simulation analysis. Approximately 1223 (CI, 1164–1282), or 46% of all patients, experienced at least 1 missed opportunity whereas 1444 (CI, 1385–1503), or 54%, had no missed opportunities. On average, patients who experienced at least 1 missed opportunity experienced 2.23 (CI, 2.11–2.37) visits representing missed opportunities, occurring in an estimated 1.44 (CI, 1.34–1.55) outpatient visits, 0.15 (CI, 0.13–0.17) inpatient visits, and 0.64 (CI, 0.59–0.69) ED visits.

Table 2 also presents a breakdown of the estimated duration of diagnostic delays among patients who experienced at least 1 missed opportunity. The mean and median duration of delays were 4.65 (CI, 3.89–5.46) days and 2.00 (CI, 2.00-2.00) days, respectively. A total of 11.3% (CI, 7.1–15.6%) of patients had a delay lasting 14 or more days.

We conducted a sensitivity analysis by including all visits whether or not an SSD was present, and results are presented in Supplementary Table 3. When all visits were treated as a potential delay, 1572 (59.0%) patients were estimated to experience a

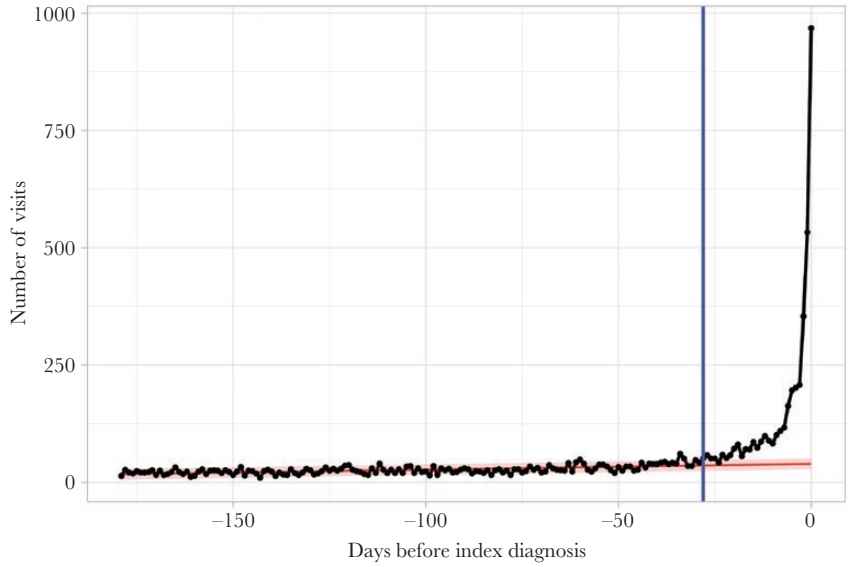

Figure 2. Symptomatically similar diagnoses (SSD) visits with change point (blue line) defining the diagnostic opportunity window and the estimated expected number of SSD visits (red line) before diagnosis. The estimated number of likely missed opportunities is represented as the difference between the observed (black line) and the upper prediction bound (red shaded area) of the expected curve.

Table 2. Number and Duration of Delayed Visits Per Patient

Number of Delayed Visits	Estimated Number of Patients/Days (% of total patients)	95% CI
0 Visits	1444 (54.1%)	1385 - 1503 (51.9–56.4%)
≥1 Visit	1223 (45.9%)	1164–1282 (43.6–48.1%)
≥2 Visits	703 (26.4%)	646–760 (24.2–28.5%)
≥3 Visits	376 (14.1%)	330–421 (12.4–15.8%)
≥4 Visit	191 (7.2%)	156–227 (5.8–8.5%)
≥5 Visit	101 (3.8%)	76–128 (2.8–4.8%)
Mean—Overall	2.23	2.11–2.37
Median—Overall	2	2–2[a]
Mean—Outpatient	1.44	1.34–1.55
Median—Outpatient	1	1–1[a]
Mean—Inpatient	0.15	0.13–0.17
Median—Inpatient	0	0–0[a]
Mean—ED	0.64	0.59–0.69
Median—ED	1	1–1[a]
Duration of Delay (Days)		
≥1	1223 (100.0%)	1164–1282 (100.0–100.0%)
≥2	685 (56.0%)	621–746 (52.3–59.7%)
≥4	477 (39.0%)	413–540 (34.5–43.1%)
≥6	345 (28.2%)	282–407 (23.5–32.6%)
≥8	268 (21.9%)	206–328 (17.3–26.3%)
≥10	217 (17.7%)	160–275 (13.4–22.0%)
≥12	181 (14.7%)	129–236 (10.8–18.9%)
≥14	138 (11.3%)	85–193 (7.1–15.6%)
≥16	101 (8.2%)	51–152 (4.3–12.2%)
≥18	76 (6.2%)	35–123 (2.9–10.0%)
Mean days delayed (among delayed)	4.65	3.89–5.46
Median days delayed (among delayed)	2	2–2[a]
Mean days delayed (overall)	2.13	1.74–2.57
Median days delayed (overall)	0	0–0[a]

Abbreviations: CI, confidence interval; ED, emergency department.
[a]CI is one point because this discrete value is predominantly or exclusively represented in the bootstrap distribution for the median.

potential delay, an increase of 13% compared with using only SSD-related visits. In addition, the mean duration of delay increased to 4.90 (CI, 3.83–6.19), only a modest increase from the primary analysis.

