Treatment of Viral Encephalitis

Allen J. Aksamit Jr, MD

KEYWORDS

- Herpes simplex encephalitis (HSE) • Anti-NMDA receptor (NMDA-R) encephalitis
- Varicella zoster virus (VZV) encephalitis • West Nile virus (WNV) encephalitis
- Eastern equine encephalitis virus (EEE)
- Progressive multifocal leukoencephalopathy (PML)

KEY POINTS

- Herpes simplex encephalitis has standardized therapy that should be started empirically if the diagnosis is considered. Rare cases can have an autoimmune NMDA receptor encephalitis following infection with herpes simplex that can be treated.
- Arthropod-borne encephalitides, such as West Nile virus encephalitis and Eastern equine encephalitis, have limited studies suggesting positive outcome with immunoglobulin treatment. Treatment of these disorders remains supportive.
- Progressive multifocal leukoencephalopathy has no proven treatment, but new attempts using immune stimulation therapy have shown limited promise.

INTRODUCTION

The timing for the submission of this article coincides with a unique time in history, when we are challenged by the pandemic of Coronavirus Disease 2019 (COVID-19). There is great uncertainty about how best to treat the COVID-19 illness, which parallels the challenges of treating viral infections in general. There are few options for treatment of viral encephalitis. Besides herpes simplex encephalitis (HSE), and its rare complication of N-methyl-D-aspartate (NMDA)-receptor encephalitis afterward due to autoimmune mechanisms that can be successfully treated, there are few well-established treatments for viral encephalitis. This discussion seeks to summarize current knowledge of treatment in selected topics of viral encephalitis. It will not cover human immunodeficiency virus (HIV) encephalitis, as its treatment parallels the treatment for HIV disease and is deserving of a discussion by itself. The treatment is nuanced and somewhat controversial, as antiretroviral therapy variably penetrates the central nervous system, although penetration may not dictate success of therapy. Most of the encephalitis-causing viruses are not mentioned in this discussion because they

Department of Neurology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA
E-mail address: aksamit@mayo.edu

Neurol Clin 39 (2021) 197–207
https://doi.org/10.1016/j.ncl.2020.09.011 **neurologic.theclinics.com**

have no specific treatment other than supportive care. Exciting new therapy that may (or may not) succeed in treating progressive multifocal leukoencephalopathy (PML) has emerged and is discussed.

By definition, encephalitis is an inflammation of the parenchyma of the brain. Viral encephalitis implies that a virus directly invades and replicates in cells within the brain. The term "encephalitis" also indicates a clinical syndrome arising from infection and inflammation in the parenchyma, rather than in the leptomeninges. When both the leptomeninges and brain parenchyma are involved, the term "meningoencephalitis" is preferred. In para-infectious encephalitis, a systemic viral infection is associated with a febrile encephalopathy, sometimes with inflammatory spinal fluid but without direct evidence of brain invasion by the virus. When a pathologically purulent infection is produced, the preferred term is cerebritis, which is more connected to bacterial infections.

Viral encephalitis has an estimated incidence of 7 per 100,000 per year.[1] In general, a specific cause is identified in less than 50% of patients in the United States.[2] Many viruses (**Boxes 1** and **2**[3,4]) have been implicated as the cause. Spinal fluid testing by serologic identification or nucleic acid identification (by polymerase chain reaction [PCR]) is generally required to identify the specific etiologic virus.[1,5] The epidemiology of each virus responsible for central nervous system infection is distinct in terms of the patients who are at highest risk, geographic distribution, and seasonal occurrence, which is especially important for the arboviruses and enteroviruses. The details of epidemiology and incidence are beyond the scope of this discussion, which is focused here on the treatment. There are several excellent consensus documents from around the world that summarize much of the data about etiology and diagnostic testing.[6–9]

A common treatment associated with encephalitis is the treatment of seizures. In the context of encephalitis, seizures are common and frequently refractory to antiepileptic drugs. However, the seizures themselves can increase morbidity and mortality,

