Diagnostic Approaches for Patients with Suspected Encephalitis

Karen C. Bloch, MD, MPH, and Carol Glaser, DVM, MPVM, MD

Corresponding author
Karen C. Bloch, MD, MPH
Vanderbilt University Medical Center, A-2200 Medical Center North, Nashville, TN 27232-2582, USA.
E-mail: karen.bloch@vanderbilt.edu

Current Infectious Disease Reports 2007, **9:**315–322
Current Medicine Group LLC ISSN 1523-3847
Copyright © 2007 by Current Medicine Group LLC

Encephalitis represents a diagnostic challenge, with an infectious etiology identified in only 40% to 70% of cases. More than 100 agents have been either definitively or anecdotally associated with encephalitis. Important considerations for diagnosis include selection of the appropriate clinical specimen (serum vs cerebrospinal fluid), determining the most sensitive diagnostic assay (serology vs polymerase chain reaction), and assessing causality when an organism is identified outside of the central nervous system (eg, a positive nasal swab for influenza). This review aims to provide an evidence-based, clinically relevant approach to the diagnostic evaluation of patients presenting with encephalitis, focusing on the most common or important causes in the immunocompetent host. Diagnostic issues associated with encephalitis due to herpes-group viruses, arboviruses (including West Nile virus), rickettsiae, bartonella, enteroviruses, and rabies are discussed in-depth. Diagnostic testing should be individualized based on clinical presentation and epidemiology.

Introduction

Encephalitis is a complex and severe neurologic syndrome associated with significant morbidity and mortality. Encephalitis implies infection of the brain parenchyma, but the clinical presentation is remarkably broad. Although no standardized case definition exists, patients typically present with alteration in consciousness, accompanied by fever, headache, seizures, and/or focal neurologic signs.

Encephalitis represents a diagnostic challenge, because an etiology is only identified in 40% to 70% of cases [1–3]. Without the identification of a neurotropic agent or confirmation of infection by brain tissue analysis, the diagnosis of encephalitis is presumptive and based on clinical characteristics, which are often mimicked by noninfectious entities. Studies suggest that approximately 10% of patients initially thought to have an infectious cause for their encephalitis are ultimately diagnosed with a noninfectious condition [1]. These noninfectious conditions include neoplasms, autoimmune diseases, stroke, vasculitides, and drug reactions, among others.

At least two forms of infection-related encephalitis exist: primary and post- or parainfectious encephalitis. Primary encephalitis results from direct central nervous system (CNS) invasion by the agent, with primary involvement of the gray matter. In postinfectious encephalitis, the white matter of the brain is typically affected. Clinically, postinfectious or parainfectious encephalitis may resemble primary encephalitis, but the illness is the result of immune-mediated demyelination, and there is often a history of preceding infectious illness or immunization. Despite the distinct pathophysiology of these two entities, there is considerable overlap in the clinical and radiologic characteristics.

Complicating the diagnostic evaluation is the vast array of agents that have been either definitively or anecdotally associated with encephalitis, and diagnostic assays are not widely available for some of these organisms. Another challenge is to determine the causative significance of an infectious agent identified outside of the CNS. For some organisms, such as *Mycoplasma pneumoniae*, influenza, or some of the herpesviruses, causality cannot be assumed despite clear evidence of acute infection at sites distant to the CNS.

This chapter aims to provide an evidence-based, clinically relevant approach to the diagnostic evaluation of patients presenting with encephalitis. Because of the breadth of this topic, the focus of this article is primarily on the most common or important causes of encephalitis in the immunocompetent host. The epidemiology and microbiology of encephalitis differs throughout the world; therefore, the diagnostic evaluation should be modified for patients with travel or residence outside of the continental United States.

Diagnostic Testing Overview

Identifying an etiologic agent in patients with encephalitis requires consideration of the most likely causative organ-

isms, the optimal diagnostic tests for these agents, and the highest yield clinical specimens for testing. Appropriate testing is dependent on the duration of symptoms, because the diagnostic window for cultures and polymerase chain reaction (PCR) is often very short. For cases with a delayed presentation, culture or molecular techniques may be negative, and testing of paired acute and convalescent sera to detect a rise in antibody titer is the most sensitive method to identify an infectious etiology. Conversely, serologic tests may be falsely negative if testing is performed on an acute serum sample before the patient has mounted a detectable humoral immune response.

Knowledge of the epidemiology and clinical presentation of these infections is critical in selecting the specific tests that are appropriate for a given patient. In particular, animal or vector exposures, geographic location, recent travel history, season of the year, exposure to ill contacts, and occupation need to be considered. Table 1 lists recommended methods of diagnostic testing for the most common or well-established causes of encephalitis among immunocompetent hosts. Further diagnostic testing may be appropriate based on individualized exposures or risk factors.

