

# Encephalitis Surveillance through the Emerging Infections Program, 1997–2010

Karen C. Bloch, Carol A. Glaser

## Medscape EDUCATION ACTIVITY

Medscape, LLC is pleased to provide online continuing medical education (CME) for this journal article, allowing clinicians the opportunity to earn CME credit.

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint providership of Medscape, LLC and Emerging Infectious Diseases. Medscape, LLC is accredited by the ACCME to provide continuing medical education for physicians.

Medscape, LLC designates this Journal-based CME activity for a maximum of 1.0 **AMA PRA Category 1 Credit(s)<sup>TM</sup>**. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

All other clinicians completing this activity will be issued a certificate of participation. To participate in this journal CME activity: (1) review the learning objectives and author disclosures; (2) study the education content; (3) take the post-test with a 75% minimum passing score and complete the evaluation at <http://www.medscape.org/journal/eid>; (4) view/print certificate.

**Release date: August 14, 2015; Expiration date: August 14, 2016**

### Learning Objectives

Upon completion of this activity, participants will be able to:

- Evaluate clinical profiles associated with different etiologic agents of encephalitis
- Assess challenges in diagnosing the etiology of encephalitis
- Distinguish the most common etiology of sporadic encephalitis in the United States
- Determine the epidemiology of the anti-N-methyl-D-aspartate receptor in encephalitis

### CME Editor

**Jean Michaels Jones**, Technical Writer/Editor, *Emerging Infectious Diseases*. *Disclosure: Jean Michaels Jones has disclosed no relevant financial relationships.*

### CME Author

**Charles P. Vega, MD**, Clinical Professor of Family Medicine, University of California, Irvine. *Disclosure: Charles P. Vega, MD, has disclosed the following financial relationships: served as an advisor or consultant for Lundbeck, Inc.; McNeil Pharmaceuticals; Takeda Pharmaceuticals North America, Inc.*

### Authors

*Disclosures: Karen C. Bloch, MD, MPH, and Carol A. Glaser, DVM, MD, have disclosed no relevant financial relationships.*

Encephalitis is a devastating illness that commonly causes neurologic disability and has a case fatality rate >5% in the United States. An etiologic agent is identified in <50% of cases, making diagnosis challenging. The Centers for Disease Control and Prevention Emerging Infections Program (EIP) Encephalitis Project established syndromic surveillance for

encephalitis in New York, California, and Tennessee, with the primary goal of increased identification of causative agents and secondary goals of improvements in treatment and outcome. The project represents the largest cohort of patients with encephalitis studied to date and has influenced case definition and diagnostic evaluation of this condition. Results of this project have provided insight into well-established causal pathogens and identified newer causes of infectious and autoimmune encephalitis. The recognition of a possible relationship between enterovirus D68 and acute flaccid paralysis with myelitis underscores the need for ongoing vigilance for emerging causes of neurologic disease.

Author affiliations: Vanderbilt University, Nashville, Tennessee, USA (K.C. Bloch); Kaiser Permanente, Oakland, California, USA (C.A. Glaser)

DOI: <http://dx.doi.org/10.3201/eid2109.150295>

Encephalitis is a potentially devastating illness: the related case-fatality rate in the United States is >5% (1), and substantial neurologic disability is common among survivors. Historically, this syndromic illness has been difficult to diagnose: an etiologic agent was identified in <50% of encephalitis cases in the United States diagnosed during 1987–1998 (2). A major barrier to diagnosis during that period was the lack of sensitive, noninvasive laboratory techniques to identify central nervous system pathogens. However, by the early 1990s, PCR was proven to be comparable to brain biopsy for the diagnosis of herpes simplex virus (HSV) encephalitis, without the need for an invasive surgical procedure (3). There was optimism that application of PCR could also improve microbiologic diagnoses of encephalitis infections caused by other pathogens and, by extension, the outcome of the illnesses. The Emerging Infections Program (EIP), which is funded by the Centers for Disease Control and Prevention, initiated the Encephalitis Project, a syndromic surveillance program for encephalitis in existing EIP sites beginning in New York in 1997, California in 1998, and Tennessee in 2000, and all ending by 2010.