Box 1
Common causes of encephalitis in the United States

A. Nonseasonal
- Herpes simplex virus type 1 (herpes simplex encephalitis)
- Herpes simplex virus type 2 (neonatal encephalitis or adult meningoencephalitis)

B. Seasonal: summer and fall—arboviruses (arthropod-borne)
- West Nile virus
- St. Louis encephalitis virus
- Eastern equine encephalitis virus
- Western equine encephalitis virus
- La Crosse/California encephalitis virus

C. Seasonal: non–arthropod-borne
- Summer and fall: enteroviruses (including coxsackie viruses, echoviruses, polioviruses, and enterovirus 71)
- Winter: influenza virus

D. Immunosuppressed patients
- Human immunodeficiency virus (chronic HIV encephalitis)
- Varicella zoster virus (subacute encephalitis)
- John Cunningham (JC) virus (progressive multifocal leukoencephalopathy)
- Cytomegalovirus (ventriculitis or encephalitis)
- Human herpesvirus 6 (subacute encephalitis)
- Epstein-Barr virus (subacute encephalitis)

Box 2
Uncommon causes of viral encephalitis in the United States

Causes originating within the United States
- Powassan encephalitis virus
- Jamestown Canyon virus
- Cache Valley Virus
- Zika virus[3]
- Chikungunya virus[4]
- Variegated squirrel borna virus
- Lymphotropic choriomeningitis virus
- Rabies
- Measles (subacute sclerosing panencephalitis)
- Mumps
- Adenovirus
- Herpes B virus (of monkeys)
- Rubella (progressive rubella panencephalitis)

Causes originating outside the United States
- Zika virus[3]
- Tick-borne encephalitis virus (Russia, Asia)
- Japanese encephalitis virus (Japan, Southeast Asia, Malaysia)
- Venezuelan equine encephalitis virus (Central and South America)
- Dengue virus (Southern Asia, Africa, South America)
- Rift Valley fever virus (east central Africa)
- Murray Valley encephalitis virus (Australia)
- Powassan encephalitis virus (Canada)
- Nipah virus (Malaysia and Bangladesh)

so vigorous treatment attempts are required. Epilepsy treatment is beyond the scope of this discussion.

HERPETIC VIRAL ENCEPHALITIDES

Herpes Simplex Encephalitis

HSE remains the most common nonepidemic viral encephalitis in the United States. It causes 10% of encephalitis in the United States.[10] Epidemiology estimates 1 case per 250,000 to 500,000 individuals per year. Great strides have been made in the success of diagnosis, with sensitive PCR techniques, and characteristic MRI findings.[11] Herpes simplex type 1 virus (HSV-1) is the usual virus identified, with more than 90% of cases related to HSV-1. It tends to cause clinical signs of focal cortical neurologic deficits including hemiparesis, aphasia, and seizures. HSE commonly involves limbic parts of the brain, which can lead to prominent behavioral changes at the beginning of the illness before the patient's level of consciousness is depressed. Focal or generalized seizures are particularly common when encephalitis affects the cerebral cortex, especially the temporal lobes.

Before acyclovir (and the drug used to treat it previously, vidarabine), 70% of patients died of infection.[12] Even using acyclovir, which is the current therapy, mortality is still 15%, and fewer than 20% of patients are able to return to full-time employment after treatment, often because of cognitive deficits that persist.

Multicenter prospective trial results emphasize that early treatment affects outcome.[13] When HSE is suspected in the acute setting by the presence of focal signs or symptoms, early empirical treatment is recommended even while the diagnostic evaluation is proceeding. The current therapy-of-choice treatment is intravenous acyclovir (10 mg/kg every 8 hours for 14–21 days). The original trial in the 1980s

was performed with 14 days of intravenous therapy.[13] However since that time, given the relatively low toxicity of acyclovir, experts have recommended 21 days of therapy for patients with severe neurologic deficits or at risk for immunosuppression or a more severe course. However, given the difficulty of obtaining prospective data in this rare disease, a controlled trial to support a longer duration of therapy or higher doses of acyclovir to improve neurologic outcomes has not been performed.