Specimens for Diagnostic Testing

Cerebrospinal fluid

All patients with a clinical presentation suspicious for CNS infection should undergo cerebrospinal fluid (CSF) analysis. Patients with underlying immunocompromise, recent seizures, or focal neurologic signs, including altered mentation or papilledema, should have either a noncontrast CT scan or MRI scan performed prior to lumbar puncture [4]. The only absolute contraindication to lumbar puncture is radiologic evidence of significant mass effect or elevated intracranial pressure. Relative contraindications to lumbar puncture include a platelet count less than 10,000/mm^3 or coagulopathy. An extra tube of CSF (2 mL or more) should be obtained and kept frozen at –70°C, so future testing can be performed based on the clinical course or results of other diagnostic tests.

Routine testing on CSF for all patients should include an opening pressure and the determination of glucose, protein, and leukocyte count. If the leukocyte count is elevated (> 5 cells/mm^3), a differential count should be requested. It is important that the specimen be analyzed promptly, as up to 50% of neutrophils will degrade within 2 hours [5]. Eosinophils in the CSF may also be misidentified as neutrophils by automated cell counters, as the cytologic features are not easily distinguished without Giemsa or Wright staining [6].

In contrast to bacterial meningitis, bacterial species causing encephalitis are fastidious and do not typically grow in routine cultures. However, because of the overlap in presentation between meningitis and encephalitis, spinal fluid should be submitted for bacterial culture in all cases. Viral culture of CSF in encephalitis has an extremely low yield and is rarely indicated [7]. The one exception is viral culture for enteroviruses (EVs), as this may allow serotyping for further characterization.

Fungal meningoencephalitis is typically a subacute illness and is relatively unusual in immunocompetent hosts. Fungal culture of the CSF should be performed in individuals who are immunocompromised or have indolent symptoms. Diagnostic testing on CSF for fungal agents in the appropriate clinical setting includes cryptococcal antigen. In patients with residence or travel to endemic areas, coccidioidomycosis, histoplasmosis, and blastomycosis should also be considered. Similarly, mycobacterial meningoencephalitis typically presents in a subacute fashion, and mycobacterial stains and cultures may be appropriate in immunocompromised patients or those with a suggestive travel or exposure history. Wet mounts of CSF to identify protozoa such as *Naegleria fowleri* should be performed by experienced pathologists in patients with recent freshwater exposure and a neutrophilic pleocytosis.

Serum

Diagnostic testing performed solely on acute serum may be misleading if insufficient time has elapsed for the host to mount a serologic response. Conversely, an isolated elevated immunoglobulin (Ig) G antibody titer on a single serum specimen may be due to acute infection, prior infection, or immunization at an undetermined time in the past. Testing of paired serum samples to demonstrate a significant rise in titer remains the gold standard for most arboviral and rickettsial infections. The limitation of paired serologic testing is that a diagnosis may not be confirmed for several weeks following the acute illness.

A practical approach that reconciles the need to make a rapid diagnosis with the time required for seroconversion is to perform diagnostic testing for the most likely pathogens listed in Table 1 at the time of presentation, and to repeat testing for these agents 10 to 21 days later on a convalescent serum specimen. It is recommended that the laboratory freeze at least 2 mL of acute serum so testing can be performed in parallel to confirm a significant rise in titer.

Nasopharyngeal and rectal swabs

Viral cultures of throat, nasopharynx, and rectum (or stool) may be helpful to identify an infectious etiology of encephalitis. For instance, influenza-associated encephalopathy, a disease primarily seen in children, may be suspected if a patient has a positive rapid antigen test during the appropriate season [8]. Enteroviral shedding from the throat and gastrointestinal tract may be prolonged, and culture of these sites may increase the diagnostic yield in patients with enteroviral encephalitis. Rotavirus antigen testing should be performed on stool specimens from young children with encephalitis and a prodromal diarrheal illness [9].

Table 1. Recommended methods of diagnostic testing for selected causes of encephalitis in immunocompetent hosts

Organism	CSF	Serum	NP swab	Rectal swab	Other	Comments
Viral						
HSV-1/2	PCR	Generally not helpful	NU	NU		PCR of CSF test is the standard. CSF antibody may be useful in retrospective diagnosis.
VZV	PCR	Generally not helpful	NU	NU		PCR of CSF test is the standard. CSF antibody may be useful in retrospective diagnosis.
EBV	PCR	EBV-specific antibodies (EBV VCA, EBNA)	NU	NU		High viral loads in CSF are usually significant. Lower viral loads (< 1000 copies/mL) are of unclear significance.
EV	PCR	N/U	PCR	Culture		Detection of enteroviruses in non-CNS sites supports but does not confirm EV as causative agent.
WNV	IgM; PCR	IgM; IgG-paired	NU	NU		CSF WNV PCR insensitive, serology remains the standard.
Other arboviruses	IgM	IgM; IgG-paired	NU	NU		
Rabies	IgG/IgM; PCR	IgG/IgM	NU	NU	Saliva-PCR; neck-DFA; corneal impressions	Combination of different assays and specimen types are needed for antemortem diagnosis. Public health officials should be contacted immediately if rabies is suspected.
LCM	IgG/IgM	IgG/IgM	NU	NU		Consider consultation with state public health laboratory if LCM is suspected.
Bacterial						
Rickettsia spp	NU	IgG-paired	NU	NU	Skin-PCR or DFA	
Ehrlichia spp	PCR	IgM; IgG-paired	NU	NU	Whole blood-PCR	Morulae may be seen on peripheral blood smears or buffy coat preparations. Sensitivity of PCR on CSF is unknown, but PCR has been validated for whole blood.
Borrelia burgdorferi	PCR; IgG index	IgG	NU	NU		
Treponema pallidum	VDRL	RPR and FTA-ABS	NU	NU		
Mycoplasma pneumoniae	PCR	IgM/IgG	PCR	NU		Positive serology or positive *Mycoplasma* PCR from respiratory tract is suggestive of etiology but not conclusive.
Bartonella spp	NU	IgG-paired	NU	NU	Lymph node-PCR	
Protozoa						
Baylisascaris procynosis	IgG	IgG	NU	NU		Consider in all cases of eosinophilic encephalitis. Testing only available in specialized laboratories.
Balamuthia mandrillaris	PCR	IgG; IgM	NU	NU	IIF of brain tissue	Testing available in specialized laboratories.