## Materials and Methods

Researchers from the 3 sites collaborated to develop shared inclusion criteria that captured both infectious and post-infectious syndromes such as acute disseminated encephalomyelitis (ADEM), using a case definition adapted from previous studies (Table 1). The case definition was constructed to maximize sensitivity, acknowledging that a proportion of cases meeting the EIP standardized definition may have had other conditions known to mimic encephalitis. Common exclusion criteria included patient age <6 months, immunocompromised status (HIV/AIDS or transplantation), and outpatient status. The California and Tennessee EIP sites collected comparable demographic, epidemiologic, and clinical information that was able to be aggregated for combined data analysis (5). The New York site focused on development of molecular diagnostic assays (6–8).

A major goal of the EIP Encephalitis Project was the implementation of a standardized diagnostic algorithm to be used at all 3 sites. However, early in the course of the project, it was recognized that there were substantial regional differences in the frequency of specific pathogens, such as arboviral and rickettsial infections. The concept of a standardized testing algorithm thus evolved to include a site-specific core set of routinely performed laboratory tests to capture the most common and most treatable etiologies, supplemented by targeted testing on the basis of season, exposures, clinical features, and geography (Table 2) (9). For instance, Powassan virus, a tickborne pathogen endemic to the northern United States and Canada and there-

**Table 1.** Case definition for encephalitis in the Emerging Infections Program Encephalitis Project, 1997–2010\*

| Criteria  |
|---|
| Major criterion (required): Altered mental status lasting $\geq 24$ h   |
| Plus $\geq 1$ of 6 minor criteria:  |
| 1. Fever $\geq 38^{\circ}\text{C}$ occurring $\leq 72$ h before or after hospital admission   |
| 2. Seizures   |
| 3. Focal neurologic deficits not previously present on examination  |
| 4. Cerebrospinal fluid pleocytosis ( $\geq 5$ leukocytes/ $\text{mm}^3$ )   |
| 5. Abnormal electroencephalogram  |
| 6. Abnormal neuroimaging (computed tomography or magnetic resonance imaging) representing an acute process  |
| *International Encephalitis Consortium case definition requires the presence of the major criteria plus $\geq 3$ minor criteria for confirmed/probable; $\geq 2$ for probable encephalitis (4). |

fore not included in the core algorithm of the Tennessee Unexplained Encephalitis Project, was diagnosed in a patient from New York who became ill during a trip to Tennessee, underscoring the importance of a thorough travel history to guide laboratory evaluation (10). This concept of tiered or individualized testing has subsequently been endorsed in management guidelines by the Infectious Diseases Society of America (11) and in a consensus statement of the International Encephalitis Consortium, an ad hoc group of subject matter experts and patient representatives (4).

A final unique feature of the EIP Encephalitis Project was the development of defined a priori pathogen-specific criteria to establish causality. Cases were classified as having a possible, probable, or confirmed etiology constructed on the basis of whether the identified pathogen was a well-established cause of encephalitis and whether there was direct evidence of central nervous system infection (12). For example, mycoplasma infection was the single most common infectious etiology identified in the California Encephalitis Project; however, in most cases, the diagnosis was based on serologic test results with no corroborating evidence of neuroinvasive disease; therefore, these cases were classified as having a “possible” diagnosis (13).

## Encephalitis Profiles

Although the findings for all patients enrolled in the study met the encephalitis case definition, there was tremendous heterogeneity in the clinical characteristics and outcomes of the cases. The large numbers of patients in these projects facilitated recognition of discrete clinical patterns. For example, temporal lobe abnormalities were predictive of HSV encephalitis. It was hypothesized that similar patterns might represent clinical clues to other infectious causes; ultimately, several subsets that had particular characteristics, referred to as encephalitis profiles, were identified (Table 3) (14). Although none of these profiles were found to be pathognomonic for a single