A trial of prolonged oral valacyclovir after the standard 2 weeks of intravenous acyclovir was performed in a group of patients who had relatively mild disease (ie, they were able to take oral medications and comply with protocol). However, oral valacyclovir did not change the severity of neurologic deficits between placebo and active oral medication at 6 and 12 months of follow-up.[14]

Herpes Simplex Encephalitis and Steroids

It has been long speculated that the severe injury to the brain as a consequence of HSE and the persistent neurologic deficits occur not only because of active infection but also because of a significant immune response to the virus by the host. Pathology with significant necrotizing immune response has been considered important in generating brain injury and persistent neurologic deficits. Because immune factors play a role in injury, corticosteroids with antiviral therapy were proposed to attenuate the immune response and lessen long-term deficits. This was initially tested in a multicenter, multinational German protocol using acyclovir and corticosteroids; 2 doses of dexamethasone, 40 mg, were given every 24 hours for 4 days with acyclovir and compared with acyclovir alone.[15] The trial closed due to insufficient enrollment, and the results have never been published.

More recently, another European multicenter trial of dexamethasone in herpes simplex virus encephalitis was initiated in the United Kingdom: https://clinicaltrials.gov/ct2/show/NCT03084783?term=encephalitis&cond=NCT03084783&rank=1=.[16,17] It is currently enrolling (Dexamethasone in Herpes Simplex Virus Encephalitis (DexEnceph) - http://www.encephalitis.info/). To combine data and improve power of the study, a trial is currently being carried out in France with the same protocol that compares dexamethasone with placebo with both arms initially treating in combination with acyclovir.[17]

N-Methyl-D-Aspartate Receptor Encephalitis After Herpes Simplex Encephalitis

Autoimmune encephalitis has been described and confirmed as a consequence in a minority of patients who have had HSE. Before this was recognized as a definitive entity, a minority of patients were recognized as having a clinical course that seemingly suggested clinical relapse after HSE. However, this apparent relapse with worsening focal clinical disease and worsening MRI abnormalities, is unaccompanied by the usual viral confirmation of herpes simplex virus PCR in the spinal fluid. This was initially described as a "biphasic illness." It typically occurs as a relapse in the first 1 to 7 weeks after the initial diagnosis of HSE. This was initially described in adults[18] and then in children who experienced HSE.[19] Eventually, once the recognition of autoimmune encephalitis-associated NMDA receptor (NMDAR) antibodies was described, testing revealed that patients who had apparent relapse of HSE without detectable virus actually had NMDAR antibodies in the spinal fluid.[20,21] The exact frequency and risk factors that determine clinical worsening and NMDAR antibodies in the spinal fluid have not been described. This rare complication of a rare disorder makes uncertainty the rule about risks and outcomes of this complication.[22]

In the largest study published to date, which enrolled 51 patients with HSE,[22] none of the patients initially had antibodies to neuronal antigens in the spinal fluid. Fourteen

(27%) of patients developed autoimmune encephalitis (date range: 17−63 days after diagnosis), and all had neuronal antibodies (cerebrospinal fluid [CSF] analysis was most sensitive). Nine (64%) had NMDAR antibodies, and 5 [36%] had other neural antibodies at or before onset of relapse symptoms. The other 37 patients did not develop autoimmune encephalitis. Among the patients who did not develop autoimmune encephalitis after herpes simplex, 11 (30%) developed antibodies (n = 3 to NMDAR, n = 8 to unknown antigens), implying that the presence of antibodies does not always predict the occurrence of autoimmune encephalitis as a complication of HSE. However, antibody detection within 3 weeks of HSE was a statistically significant risk factor for autoimmune encephalitis.