Table 3 presents results of the logistic regression model estimating the likelihood of experiencing a potential missed opportunity during a visit on a given day. The variables for migraines, anxiety disorders, alcohol and substance abuse disorders, dementia or other cognitive disorders, and mood disorders were removed through a backwards-elimination procedure. However, sex and age were retained due to interest in these variables, despite having overall modest effects on model fit.

Table 3 demonstrates that several patient-level factors were associated with increased likelihood of being missed. Estimates for the effect of age are presented with those aged 56 to 65 as the reference group. Patients aged 0 to 17 had a higher likelihood of potential missed opportunities compared with the reference group, whereas all other age groups had lower odds of potential misses compared with the reference group. However, none of these estimates were statistically significant except the category for patients older than 65 (odds ratio [OR] of 0.759; CI, 0.609–0.947). Patients who had 2 or more visits for sinusitis in the period of 60–365 days before the index HSE diagnosis had greater odds of a potential miss (OR of 2.512; CI, 1.340–4.711), as did patients with 2 or more visits for psychotic disorders in that timeframe (OR of 2.485; CI, 0.978–6.317).

Context and healthcare-setting factors were also significantly associated with missed opportunities. Misses were less likely to occur among patients in metropolitan locations (0.777; CI, 0.632–0.954). Compared with outpatient settings alone, missed opportunities were less likely to occur on days involving only an inpatient visit (0.017; CI, 0.014–0.022), both an inpatient and outpatient visit (0.018; CI, 0.014–0.022), both an inpatient and ED visit (0.020; CI, 0.015–0.026), or all 3 setting types (0.016; CI, 0.011–0.024). Visits to the ED appeared to increase the risk of a missed opportunity. Compared with outpatient settings alone, missed opportunities were more common on days when patients visited ED settings only (4.300; CI, 2.383–7.758).

Table 3. Likelihood of Experiencing a Missed Opportunity: Logistic Regression Model Results

Coefficient	OR Estimate	95% CI
Age 0–17	1.332	0.909–1.951
Age 18–35	0.757	0.557–1.027
Age 36–45	0.837	0.623–1.124
Age 46–55	0.906	0.704–1.166
Age 56–65	Ref	Ref
Age >65	0.759	0.609–0.954
Female	1.028	0.873–1.210
Urban vs not urban	0.777	0.632–0.954
Settings Visited		
Outpatient only	Ref	Ref
Inpatient, outpatient, and ED (all 3)	0.016	0.011–0.024
ED Only	4.300	2.383–7.758
Inpatient and ED	0.02	0.015–0.026
Inpatient and outpatient	0.018	0.014–0.022
Inpatient only	0.017	0.014–0.022
Outpatient and ED	0.673	0.512–0.884
Sinusitis history (≥2 visits 60–365 days before index)	2.512	1.340–4.711
Schizophrenia/psychotic disorder history (≥2 visits 60–365 days before index)	2.485	0.978–6.317

Abbreviations: CI, confidence interval; ED, emergency department; OR, odds ratio; Ref, reference group.

DISCUSSION

Our results demonstrate that a substantial proportion of patients diagnosed with HSE (53%) have at least 1 potential missed diagnostic opportunity in the 28 days before their HSE diagnosis. Furthermore, we estimated that for most of these patients, these visits represented a missed opportunity. More importantly, a small, but substantial, proportion of patients experience multiple such visits before their eventual HSE diagnosis. The most common SSDs in the 28 days before an HSE diagnosis included diagnoses of headache, convulsions, fever, malaise/fatigue, and alteration of consciousness. Finally, diagnostic delays were more common among patients who were seen only in the ED and among patients who had a past medical history of sinusitis or psychotic disorders.

Diagnostic delays are increasingly being recognized as an important threat to patient safety [21]. To date, little is known about the incidence of and risk factors for diagnostic delays, and most prior work has focused on myocardial infarction and stroke [19]. Beyond diseases affecting the cardiovascular system, diagnostic delays associated with infectious diseases may be especially important to consider, given that delays in the treatment of infectious diseases are associated with worse clinical outcomes [22–27], herpes simplex encephalitis is one such disease. Accordingly, a better understanding of diagnostic delays associated with HSE may improve clinical outcomes.