**Table 2.** Core diagnostic testing algorithm for the Emerging Infections Program Encephalitis Project, 1997–2010\*

| Pathogen                     | Specimen type | Test type | Seasonality    |
|------------------------------|---------------|-----------|----------------|
| <b>Viruses</b>               |               |           |                |
| Adenovirus                   | NP swab       | PCR       | Year-round     |
| Arbovirus panel†             | Serum         | Serology  | May–October    |
| Enteroviruses                | CSF           | PCR       | Year-round     |
|                              | NP swab       | PCR       | Year-round     |
|                              | Rectal swab   | PCR       | Year-round     |
| Epstein-Barr virus           | CSF           | PCR       | Year-round     |
|                              | Serum         | Serology  | Year-round     |
| Herpes simplex virus 1 and 2 | CSF           | PCR       | Year-round     |
| Human herpesvirus 6          | CSF           | PCR       | Year-round     |
| Influenza virus A and B      | NP swab       | PCR       | November–April |
| Parainfluenza virus 1–3      | NP swab       | PCR       | November–April |
| Rotavirus                    | Rectal swab   | Antigen   | November–April |
| Varicella zoster virus       | CSF           | PCR       | Year-round     |
| West Nile virus              | CSF           | Serology  | May–October    |
|                              | Serum         | Serology  | May–October    |
| <b>Bacteria</b>              |               |           |                |
| <i>Bartonella</i> spp.       | Serum         | Serology  | Year-round     |
| <i>Chlamydia pneumoniae</i>  | NP swab       | PCR       | Year-round     |
| <i>Ehrlichia</i> spp.        | Whole blood   | PCR       | May–October    |
|                              | Serum         | Serology  | May–October    |
| <i>Mycoplasma pneumoniae</i> | NP swab       | PCR       | Year-round     |
|                              | Serum         | Serology  | Year-round     |
| Rickettsia spp.              | Serum         | Serology  | May–October    |
| <i>Treponema pallidum</i>    | CSF           | VDRL      | Year-round     |
|                              | Serum         | RPR       | Year-round     |

\*Diagnostic testing algorithm at the Tennessee site; regional differences and testing availability associated with minor variations in core testing at the California site. Additional supplementary testing was performed when indicated based on individualized epidemiologic, demographic, clinical, or radiographic features. CSF, cerebrospinal fluid; NP, nasopharyngeal; VDRL, venereal disease research laboratory test; RPR, rapid plasma reagin.

†Arbovirus panel included Lacrosse virus, St. Louis encephalitis virus, Western equine encephalitis virus, and Eastern equine encephalitis virus.

pathogen, this schema has yielded new insights into the epidemiology and potentially to the treatment of subsets of patients who have encephalitis. For instance, the California Encephalitis Project identified a group of patients with profound refractory seizures, accounting for 5% of all cases enrolled at this site (15). This profile, subsequently characterized as idiopathic catastrophic epileptic encephalopathy or febrile infection-related epilepsy syndrome, is now widely acknowledged as a particularly severe form of encephalitis. Although the cause of this syndrome remains unknown, by identifying this unique phenotype, promising therapies such as initiation of a ketogenic diet have been identified (16).

### Unexplained Cases

The EIP Encephalitis Project represents the largest cohort of patients (>5,000) with encephalitis studied to date: >4,000 case-patients were enrolled in the California Encephalitis Project and >700 in the Tennessee Unexplained Encephalitis Project. (Cases at the New York site were enrolled for diagnostic testing only.) Despite the rigorous diagnostic testing algorithm, in approximately half of all cases, no underlying cause for encephalitis was identified. Several factors likely contribute to the frustratingly high proportion of cases that had unidentified pathogens. Foremost is that, for many pathogens other than HSV, PCR of cerebrospinal fluid