CNS—central nervous system; CSF—cerebrospinal fluid; DFA—direct fluorescent antibody; EBNA—Epstein-Barr nuclear antigen; EBV—Epstein-Barr virus; EV—enterovirus; FTA-ABS—fluorescent treponemal antibody absorbed; HSV—herpes simplex virus; Ig—immunoglobulin; IIF—indirect immunofluorescence; LCM—lymphocytic choriomeningitis; NP—nasopharyngeal; NU—no utility; PCR—polymerase chain reaction; RPR—rapid plasma reagin; VCA—viral capsid antigen; VDRL—Venereal Disease Research Laboratory.

Brain tissue

Brain biopsies are seldom performed due to the invasive nature and advent of molecular diagnostics on CSF. However, in challenging cases, particularly those with focal radiographic abnormalities, there may be a role for brain biopsy in establishing an etiologic diagnosis in a patient with encephalitis.

Etiologic Agents

Herpes simplex virus 1

Herpes simplex virus (HSV) 1 is the most commonly identified etiology of sporadic encephalitis and is one the most severe of all viral infection of the CNS [10]. Herpes simplex encephalitis (HSE) is estimated to occur in one to four per 10^6 individuals [11,12]. Approximately two thirds of HSE cases result from reactivation of latent HSV-1, whereas the other third are a result of primary infection. HSE at the time of primary infection is thought to involve infection of olfactory neurons followed by retrograde spread to the brain, whereas reactivation of latent virus in the trigeminal ganglia with spread via tentorial nerves to the frontal and temporal lobes accounts for the remainder. Alteration of consciousness, fever, and headache are common clinical presentations. Personality changes and aphasia are also frequently observed at presentation and may be helpful clues in considering the diagnosis. Neuroimaging often shows temporal lobe involvement, with MRI being more sensitive than CT [13].

Early recognition of HSE is important, because treatment with acyclovir significantly decreases morbidity and mortality [14]. Historically, brain biopsy was the diagnostic test of choice, but in the last decade molecular techniques have revolutionized the diagnostic approach for patients with suspected HSE. Although the current gold standard for establishing the diagnosis of HSE is the detection of HSV-1 by PCR methodology [12], there is no standardization with respect to the nucleic acid detection test itself. Laboratories use different primer sets targeting different regions of the HSV gene, different reaction conditions, and different methods for confirmation of the amplified products. Gene targets for primers include the viral thymidine kinase genes in addition to the genes encoding glycoproteins B, C, D, or G and a DNA-binding protein [15•].

In experienced laboratories, HSV CSF PCR has a sensitivity of 94% to 98%, and results typically remain positive for up to 1 week, even if the patient is on antiviral therapy [12]. It has become standard practice to continue empiric acyclovir until the HSV PCR returns negative. However, as with all diagnostic tests, results need to be interpreted in the context of the clinical illness. False negatives can occur, especially early in the disease course, and in individuals with temporal lobe involvement and no alternative explanation for their presentation of encephalitis, empiric treatment should be continued until HSV PCR is repeated on a later CSF sample [16]. Quantitative viral loads may be helpful for management and prognosis, but this test is not widely available, and its utility remains unknown [17].

Intrathecal antibody synthesis of HSV antibodies may be a complementary method to diagnose HSE. Although antibodies to HSV may not be detectable in the CSF initially, they are typically present 10 to 12 days after the onset of symptoms [11,18].

Herpes simplex virus 2

HSV-2 is a well-known cause of neonatal herpes encephalitis. However, outside the newborn period, HSV-2 is more commonly associated with lymphocytic meningitis, relapsing meningitis, and myelitis as opposed to encephalitis. Unlike HSV-1, HSV-2 is more likely to cause disseminated encephalitis and does not generally localize to the temporal and inferior frontal regions of the brain [19]. Molecular testing of CSF for the presence of nucleic acid is the most reliable method for diagnosis.