The diagnosis of HSE is challenging for 3 major reasons. First, the classic signs and symptoms of the disease are shared by other much more common diseases. In most cases, patients presenting with headache and confusion exhibit symptoms caused by other more common diseases. Interestingly, we found that patients were frequently diagnosed with infections that do not affect the central nervous system (eg, urinary tract infection). Second, the gold-standard test, HSV PCR of spinal fluid, requires a lumbar puncture, which cannot be easily performed in many settings. Even if available, some healthcare providers may be reluctant or unable to perform the test. In addition, some patients have contraindications that slow the procedure down or make it more difficult (ie, spinal deformities, pre-existing anticoagulation). Third, rare diseases, like HSE, are especially likely to be associated with diagnostic delays [28]. Most healthcare providers will see very few cases and may not suspect HSE.

Our results highlight directions for improving diagnostic approaches. However, our most intriguing finding is that some patients may begin to develop signs and symptoms a few weeks before their diagnosis. More specifically, we found that healthcare visits, both overall and attributed to SSDs, started to increase beginning as far as 28 days before diagnosis. Within this time period, we estimated that 26.4% of patients had at least 2 visits with SSDs, and 7.2% of patients had at least 4 visits with SSDs. However, the majority of potentially missed opportunities occurred in the 14 days before diagnosis. Although it may not be possible or reasonable to perform HSV PCR of spinal fluid at the earliest visits, our findings suggest the importance of close follow-up of patients with new signs or symptoms that could be consistent with HSE. Finally, the relatively long prodromal course that we observe stresses the importance of taking a careful history and seeking information from caregivers and family members regarding the patient's condition before presentation.

We identified some risk factors that could help inform future approaches to decrease diagnostic delays. For example, we found that people older than 65 years were less likely to experience a delayed diagnosis. Although increasing age is a risk factor for HSE, healthcare providers may be less likely to consider HSE in younger patients. In addition, we found that patients presenting to the ED were more likely to experience a delay. Misdiagnosis and diagnostic delays commonly occur in this busy clinical setting [29, 30]. Emergency department physicians generally do not have prior clinical interactions with their patients and may not have time to take a detailed medical history [31].

In recent years, cognitive biases have emerged as an important contributing factor for diagnostic errors [32, 33]. For example, availability bias, where providers make decisions based on easily available information, is common [34]. Awareness of these biases may help clinicians improve their diagnostic skills and thus reduce diagnostic errors [35]. Medical educators are currently developing strategies to help improve awareness and clinical decision making [32, 35–37]. Specific to this study, we found that patients with a history of sinusitis and psychotic disorders were at greater risk for delays. Among patients presenting with a past medical history for sinusitis, instead of considering

HSE, such patients were assumed to have a repeat episode of sinusitis. Sinus infections frequently recur and share some symptoms with HSE (eg, fever, headaches). Among patients presenting with a history of psychosis, it is likely that healthcare providers mistakenly assume that confusion or bizarre behavior is more likely due to the patient's underlying psychiatric history. These results could help inform strategies to more accurately diagnose HSE.

There are several limitations to this study. First, we used administrative data and diagnostic codes to identify cases of HSE. The ICD codes have varying sensitivity and specificity, and it is possible that some cases we identify capture other forms of infection (eg, herpes simplex meningitis). However, because there is a specific diagnostic test for HSE, incorrect coding is probably uncommon. Furthermore, to improve the validity of our case definition, in addition to using diagnostic codes, we only included patients who had a brain MRI or lumbar puncture within 2 days of the diagnosis. Second, some of the non-SSD-related visits preceding the HSE diagnosis may represent missed opportunities if patient symptoms were not recorded in the diagnostic codes. Thus, we performed a sensitivity analysis where we included all visits, not just those with SSDs. Third, our data only contain patients with private insurance. Patients with Medicaid, traditional Medicare, other public insurance, or without insurance are not included. Patients with private insurance may be more likely to visit the doctor, and diagnostic delays may be more common among patients with Medicaid or who are uninsured. Finally, we did not investigate the clinical outcomes associated with diagnostic delays. Future work will need to address this important topic.

CONCLUSIONS

Despite the limitations associated with our work, our results highlight the substantial number of missed opportunities to diagnose HSE that routinely occur. Our findings, taken together, highlight the need for new diagnostic tests for HSE. In the absence of such diagnostic tests, our results highlight the need for clinical suspicion, especially for patients who have repeat visits and patients with past medical histories for diseases that can mimic HSE.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Financial support. This publication was supported by a grant (R01HS027375) from by the Agency for Healthcare Research and Quality, and a grant (UL1TR002537) from by the National Center for Advancing Translational Sciences.

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