(CSF) was not an optimal diagnostic test. The high sensitivity of PCR in some instances lead to detection of reactivated viruses in CSF of questionable significance, such as Epstein-Barr virus (17) and human herpesvirus 6 (18). Also, for many organisms, serologic testing was superior to PCR, but antibodies were often not detectable until several weeks after the acute infection, and serum samples from the convalescent period was not always available. Issues related to specimen integrity such as volume, storage, and timing of collection likely contributed to inability to identify a cause in some cases. Finally, it has become increasingly clear that >5% of case-patients in whom encephalitis was presumed to have been caused by an infectious organism actually had autoimmune encephalitis. Retrospective testing of specimens from case-patients with undiagnosed disease in the California Encephalitis Project identified a newly described autoimmune syndrome, termed anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, as the leading cause of encephalitis among patients ≤30 years of age (19). Our initial supposition that the large proportion of undiagnosed cases might be caused by the presence of undiscovered pathogens does not appear to be the case; independent testing of numerous samples at several research laboratories using multiple different techniques, including next-generation sequencing, did not identify any novel infectious agents.

## Results

### Established Causes of Encephalitis

A confirmed or probable cause of encephalitis was identified in approximately one third of cases studied. HSV, the most frequent cause of sporadic encephalitis in the United States (1), was underrepresented in this cohort, reflecting a referral bias toward more diagnostically challenging cases. In fact, clinician referral to one of the EIP encephalitis projects was often deferred until a commercially available HSV PCR test returned negative results, which led to the recognition that HSV PCR analysis early in the disease course could represent a false-negative result (20). On the basis of this observation, the recommendation for repeat HSV PCR on a subsequent CSF specimen for patients whose symptoms indicate a high clinical suspicion for HSV encephalitis has been incorporated into national management guidelines (11).

The substantial number of patients with encephalitis identified through this project enabled robust pathogen-specific case series of well-established but relatively rare causes of encephalitis. These included large series of patients with enteroviral encephalitis (21), tuberculosis meningoencephalitis (22), and amebic granulomatous encephalitis (23). Furthermore, the project was able to explore the putative association of several organisms for which a causal relationship with encephalitis remains tenuous, such as rotavirus (24), human metapneumovirus (25), and *Mycoplasma pneumoniae* (13). Although the latter organism remains a controversial cause of encephalitis because of the difficulty in demonstrating neuroinvasion, the frequency with which it is detected, particularly in children, has led to the inclusion of *Mycoplasma* serologic testing as part of the recommended pediatric testing algorithm (4).

### Autoimmune Cases of Encephalitis

Before the start of the EIP Encephalitis Project, it was well recognized that paraneoplastic syndromes could cause

limbic encephalitis, albeit infrequently. In 2007, Josep Dalmau and colleagues described anti-NMDAR encephalitis, a novel form of autoimmune encephalitis (26). This syndrome was initially reported in women with ovarian teratomas and was believed to represent a paraneoplastic phenomenon. Testing of residual samples from the California Encephalitis Project confirmed that anti-NMDAR encephalitis affects a much broader spectrum of patients, including male and pediatric patients without a neoplastic antigenic stimulus (27). Among patients  $\leq 30$  years of age, anti-NMDAR encephalitis accounted for more cases than HSV, West Nile virus (WNV), and varicella zoster virus combined (19). A recent study showed that HSV encephalitis may serve as an antigenic trigger for subsequent development of anti-NMDAR encephalitis (28).

### Vaccine-Preventable Cases of Encephalitis

The widespread implementation of the varicella vaccine in the 1990s has essentially eliminated varicella zoster virus as a cause of pediatric encephalitis (29). Although various immunizations have been linked to encephalitis (30), a large review of pediatric cases showed no temporal relationship between vaccination and subsequent encephalitis, confirming the rarity of vaccine-associated neurologic complications (31). This finding, coupled with the identification of encephalitis as a potentially fatal complication of vaccine-preventable infections such as measles (32) and influenza virus (33), highlights the critical importance of universal immunization.