Varicella zoster virus

Infection with varicella zoster virus (VZV) is traditionally characterized as either primary varicella infection (chicken pox) or reactivation disease causing shingles or herpes zoster. Both entities are rarely associated with clinically apparent neurologic involvement. With the availability of pediatric immunization against varicella, CNS complications of primary infections have become uncommon. Among nonimmunized hosts, neurologic disease with primary varicella is typically characterized by localized cerebellar involvement, presenting as ataxia or nystagmus, often without altered mentation [20].

Following primary infection, VZV lives quiescently in dorsal root ganglia, but can reactivate, causing the dermatomal skin eruption characteristic of herpes zoster. Dissemination to extracutaneous sites including the CNS is uncommon, but the risk is increased among immunocompromised patients [21]. Complicating the diagnosis is the finding that as many as 44% of patients with VZV encephalitis will lack cutaneous findings, termed herpes sine zoster or pre-eruptive varicella [22]. Although the clinical presentation is nonspecific, VZV encephalitis is pathologically characterized by vasculopathy involving either large or small vessels [23].

VZV encephalitis should be suspected both in patients with and without the characteristic skin findings. The diagnosis can be confirmed by detection of VZV DNA or VZV antibody in the CSF [24]. Identification of antibody in the CSF may be more sensitive than PCR [25], but intrathecal synthesis is often delayed by a week or more after the onset of neurologic symptoms [26]. Separating intrathecal antibody synthesis from contamination of CSF through a traumatic tap may be accomplished by calculation of an antibody index [27].

Epstein-Barr virus

Epstein-Barr virus (EBV) is ubiquitous, with most individuals infected by the time they reach adulthood. The most common clinical manifestation of EBV is infectious mononucleosis. Following acute infection, there is lifelong persistence, with latent infection of B lymphocytes. Neurologic complications of EBV are estimated to occur in 1% to 5% of acute EBV infections [28]. Importantly, individuals who develop CNS complications often lack the classic mononucleosis symptoms of pharyngitis and adenopathy. Several different neurologic complications have been described, including meningitis, Guillain-Barré syndrome, acute disseminated encephalomyelitis, myelitis, cranial nerve palsy, and encephalitis. Most cases of encephalitis are reported in the pediatric age group [29••].

Standard diagnostic testing for infectious mononucleosis includes the heterophil test, which is both rapid and specific in individuals older than 4 years of age. This test is widely available, but it may be misleading because a significant number of patients with EBV-associated encephalitis have a negative heterophil test [30]. For diagnosis of CNS complications, current recommendations include a combination of serologic and molecular methods [30]. PCR results should be interpreted with caution, however, because the significance of a positive EBV PCR in spinal fluid, especially in patients with low EBV-viral loads, may represent incidental detection of latent virus [31]. Quantitative viral load may be helpful, as a high viral load supports a significant CNS infection [32]. Conversely, a negative PCR in the setting of serology suggestive of acute infection may be seen in patients with CNS disease. Serologic testing should include antibody to EBV viral capsid antigen and Epstein-Barr nuclear antigen.

Other herpesviruses

The role of other herpesviruses in causing encephalitis is controversial. Cytomegalovirus is an important cause of encephalitis in the immunocompromised host but does not appear to be a significant cause in the general population [33••]. Similarly, human herpes virus 6 has been established as a cause of encephalitis in immunocompromised patients, particularly stem cell transplant recipients, but its role in the normal host is not known [34].

West Nile virus

West Nile virus (WNV) is a mosquito-borne virus that was first detected in the northern hemisphere in 1999 and has since emerged as the most common form of endemic encephalitis in the United States. The clinical spectrum of WNV illness ranges from asymptomatic infection to encephalomyelitis. In 2006, more than 4000 cases of WNV were reported to the US Centers for Disease Control and Prevention, and one third of these were categorized as neuroinvasive infection. Neurologic involvement is more common among the elderly and the immunocompromised. Although there is no pathognomonic presentation of WNV encephalitis, weakness, including acute flaccid paralysis, is a characteristic finding [35].

The duration of viremia for WNV often precedes the onset of neurologic symptoms, making the diagnostic yield of WNV PCR on serum and CSF low [36]. However, molecular testing has an important role in screening blood products from asymptomatic donors, and has markedly decreased the incidence of transfusion-associated infection. Immunocompromised hosts often have prolonged viremia coupled with a delayed serologic response, and PCR of CSF or serum may be diagnostic in this population [37,38].

The gold standard for diagnosis of WNV infection is detection of antibody via IgM antibody-capture enzyme-linked immunosorbent assay (MAC-ELISA). Approximately 90% of patients with neuroinvasive disease will have detectable CSF IgM antibody by 8 to 10 days after symptom onset [39]. However, complicating the interpretation of these results is the fact that WNV IgM may persist for prolonged periods, with IgM titers detectable more than 500 days after presentation in individuals with neuroinvasive disease [40]. Furthermore, serologic cross-reactivity exists between the flaviviruses, such that individuals naturally infected or vaccinated against other flaviviruses (ie, St. Louis encephalitis virus [SLE], dengue virus, yellow fever virus, or Japanese encephalitis virus) could test positive for WNV by MAC-ELISA. Differentiation of WNV from other flaviviruses may be performed by a plaque reduction neutralization test or through a positive-to-negative optical density ratio [41].

