

Missed and Delayed Diagnosis of Herpes Simplex Encephalitis in Inpatient and Ambulatory Care Settings

Introduction

Herpes simplex encephalitis (HSE) is a severe infection. The disease is often associated with debilitating neurologic sequelae.

Effective treatment is available but treatment delays are associated with adverse outcomes. Thus, timely diagnosis and the initiation of appropriate antiviral treatment is critical.

The diagnosis of HSE can be challenging especially when patients first develop symptoms and thus the diagnosis may be missed or delayed.

Little is known about the frequency of and factors associated with delayed diagnosis.

The goal of this project is to estimate the number of missed and delayed diagnoses associated with HSE.

Methods

Data:

- Retrospective cohort study using Truven Marketscan Commercial Claims and Encounters Database 2011-2016
- >105 Million enrollees represented
- Longitudinal inpatient, outpatient and prescription-drug claims

Identifying Diagnostic Delays:

- Identify index HSE diagnosis (first diagnosis)
- Analyze prior visits for symptoms associated with HSE: fever, headaches/migraines, changes in mental state, neurologic symptoms, seizures

Analyzing/Validating Diagnostic Delays:

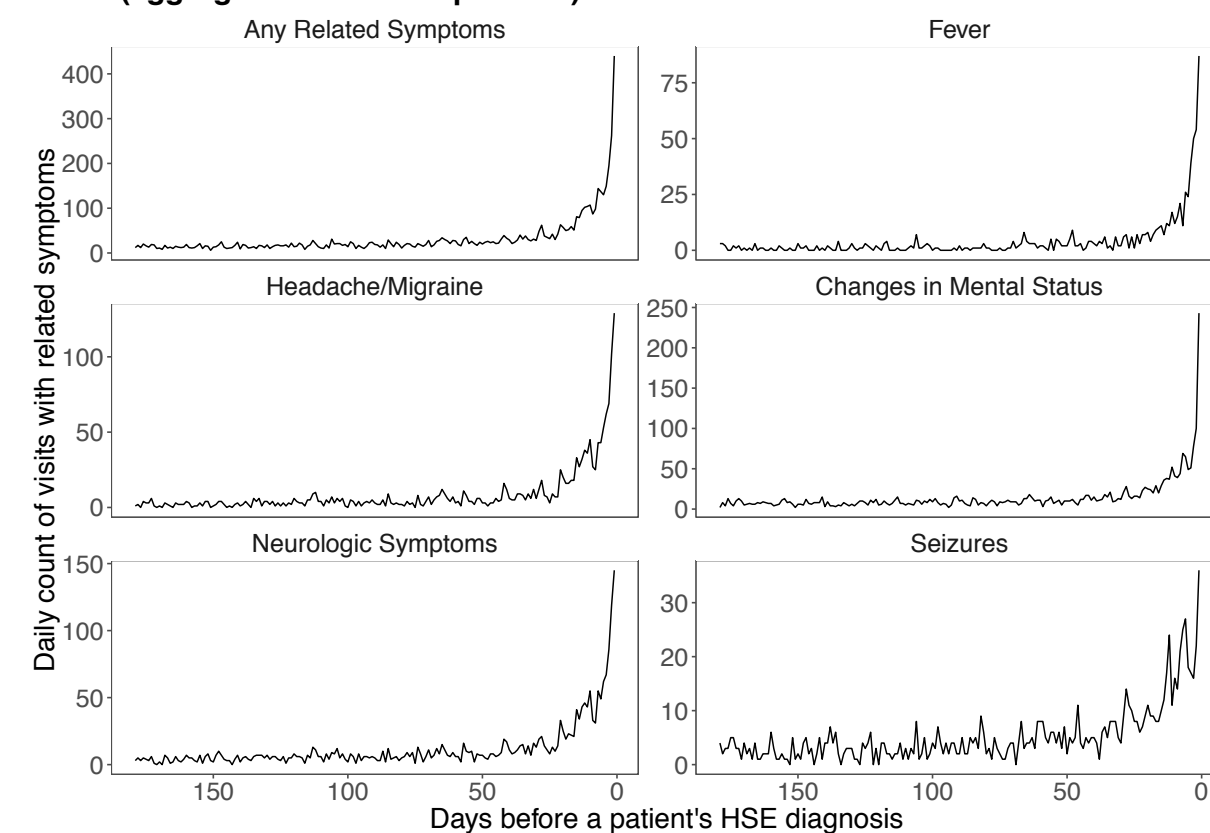
- Time-series change-point model to detect point before index HSE diagnosis where symptoms begin to emerge (increased occurrence)
- Simulation analysis to estimate frequency of true diagnostic delay. Randomly draw "expected" symptoms prior to index. Compare expected draw to observed symptoms
- Logistic regression analysis to analyze risk factors associated with potential delay

Results

We identified 3,390 index cases of HSE; of these 1,995 were diagnosed in outpatient or ED settings and 1,395 in inpatient settings.