### Emerging Pathogens and Syndromes

When the EIP Encephalitis Project was initiated, it was unforeseeable that a virus never before identified in the Western Hemisphere would cause an encephalitis epidemic in the United States. Yet, during 1999–2013, more than 17,000 cases of West Nile neuroinvasive disease were diagnosed; the case-fatality rate was 9% (34). After the emergence of WNV in 1999, the New York site was uniquely

**Table 3.** Emerging Infections Program Encephalitis Project clinical profiles, 1997–2010\*

| Clinical profile                       | Patient description   | Comments  |
|--|---|---|
| <b>Focal</b>                           |   |   |
| Temporal lobe                          | Temporal lobe enhancement on imaging or activity on EEG                                       | HSV accounted for approximately one third of cases  |
| Extrapyramidal<br>Cerebellar           | Movement disorder<br>Ataxia or gait disorder, or focal cerebellar lesion on imaging           | Measles (SSPE), autoimmune encephalitides<br>Acute EBV infection seen in a minority of cases      |
| <b>Generalized</b>                     |   |   |
| Cerebral edema<br>Intractable seizures | Neuroimaging showing diffuse brain edema<br>Seizures requiring anesthetic coma for management | Deaths exceed 70%<br>Majority of case-patients: pediatric patients with prolonged hospitalization |
| Seizure with rapid recovery            | Onset with seizure and return to baseline mental status in <96 h                              | CSF typically bland; <i>Bartonella</i> spp. most common cause (cat-scratch encephalopathy)        |
| Psychosis                              | New onset of prominent psychiatric symptoms   | Anti-NMDAR antibodies common<br>in this syndrome  |

\*EEG, electroencephalogram; HSV, herpes simplex virus; SSPE, subacute sclerosing panencephalitis; EBV, Epstein-Barr virus; NMDAR, anti-N-methyl-D-aspartate receptor.

positioned to assist with the identification of this unexpected pathogen, and to perform surveillance for additional cases (35). As the virus spread throughout the continental United States, the large numbers of patients referred to California Encephalitis Project enabled analysis of WNV encephalitis among pediatric patients (36) and identification of risk factors predisposing to neuroinvasive disease (37).

The infrastructure that proved invaluable in enabling a rapid response to the WNV epidemic also was instrumental in identifying an emerging neurologic syndrome characterized by acute flaccid paralysis. In 2012, several physicians familiar with the California Encephalitis Project contacted the project, reporting cases of previously healthy patients with acute onset of a polio-like illness. Routine testing for organisms associated with acute flaccid paralysis returned negative results, raising concern for a novel agent or pathogen causing this syndrome. These sporadic cases occurred at geographically disparate sites and likely would not have been recognized without an existing surveillance mechanism. Ultimately, more than 23 cases were identified in California (38). The sentinel cluster of cases in California triggered national surveillance, resulting in 88 cases identified to date in 32 states (39). Investigation is ongoing, and although no causative pathogen has been identified, enterovirus D68 has been implicated in several cases (40).

## Discussion

The EIP Encephalitis Project has demonstrated the value of syndromic surveillance in a constantly changing environment. Globally, this project represents the largest known cohort of patients with encephalitis. The robust sample size provided sufficient power to investigate recognized pathogens and to identify newer causes of encephalitis, both infectious and autoimmune. Syndromic surveillance confirmed that previously common causes of pediatric encephalitis such as VZV have been all but eliminated by vaccination, and conversely, that childhood immunization is not substantially associated with development of encephalitis. The recognition of an emerging syndrome of acute flaccid paralysis with myelitis, possibly caused by enterovirus D68, underscores the need for ongoing vigilance for emerging causes of neurologic disease.

Support for the EIP Encephalitis Project was provided by a grant from the Centers for Disease Control and Prevention Emerging Infections Program to the California Department of Health (U50/CCU915546-09) and to the Tennessee Department of Health (U50/CCU416123-09).

Dr. Bloch is an Associate Professor in Medicine (Infectious Diseases) and Health Policy at Vanderbilt University in Nashville. She served as the principal investigator for the Tennessee Unexplained Encephalitis Surveillance Project. Her research interests focus on the study of encephalitis and arthropod-borne infections.

Dr. Glaser is a pediatric infectious disease physician at Kaiser Permanente in Oakland, California who served as the principal investigator for the California Encephalitis Project. Her primary research interests are zoonotic illness and neurologic disease.