Other arboviruses

In addition to WNV, several other arthropod-borne viruses have been associated with human cases of encephalitis in the United States. La Crosse virus, SLE, Eastern equine encephalitis (EEE) virus, and Western equine encephalitis virus all cause endemic and occasionally epidemic disease, but they vary greatly in terms of their distribution, incidence, and clinical presentation.

La Crosse virus is endemic throughout the eastern and midwestern United States, with approximately 70 cases reported annually [42]. Symptomatic infection due to this agent occurs almost exclusively in children, and even in this group, a febrile illness or aseptic meningitis is more frequent than encephalitis. In contrast, SLE causes low-level endemic disease west of the Mississippi River, with sporadic large outbreaks every 10 to 15 years [42]; neurologic disease is more common in the elderly. EEE is distinguished by a mortality rate of 33% to 50% [43]. Human infection is relatively rare, with an average of five cases reported annually to the US Centers for Disease Control and Prevention. Most cases of EEE occur in coastal regions in the Gulf and Mid-Atlantic states. No human Western equine encephalitis has been reported in the last 5 years, although in previous years, infections occurred in the central United States in a band-like distribution from Texas to North Dakota.

Despite these epidemiologic differences, the standard method for diagnosis of these arboviruses is similar, namely through detection of a fourfold or greater rise in antibody titer on paired acute and convalescent sera [42]. This method allows retrospective diagnosis of infection, but making a diagnosis at the time of presentation is a challenge. Diagnosis may be suggested by an elevated antibody titer on a single serum specimen, or it may be confirmed by demonstration of antibody in the CSF. Nucleic acid amplification techniques exist, but are not widely available outside the research setting [44].

Tick-borne rickettsial diseases

Tick-borne rickettsial diseases (TBRD), including Rocky Mountain spotted fever, which is caused by *Rickettsia rickettsii*; human monocytic ehrlichiosis (HME), which is caused by *Ehrlichia chaffeensis*; and human granulocytic anaplasmosis (HGA), which is caused by *Anaplasma phagocytophilum*, are important and treatable causes of encephalitis in the United States. Distribution of these bacteria differs with respect to vector and geography; however, all three cause a similar nonfocal febrile syndrome typically associated with headache. Altered mental status is estimated to occur in as many as 20% of cases [45,46].

The CNS manifestations of TBRD are nonspecific, but several features may increase clinical suspicion for these infections. Because all three pathogens are spread by tick bites, infection with these agents is primarily restricted to the late spring through early fall months, when arthropod activity is maximal. Fever and headache are almost universal findings. Rash is seen in as many as 90% of patients with Rocky Mountain spotted fever but often lags several days after the onset of fever. Skin involvement is much less common in HME and HGA. Thrombocytopenia and elevated liver transaminases may be seen with all three TBRD, although leukopenia is more common with HME and HGA. CSF pleocytosis, when present, is typically less than 100 cells/mm^3 with a lymphocytic predominance.

Confirmation of TBRD presents a diagnostic challenge. Detection of a fourfold rise in antibody titer is definitive evidence of a TBRD but is only useful for retrospective diagnosis. The presence of a single elevated titer in a patient with a compatible clinical history is suggestive of TBRD, but at the time of presentation, only a minority of patients are seropositive [47]. PCR on whole blood has been reported to have a sensitivity of 56% to 100% for the diagnosis of HME [48,49]. *Ehrlichia* spp can rarely be amplified from CSF [50]. Because *R. rickettsii* infects vascular endothelial cells, diagnosis of this infection may be confirmed by immunohistochemical staining of skin biopsy specimens.

Bartonella species

Cat scratch disease encephalopathy is an uncommon complication of *Bartonella* spp infection, occurring in 1% to 7% of cases of cat scratch fever. The vast majority of cases occur in children, and a male predominance has been reported [50]. Seizures, including status epilepticus, are common, but in general, recovery is rapid and neurologic sequelae are rare. A history of cat exposure (although not necessarily of a documented bite or scratch) and detection of lymphadenopathy on physical examination are important clues to considering this diagnosis.

Little is known about the pathogenesis of cat scratch disease encephalopathy. The absence of fever, relatively acellular CSF, and rapid recovery without directed treatment all argue against direct infection of the CNS. This is supported by the relative infrequency with which the bacteria are detected in CSF [51] or brain tissue [52]. An indirect fluorescent antibody titer of greater than 1:64 has been reported to have a sensitivity of greater than 85% and a specificity of greater than 95% for confirmation of cat scratch disease [53]. Although PCR of CSF or brain tissue has a limited role, *Bartonella* PCR of lymph node tissue may be diagnostic [54].

