Epidemiology of Human Herpesvirus-6 Meningoencephalitis in Los Angeles County, 2016-2020

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Background

Human herpesvirus 6 (HHV-6) is ubiquitous, and a known central nervous system (CNS) pathogen. However, HHV-6 in cerebrospinal fluid (CSF) without clinical findings of meningoencephalitis (ME) may not represent true infection, but rather, asymptomatic viral reactivation, chromosomal integration, or latent activation. With the introduction in 2015 of a rapid polymerase chain reaction (PCR) multiplex panel that simultaneously tests for 14 CNS pathogens, reports of HHV-6 PCR positive ME have increased. We sought to understand the epidemiology of HHV-6 ME by evaluating reported cases in Los Angeles County (LAC) between 2016-2020.

Methods

- ME is a reportable condition in LAC
- We reviewed clinical, laboratory, and radiologic data for all HHV-6 PCR positive cases reported in LAC between 2016-2020
- We developed case classification categories, “unlikely,” “possible,” and “likely”, based on symptoms, CSF profile, and alternative diagnoses

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Criteria

Classification Criteria for HHV-6 ME in Patients with HHV-6 PCR Positive CSF

1. **Patient with an alternative diagnosis for symptoms of ME*: Unlikely**
2. **If no alternative diagnosis:**

	Symptoms of ME*	No Symptoms of ME
CSF normal	Possible	Unlikely
CSF abnormal**	Likely	Possible

Definitions:
*Symptoms of meningoencephalitis: fever plus seizure, altered mental status, bulging fontanelle, headache, meningismus, or new neurological symptoms

**Abnormal CSF:
-WBC >$5x10^3/\mu L^{\dagger}$ (> 20 in neonates)
-Protein >58 mg/dL (>150 in infants)
† Except in cases of systemic leukopenia, defined as <$4.4x10^3$ cells/µL (or local lab lower limit of normal)

Results

67 HHV-6 ME cases were reported 2016-2020:

- Reports increased over time, with one in 2016, 12 in 2017, 17 in 2018, 20 in 2019, and 17 in 2020
- Median patient age was 9 months (range 0d-78y), 47 (70%) were < 3 years old
- Forty-four patients (66%) were male
- Six (9%) were immunocompromised, including one hematopoietic stem cell transplant recipient
- Nineteen (28%) had abnormal CSF, and eight (12%) received therapy for HHV-6

- Five cases (7%) were classified as “likely” HHV-6 ME
- 12 cases (18%) were classified as “possible” HHV-6 ME
- 50 cases (75%) were classified as “unlikely” HHV-6 ME

“Likely” cases ranged from 7 months to 12 years old; none was immunocompromised. One received antiviral therapy and was discharged to a rehabilitation facility; four were discharged home fully recovered

Year	Likely	Possible	Unlikely	Total
2016	0	0	1 (100%)	1
2017	0	1 (8%)	11 (92%)	12
2018	2 (12%)	4 (24%)	11 (65%)	17
2019	1 (5%)	2 (10%)	17 (85%)	20
2020	2 (12%)	5 (29%)	10 (59%)	17
Total	5 (7%)	12 (18%)	50 (75%)	67

Limitations and Future Directions

- Classifying cases with alternative diagnoses as ‘unlikely” HHV-6 ME may miss cases with multiple true infections, particularly in the immunocompromised
- These criteria are to better understand epidemiology and not to guide clinical care
- The presence of HHV-6 DNA in CSF without evidence of inflammation is not fully understood

Conclusion

- The majority of reported HHV-6 ME cases were classified as “unlikely” based on our criteria
- The significance of HHV-6 in CSF remains challenging to determine both clinically and epidemiologically
- In the setting of increased testing, increased detection of HHV-6 in CSF may not reflect increasing rates of HHV-6 ME
- It is important to consider clinical presentation, CSF profile and other diagnoses to understand the true burden of HHV-6 ME