## References

- Vora NM, Holman RC, Mehal JM, Steiner CA, Blanton J, Sejvar J. Burden of encephalitis-associated hospitalizations in the United States, 1998–2010. *Neurology*. 2014;82:443–51. <http://dx.doi.org/10.1212/WNL.000000000000086>
- Khetsuriani N, Holman RC, Anderson LJ. Burden of encephalitis-associated hospitalizations in the United States, 1988–1997. *Clin Infect Dis*. 2002;35:175–82. <http://dx.doi.org/10.1086/341301>
- Lakeman FD, Whitley RJ. Diagnosis of herpes simplex encephalitis: application of polymerase chain reaction to cerebrospinal fluid from brain-biopsied patients and correlation with disease. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. *J Infect Dis*. 1995;171:857–63. <http://dx.doi.org/10.1093/infdis/171.4.857>
- Venkatesan A, Tunkel AR, Bloch KC, Lauring AS, Sejvar J, Bitnun A, et al.; International Encephalitis Consortium. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the International Encephalitis Consortium. *Clin Infect Dis*. 2013;57:1114–28. <http://dx.doi.org/10.1093/cid/cit458>
- DuBray K, Anglemyer A, LaBeaud AD, Flori H, Bloch K, Joaquin KS, et al. Epidemiology, outcomes and predictors of recovery in childhood encephalitis: a hospital-based study. *Pediatr Infect Dis J*. 2013;32:839–44.
- Campbell WP, Huang C. Sequence comparisons of medium RNA segment among 15 California serogroup viruses. *Virus Res*. 1999;61:137–44. [http://dx.doi.org/10.1016/S0168-1702\(99\)00033-7](http://dx.doi.org/10.1016/S0168-1702(99)00033-7)
- Huang C, Campbell W, Grady L, Kirouac I, LaForce FM. Diagnosis of Jamestown Canyon encephalitis by polymerase chain reaction. *Clin Infect Dis*. 1999;28:1294–7. <http://dx.doi.org/10.1086/514789>
- Huang C, Morse D, Slater B, Anand M, Tobin E, Smith P, et al. Multiple-year experience in the diagnosis of viral central nervous system infections with a panel of polymerase chain reaction assays for detection of 11 viruses. *Clin Infect Dis*. 2004;39:630–5. <http://dx.doi.org/10.1086/422650>
- Bloch KC, Glaser C. Diagnostic approaches for patients with suspected encephalitis. *Curr Infect Dis Rep*. 2007;9:315–22. <http://dx.doi.org/10.1007/s11908-007-0049-5>
- Hicar MD, Edwards K, Bloch K. Powassan virus infection presenting as acute disseminated encephalomyelitis in Tennessee. *Pediatr Infect Dis J*. 2011;30:86–8. <http://dx.doi.org/10.1097/INF.0b013e3181f2f492>
- Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, et al.; Infectious Diseases Society of America. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2008;47:303–27. <http://dx.doi.org/10.1086/589747>
- Glaser CA, Gilliam S, Schnurr D, Forghani B, Honarmand S, Khetsuriani N, et al.; California Encephalitis Project. In search of encephalitis etiologies: diagnostic challenges in the California Encephalitis Project, 1998–2000. *Clin Infect Dis*. 2003;36:731–42. <http://dx.doi.org/10.1086/367841>
- Christie LJ, Honarmand S, Talkington DF, Gavali SS, Preas C, Pan CY, et al. Pediatric encephalitis: what is the role of *Mycoplasma pneumoniae*? *Pediatrics*. 2007;120:305–13. <http://dx.doi.org/10.1542/peds.2007-0240>