Enteroviruses

More than 68 EV serotypes have been identified, and these are associated with a diverse group of clinical syndromes. Particular serotypes are sometimes associated with a characteristic syndrome, but serotyping is not routinely performed. EVs are a well-known cause of aseptic meningitis and have recently been identified as a relatively common cause of encephalitis. In a recently published study, EVs were the leading infectious agents identified, with 75% of cases occurring among children [29••]. Clinically, many of these infections may be less severe; however, EV71 (the cause of hand, foot, and mouth disease) has recently caused an outbreak associated with brainstem encephalitis in Asia [55].

Prior to molecular technologies, viral isolation was the gold standard for diagnosis but had poor sensitivity in CSF. Currently, the most sensitive method for diagnosis is PCR detection of EV in the CSF using the highly conserved sequence in the 5' noncoding region [56]. The disadvantage of this method is that it does not differentiate between serotypes. Other nucleic acid detection methodologies directed to the capsid regions of the genome are less cross-reactive, but allow the product to be sequenced for serotype identification [57]. Viral culture or nucleic acid detection of an EV from a non-CNS site (eg, throat, stool) supports but does not confirm the virus as a cause of the CNS disease [58].

Rabies

Rabies is rare in the United States but deserves inclusion because of its severity and the importance of rapid prophylaxis of potential contacts. Rabies has one of the highest fatality rates of all infectious diseases, and rabies encephalitis should be considered in any patient with rapidly progressive encephalitis. It is usually contracted through the bite of an infected animal and is almost always fatal

without postexposure prophylaxis. Recently, transmission through infected organs at the time of transplantation has been reported. The onset of rabies is usually nonspecific and includes symptoms such as fever, sore throat, chills, malaise, cough, and weakness.

Antemortem diagnosis of rabies is possible but requires highly specialized testing using a combination of different assays and specimens types in a public health laboratory. Molecular, isolation, and immunofluorescence methods are used to detect the rabies virus from corneal impression smears, skin biopsy specimens from the nape of the neck, CSF, brain tissue, and saliva. Detection of antibody in CSF or serum in an unimmunized individual may also be useful [59]. Consultation with local, state, and federal public health authorities prior to submission of specimens is strongly recommended.

Conclusions

Although an infectious cause of encephalitis is rarely identified, prompt and thorough diagnostic testing is encouraged in all cases. For treatable infections such as HSV encephalitis and rickettsia, rapid diagnosis and treatment may be life-saving. For infections without specific antiviral therapy, use of costly or potentially toxic antimicrobials can be minimized. Knowledge of the cause of encephalitis may help with prognosis. For instance, a diagnosis of rabies, an almost universally fatal infection, might prompt removal of life-support measures, whereas a diagnosis of *Bartonella*, which is typically associated with complete neurologic recovery, would mandate aggressive supportive care. For reportable agents such as WNV, identification of an etiologic agent may provide important epidemiologic information and prevent further illnesses in the community through a prompt public health response. As new pathogens causing encephalitis are identified, the diagnostic spectrum will continue to evolve.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. 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:**731–742.
2. Kolski H, Ford-Jones EL, Richardson S, et al.: **Etiology of acute childhood encephalitis at The Hospital for Sick Children, Toronto, 1994-1995.** *Clin Infect Dis* 1998, **26:**398–409.
3. Rantalaiho T, Farkkila M, Vaheri A, et al.: **Acute encephalitis from 1967 to 1991.** *J Neurol Sci* 2001, **184:**169–177.
4. Tunkel AR, Hartman BJ, Kaplan SL, et al.: **Practice guidelines for the management of bacterial meningitis.** *Clin Infect Dis* 2004, **39:**1267–1284.
5. Steele RW, Marmer DJ, O'Brien MD, et al.: **Leukocyte survival in cerebrospinal fluid.** *J Clin Microbiol* 1986, **23:**965–966.
6. Kuberski T, Wallace GD: **Clinical manifestations of eosinophilic memingitis due to Angiostrongylus cantonensis.** *Neurology* 1979, **29:**1566–1570.
7. Polage CR, Petti CA: **Assessment of the utility of viral culture of cerebrospinal fluid.** *Clin Infect Dis* 2006, **43:**1578–1579.
8. Morishima T, Togashi T, Yokota S, et al.: **Encephalitis and encephalopathy associated with an influenza epidemic in Japan.** *Clin Infect Dis* 2002, **35:**512–517.
9. Lynch M, Lee B, Azimi P, et al.: **Rotavirus and central nervous system symptoms: cause or contaminant? Case reports and review.** *Clin Infect Dis* 2001, **33:**932–938.
10. Whitley RJ, Lakeman F: **Herpes simplex virus infections of the central nervous system: therapeutic and diagnostic considerations.** *Clin Infect Dis* 1995, **20:**414–420.
11. Fomsgaard A, Kirkby N, Jensen IP, et al.: **Routine diagnosis of herpes simplex virus (HSV) encephalitis by an internal DNA controlled HSV PCR and an IgG-capture assay for intrathecal synthesis of HSV antibodies.** *Clin Diagn Virol* 1998, **9:**45–56.
12. 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:**857–863.
13. Demaerel P, Wilms G, Robberecht W, et al.: **MRI of herpes simplex encephalitis.** *Neuroradiology* 1992, **34:**490–493.
14. Whitley RJ, Alford CA, Hirsch MS, et al.: **Vidarabine versus acyclovir therapy in herpes simplex encephalitis.** *N Engl J Med* 1986, **314:**144–149.
15. • Tyler KL: **Herpes simplex virus infections of the central nervous system: encephalitis and meningitis, including Mollaret's.** *Herpes* 2004, **11 (Suppl 2):**57A–64A.