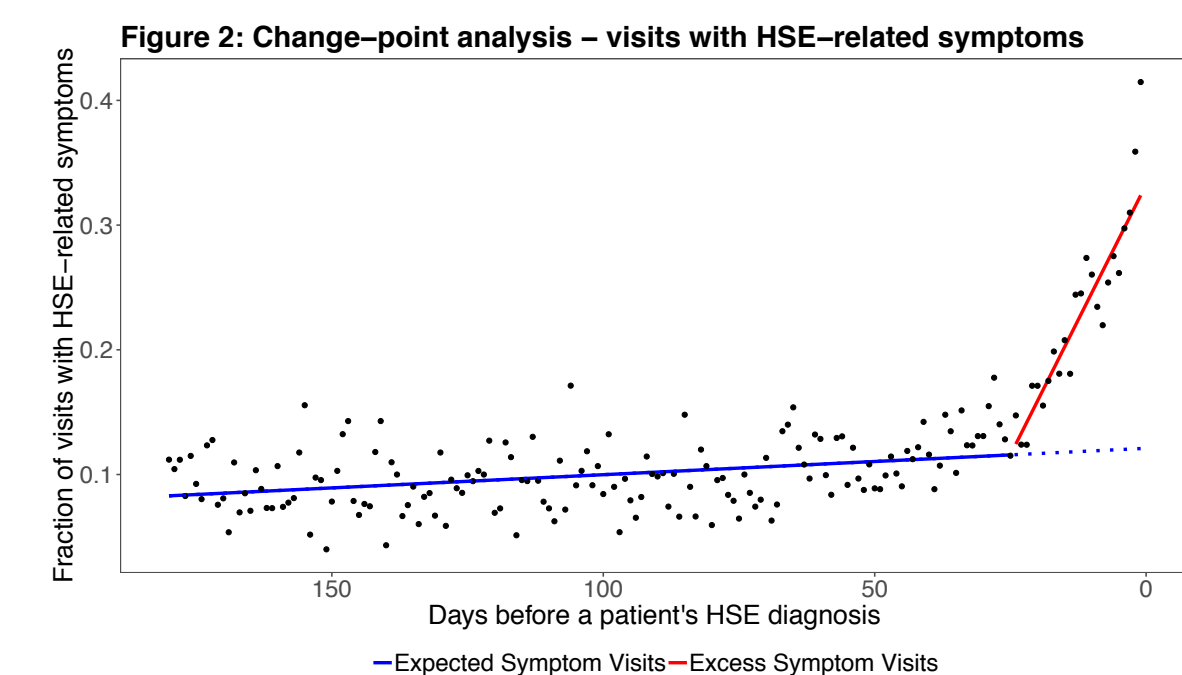
In the 24 days prior to the index HSE diagnosis, there were 2,656 visits from 938 patients with possible symptoms of HSE. There is a dramatic spike in HSE-related symptoms in the two weeks prior to the index diagnosis (Figure 1).

Figure 1: Counts of visits for HSE-related symptoms prior to HSE diagnosis (aggregated across all patients)



Time Series Analysis

For each day prior to the index HSE diagnosis, we computed the fraction of visits associated with HSE symptoms. We then fit a piecewise linear model to identify the point where HSE-related symptoms exceeded expected rates. The difference between observed symptomatic visits (red line) and expected visits (blue line) represent potential diagnostic delays.



For each symptom, we used the changepoint analysis to identify symptom visits representing potential delays. Table 1 reports the median days prior to index and the number of patients with potential delays.

Table 1: Median length and number of potential delays

Condition	Median Days Prior	Patients with potential delay
Fever	4	247
Headache/Migraine	6	421
Changes in Mental Status	6	530
Neurologic Symptoms	7	520
Seizures	19	219
Any	7	1041

Simulation Analysis

We estimated the true number of diagnostic delays through simulation. The simulation analysis produced the following estimates:

- 1,355 (CI 1,195-1,490) of 2,656 prior visits represented diagnostic delays
- Around 20.0% (CI 18.8-21.0) of patients with HSE experienced diagnostic delay
- 835 (CI 739-944) delays occurred in outpatient settings, 313 (CI 252-354) in the ED, and 259 (226-291) in inpatient settings

Risk Factors for Delay

Table 2: Regression results for predicting diagnostic delay

Risk Factor	Odds Ratio for Delay	95% CI
Location		
Outpatient	-	-
Inpatient	0.24	(0.21-0.28)
Emergency Department	15.86	(10.89-24.10)
Female	0.90	(0.80-1.01)
Age		
<18	-	-
18-34	1.15	(0.89-1.50)
34-44	1.40	(1.08-1.84)
45-64	1.54	(1.23-1.94)
≥65	2.22	(1.76-2.81)
History of Migraine/Headache	1.85	(1.50-2.28)

Discussion/Conclusions

Diagnostic delays appear to be common among patients ultimately diagnosed with HSE. We estimate that 20 percent of patients experience diagnostic delay.

Delays were substantially more common in emergency department settings than hospital settings (odds ratio: 15.86). Perhaps because patients admitted to the hospital are more likely to have a lumbar puncture.

Patients with a history of a diagnosis for "migraine" or "headache" were more likely to experience a diagnostic delay (odds ratio: 1.85).

Patients with visits for fevers had the shortest length of diagnostic delays.

Given the relatively high numbers of patients who experience a delay and the duration of the delays, new approaches are needed to:

- identify patients at risk for HSE sooner;
- test patients sooner;
- improve diagnostic testing;
- determine and refine risk factors for HSE or for missing HSE

Limitations and Future Studies

- Administrative claims data alone cannot be used to validate diagnosis or delay (no microbiology results are contained in the data set).
- This work did not consider medication use.
- Future work should validate diagnostic delay results using clinic/EMR records.
- Future work should investigate building models to forecast HSE based on presenting complaints, diagnoses and patterns of care to develop decision rules.
- Future work should investigate outcomes associated with diagnostic delays for HSE.