14. Glaser CA, Honarmand S, Anderson LJ, Schnurr DP, Forghani B, Cossen CK, et al. Beyond viruses: clinical profiles and etiologies associated with encephalitis. *Clin Infect Dis*. 2006;43:1565–77. <http://dx.doi.org/10.1086/509330>
15. Glaser CA, Gilliam S, Honarmand S, Tureen JH, Lowenstein DH, Anderson LJ, et al. Refractory status epilepticus in suspect encephalitis. *Neurocrit Care*. 2008;9:74–82. <http://dx.doi.org/10.1007/s12028-007-9042-y>
16. Singh RK, Joshi SM, Potter DM, Leber SM, Carlson MD, Shellhaas RA. Cognitive outcomes in febrile infection-related epilepsy syndrome treated with the ketogenic diet. *Pediatrics*. 2014;134:e1431–5. <http://dx.doi.org/10.1542/peds.2013-3106>
17. Weinberg A, Bloch KC, Li S, Tang YW, Palmer M, Tyler KL. Dual infections of the central nervous system with Epstein-Barr virus. *J Infect Dis*. 2005;191:234–7. <http://dx.doi.org/10.1086/426402>
18. Yao K, Honarmand S, Espinosa A, Akhyani N, Glaser C, Jacobson S. Detection of human herpesvirus-6 in cerebrospinal fluid of patients with encephalitis. *Ann Neurol*. 2009;65:257–67. <http://dx.doi.org/10.1002/ana.21611>
19. Gable MS, Sheriff H, Dalmaj J, Tilley DH, Glaser CA. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. *Clin Infect Dis*. 2012;54:899–904. <http://dx.doi.org/10.1093/cid/cir1038>
20. To TM, Soldatos A, Sheriff H, Schmid DS, Espinosa N, Cosentino G, 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. <http://dx.doi.org/10.1097/INF.0000000000000422>
21. Fowlkes AL, Honarmand S, Glaser C, Yagi S, Schnurr D, Oberste MS, et al. Enterovirus-associated encephalitis in the California encephalitis project, 1998–2005. *J Infect Dis*. 2008;198:1685–91. <http://dx.doi.org/10.1086/592988>
22. Christie LJ, Loeffler AM, Honarmand S, Flood JM, Baxter R, Jacobson S, et al. Diagnostic challenges of central nervous system tuberculosis. *Emerg Infect Dis*. 2008;14:1473–5. <http://dx.doi.org/10.3201/eid1409.070264>
23. Schuster FL, Yagi S, Gavali S, Michelson D, Raghavan R, Blomquist I, et al. Under the radar: *Balamuthia* amoebic encephalitis. *Clin Infect Dis*. 2009;48:879–87. <http://dx.doi.org/10.1086/597260>
24. Lynch M, Lee B, Azimi P, Gentsch J, Glaser C, Gilliam S, et al. Rotavirus and central nervous system symptoms: cause or contaminant? Case reports and review. *Clin Infect Dis*. 2001;33:932–8. <http://dx.doi.org/10.1086/322650>
25. Arnold JC, Singh KK, Milder E, Spector SA, Sawyer MH, Gavali S, et al. Human metapneumovirus associated with central nervous system infection in children. *Pediatr Infect Dis J*. 2009;28:1057–60. <http://dx.doi.org/10.1097/INF.0b013e3181acd221>
26. Dalmaj J, Tüzün E, Wu HY, Masjuan J, Rossi JE, Voloschin A, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol*. 2007;61:25–36. <http://dx.doi.org/10.1002/ana.21050>
27. Gable MS, Gavali S, Radner A, Tilley DH, Lee B, Dwyer L, et al. Anti-NMDA receptor encephalitis: report of ten cases and comparison with viral encephalitis. *Eur J Clin Microbiol Infect Dis*. 2009;28:1421–9. <http://dx.doi.org/10.1007/s10096-009-0799-0>
28. Armangue T, Leypoldt F, Málaga I, Raspall-Chaure M, Martí I, Nichter C, et al. Herpes simplex virus encephalitis is a trigger of brain autoimmunity. *Ann Neurol*. 2014;75:317–23.