A thorough review of clinical manifestations, diagnosis, and treatment of HSV infections of the CNS.

16. Weil AA, Glaser CA, Amad Z, et al.: **Patients with suspected herpes simplex encephalitis: rethinking an initial negative polymerase chain reaction result.** *Clin Infect Dis* 2002, **34:**1154–1157.
17. Domingues RB, Lakeman FD, Mayo MS, et al.: **Application of competitive PCR to cerebrospinal fluid samples from patients with herpes simplex encephalitis.** *J Clin Microbiol* 1998, **36:**2229–2234.
18. Linde A, Klapper PE, Monteyne P, et al.: **Specific diagnostic methods for herpesvirus infections of the central nervous system: a consensus review by the European Union Concerted Action on Virus Meningitis and Encephalitis.** *Clin Diagn Virol* 1997, **8:**83–104.
19. McCabe K, Tyler K, Tanabe J: **Diffusion-weighted MRI abnormalities as a clue to the diagnosis of herpes simplex encephalitis.** *Neurology* 2003, **61:**1015–1016.
20. Connolly AM, Dodson WE, Prensky AL, et al.: **Course and outcome of acute cerebellar ataxia.** *Ann Neurol* 1994, **35:**673–679.
21. Hackanson B, Zeiser R, Bley TA, et al.: **Fatal varicella zoster virus encephalitis in two patients following allogeneic hematopoietic stem cell transplantation.** *Clin Transplant* 2005, **19:**566–570.
22. Koskiniemi M, Piiparinen H, Rantalaiho T, et al.: **Acute central nervous system complications in varicella zoster virus infections.** *J Clin Virol* 2002, **25:**293–301.
23. Kleinschmidt-DeMasters BK, Amlie-Lefond C, Gilden DH: **The patterns of varicella zoster virus encephalitis.** *Hum Pathol* 1996, **27:**927–938.
24. Gilden D: **Varicella zoster virus and central nervous system syndromes.** *Herpes* 2004, **11(Suppl 2):**89A–94A.
25. Nagel MA, Forghani B, Mahalingam R, et al.: **The value of detecting anti-VZV IgG antibody in CSF to diagnose VZV vasculopathy.** *Neurology* 2007, **68:**1069–1073.

26. Gregoire SM, van Pesch V, Goffette S, et al.: **Polymerase chain reaction analysis and oligoclonal antibody in the cerebrospinal fluid from 34 patients with varicella-zoster virus infection of the nervous system.** *J Neurol Neurosurg Psychiatry* 2006, **77:**938–942.
27. Denne C, Kleines M, Dieckhofer A, et al.: **Intrathecal synthesis of anti-viral antibodies in pediatric patients.** *Eur J Paediatr Neurol* 2007, **11:**29–34.
28. Jenson HB: **Acute complications of Epstein-Barr virus infectious mononucleosis.** *Curr Opin Pediatr* 2000, **12:**263–268.
29.•• Glaser CA, Honarmand S, Anderson LJ, et al.: **Beyond viruses: clinical profiles and etiologies associated with encephalitis.** *Clin Infect Dis* 2006, **43:**1565–1577.

A large, ongoing prospective cohort study using state-of-the-art diagnostic testing to identify infectious causes of encephalitis.

30. Doja A, Bitnun A, Jones EL, et al.: **Pediatric Epstein-Barr virus-associated encephalitis: 10-year review.** *J Child Neurol* 2006, **21:**385–391.
31. Weinberg A, Bloch KC, Li S, et al.: **Dual infections of the central nervous system with Epstein-Barr virus.** *J Infect Dis* 2005, **191:**234–237.
32. Weinberg A, Li S, Palmer M, et al.: **Quantitative CSF PCR in Epstein-Barr virus infections of the central nervous system.** *Ann Neurol* 2002, **52:**543–548.
33.•• Huang C, Morse D, Slater B, 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:**630–635.

A cross-sectional study evaluating the diagnostic yield of a panel of PCR tests directed at the most common viral causes of encephalitis in the United States.

34. Zerr DM: **Human herpesvirus 6 and central nervous system disease in hematopoietic cell transplantation.** *J Clin Virol* 2006, **37(Suppl 1):**S52–56.
35. Sejvar JJ, Bode AV, Marfin AA, et al.: **West Nile virus-associated flaccid paralysis.** *Emerg Infect Dis* 2005, **11:**1021–1027.
36. Lanciotti RS, Kerst AJ, Nasci RS, et al.: **Rapid detection of West Nile Virus from human clinical specimens, field-collected mosquitoes, and avian samples by a TaqMan reverse transcriptase-PCR assay.** *J Clin Microbiol* 2000, **38:**4066–4071.
37. Hiatt B, DesJardin L, Carter T, et al.: **A fatal case of West Nile virus infection in a bone marrow transplant recipient.** *Clin Infect Dis* 2003, **37:**e129–131.
38. Huang C, Slater B, Rudd R, et al.: **First isolation of West Nile virus from a patient with encephalitis in the United States.** *Emerg Infect Dis* 2002, **8:**1367–1371.
39. Solomon T, Ooi MH, Beasley DW, et al.: **West Nile encephalitis.** *BMJ* 2003, **326:**865–869.
40. Roehrig JT, Nash D, Maldin B, et al.: **Persistence of virus-reactive serum immunoglobulin m antibody in confirmed West Nile virus encephalitis cases.** *Emerg Infect Dis* 2003, **9:**376–379.
41. Martin DA, Noga A, Kosoy O, et al.: **Evaluation of a diagnostic algorithm using immunoglobulin M enzyme-linked immunosorbent assay to differentiate human West Nile Virus and St. Louis Encephalitis virus infections during the 2002 West Nile Virus epidemic in the United States.** *Clin Diagn Lab Immunol* 2004, **11:**1130–1133.
42. Calisher CH: **Medically important arboviruses of the United States and Canada.** *Clin Microbiol Rev* 1994, **7:**89–116.
43. Deresiewicz RL, Thaler SJ, Hsu L, et al.: **Clinical and neuroradiographic manifestations of eastern equine encephalitis.** *N Engl J Med* 1997, **336:**1867–1874.
44. Lambert AJ, Nasci RS, Cropp BC, et al.: **Nucleic acid amplification assays for detection of La Crosse virus RNA.** *J Clin Microbiol* 2005, **43:**1885–1889.
45. Hongo I, Bloch KC: **Ehrlichia infection of the central nervous system.** *Curr Treat Options Neurol* 2006, **8:**179–184.
46. Kirk JL, Fine DP, Sexton DJ, et al.: **Rocky Mountain spotted fever. A clinical review based on 48 confirmed cases, 1943-1986.** *Medicine (Baltimore)* 1990, **69:**35–45.
47. Paddock CD, Greer PW, Ferebee TL, et al.: **Hidden mortality attributable to Rocky Mountain spotted fever: immunohistochemical detection of fatal, serologically unconfirmed disease.** *J Infect Dis* 1999, **179:**1469–1476.
48. Olano JP, Masters E, Hogrefe W, et al.: **Human monocytotropic ehrlichiosis, Missouri.** *Emerg Infect Dis* 2003, **9:**1579–1586.
49. Standaert SM, Yu T, Scott MA, et al.: **Primary isolation of Ehrlichia chaffeensis from patients with febrile illnesses: clinical and molecular characteristics.** *J Infect Dis* 2000, **181:**1082–1088.
50. Dunn BE, Monson TP, Dumler JS, et al.: **Identification of Ehrlichia chaffeensis morulae in cerebrospinal fluid mononuclear cells.** *J Clin Microbiol* 1992, **30:**2207–2210.
51. Parrott JH, Dure L, Sullender W, et al.: **Central nervous system infection associated with Bartonella quintana: a report of two cases.** *Pediatrics* 1997, **100:**403–408.
52. Gerber JE, Johnson JE, Scott MA, et al.: **Fatal meningitis and encephalitis due to Bartonella henselae bacteria.** *J Forensic Sci* 2002, **47:**640–644.
53. Dalton MJ, Robinson LE, Cooper J, et al.: **Use of Bartonella antigens for serologic diagnosis of cat-scratch disease at a national referral center.** *Arch Intern Med* 1995, **155:**1670–1676.
54. Hansmann Y, DeMartino S, Piemont Y, et al.: **Diagnosis of cat scratch disease with detection of Bartonella henselae by PCR: a study of patients with lymph node enlargement.** *J Clin Microbiol* 2005, **43:**3800–3806.
55. Huang CC, Liu CC, Chang YC, et al.: **Neurologic complications in children with enterovirus 71 infection.** *N Engl J Med* 1999, **341:**936–942.
56. Rotbart HA: **Enzymatic RNA amplification of the enteroviruses.** *J Clin Microbiol* 1990, **28:**438–442.
57. Nix WA, Oberste MS, Pallansch MA: **Sensitive, seminested PCR amplification of VP1 sequences for direct identification of all enterovirus serotypes from original clinical specimens.** *J Clin Microbiol* 2006, **44:**2698–2704.
58. Kupila L, Vuorinen T, Vainionpaa R, et al.: **Diagnosis of enteroviral meningitis by use of polymerase chain reaction of cerebrospinal fluid, stool, and serum specimens.** *Clin Infect Dis* 2005, **40:**982–987.
59. Noah DL, Drenzek CL, Smith JS, et al.: **Epidemiology of human rabies in the United States, 1980 to 1996.** *Ann Intern Med* 1998, **128:**922–930.