29. Pahud BA, Glaser CA, Dekker CL, Arvin AM, Schmid DS. Varicella zoster disease of the central nervous system: epidemiological, clinical, and laboratory features 10 years after the introduction of the varicella vaccine. *J Infect Dis*. 2011;203:316–23. <http://dx.doi.org/10.1093/infdis/jiq066>
30. Melekhin VV, Karem KL, Damon IK, Bloch KC. Encephalitis after secondary smallpox vaccination. *Clin Infect Dis*. 2009;48:e1–2. <http://dx.doi.org/10.1086/595555>
31. Pahud BA, Rowhani-Rahbar A, Glaser C, Gavali S, Salibay CJ, Fireman B, et al. Lack of association between childhood immunizations and encephalitis in California, 1998–2008. *Vaccine*. 2012;30:247–53. <http://dx.doi.org/10.1016/j.vaccine.2011.10.104>
32. Honarmand S, Glaser CA, Chow E, Sejvar JJ, Preas CP, Cosentino GC, et al. Subacute sclerosing panencephalitis in the differential diagnosis of encephalitis. *Neurology*. 2004;63:1489–93. <http://dx.doi.org/10.1212/01.WNL.0000142090.62214.61>
33. Rellosa N, Bloch KC, Shane AL, Debiasi RL. Neurologic manifestations of pediatric novel H1N1 influenza infection. *Pediatr Infect Dis J*. 2011;30:165–7. <http://dx.doi.org/10.1097/INF.0b013e3181f2de6f>
34. Centers for Disease Control and Prevention. ArboNET. West Nile virus disease cases and deaths reported to CDC by year and clinical presentation, 1999–2013 [cited 2015 Feb 10]. [http://www.cdc.gov/westnile/resources/pdfs/cummulative/99\\_2013\\_CasesAndDeathsClinicalPresentationHumanCases.pdf](http://www.cdc.gov/westnile/resources/pdfs/cummulative/99_2013_CasesAndDeathsClinicalPresentationHumanCases.pdf)
35. Briese T, Jia XY, Huang C, Grady LJ, Lipkin WI. Identification of a Kunjin/West Nile-like flavivirus in brains of patients with New York encephalitis. *Lancet*. 1999;354:1261–2. [http://dx.doi.org/10.1016/S0140-6736\(99\)04576-6](http://dx.doi.org/10.1016/S0140-6736(99)04576-6)
36. Francisco AM, Glaser C, Frykman E, Cole B, Cheung M, Meyers H, et al. 2004 California pediatric West Nile virus case series. *Pediatr Infect Dis J*. 2006;25:81–4. <http://dx.doi.org/10.1097/01.inf.0000195612.04911.b2>
37. Jean CM, Honarmand S, Louie JK, Glaser CA. Risk factors for West Nile virus neuroinvasive disease, California, 2005. *Emerg Infect Dis*. 2007;13:1918–20. <http://dx.doi.org/10.3201/eid1312.061265>
38. Ayscue P, Van Haren K, Sheriff H, Waubant E, Waldron P, Yagi S, et al.; Centers for Disease Control and Prevention. Acute flaccid paralysis with anterior myelitis—California, June 2012–June 2014. *MMWR Morb Mortal Wkly Rep*. 2014;63:903–6.
39. Centers for Disease Control and Prevention. Notes from the field: acute flaccid myelitis among persons aged ≤21 years—United States, August–November 2014. *MMWR Morb Mortal Wkly Rep*. 2015;63:1243–4.
40. Messacar K, Schreiner TL, Maloney JA, Wallace A, Ludke J, Oberste MS, et al. A cluster of acute flaccid paralysis and cranial nerve dysfunction temporally associated with an outbreak of enterovirus D68 in children in Colorado, USA. *Lancet*. 2015;385:1662–71. [http://dx.doi.org/10.1016/S0140-6736\(14\)62457-0](http://dx.doi.org/10.1016/S0140-6736(14)62457-0)

---

Address for correspondence: Karen C. Bloch, Departments of Medicine (Infectious Diseases) and Health Policy, A-2200 Medical Center North, Vanderbilt University Medical Center, Nashville, TN 37232-2582, USA; email: karen.bloch@vanderbilt.edu