Autoimmune-relapse, post-HSE may respond to corticosteroids, intravenous immunoglobulin (IVIg), or plasma exchange, but no randomized trials are available. There is no universal agreement about how to treat this entity. Once clinical deterioration and worsening imaging has been detected, patients typically receive 5 days of intravenous (IV) methylprednisolone, 1 g each day, followed by oral steroids initiated typically at 60 mg of prednisone per day followed by a taper.[22] IVIg may be considered in patients who cannot tolerate steroids. Plasma exchange may be used in patients with treatment-refractory disease or in patients with contraindications to other treatments.

Other Viruses in the Herpes Virus Group

Varicella zoster virus meningoencephalitis

Although rare, varicella zoster virus (VZV) meningoencephalitis can occur as a complication of cutaneous zoster, occasionally without overt cutaneous manifestations. Older individuals and immunosuppressed hosts are most vulnerable to this complication of zoster encephalitis. Typical treatment is a regimen similar to that for HSE with acyclovir, 10 mg/kg, IV, every 8 hours for 14 days. No prospective trials exist to confirm that this is satisfactory, and some investigators suggest a $\geq$21-day course of acyclovir, particularly in immunosuppressed hosts with more severe disease.[9,23]

Cytomegalovirus meningoencephalitis

Cytomegalovirus (CMV) produces a characteristic ventriculitis or ascending asymmetric polyradiculopathy in immunosuppressed hosts, best described in patients with acquired immunodeficiency syndrome (AIDS). Improvements in antiretroviral therapy in the past 20 years have made this serious neurologic infection uncommon. MRI shows characteristic ependymal ventricular enhancement with gadolinium imaging. CMV PCR in the spinal fluid is usually positive and confirmatory of CSF dissemination of the virus. Typical treatment for cytomegalovirus is ganciclovir, 5 mg/kg IV every 12 hours plus foscarnet 90 mg/kg for 2 weeks.[9,24] Cidofovir, administered at 5 mg/kg IV weekly for 2 weeks, is more controversial because it does not penetrate the blood-brain barrier.

Epstein-Barr virus encephalitis

Diagnosis of this entity is challenging because the spinal fluid of patients with immunosuppressive illness and other causes for encephalitis can yield false-positive PCR results. Epstein-Barr serology in the blood is ubiquitous in the population and is not sensitive or specific for patients with encephalitis. Furthermore, Epstein-Barr virus (EBV) can reactivate systemically at times of other illness, and lymphocytes carrying EBV from the systemic circulation can be recruited to the nervous system as part of the inflammatory response. This may produce a false-positive PCR, when another agent is responsible for the patient's clinical encephalitis. PCR for EBV has, however,

been useful in detecting opportunistic, EBV-driven lymphoma in immunosuppressed hosts and in the AIDS population. Currently, no specific treatments are effective for EBV. Patients have variably been treated with corticosteroids, but the potential risks must be weighed against the benefits.[9]

Human herpes virus 6

Variable success has been reported for treatment of human herpes virus 6 (HHV-6) encephalitis in hematopoietic stem cell transplant recipients using ganciclovir, foscarnet, or valganciclovir, alone or in combination.[25] The treatment recommendation for HHV-6 encephalitis is foscarnet (60 mg/kg every 8 hours for both A and B variants). Ganciclovir (5 mg/kg every 12 hours) is an alternative option only for the B variant of HHV-6 encephalitis.[7]

Effective antiviral therapy does not exist for most forms of viral encephalitis, except for HSE.[12] However, because of the usual delay in establishing or excluding the diagnosis of HSE, patients suspected of having encephalitis should start acyclovir therapy (10 mg/kg IV every 8 hours for 2 weeks), while specific serologic and spinal fluid analyses are being performed to make a diagnosis. Supportive measures for patients with encephalitis typically include intensive care unit treatment in the initial phases of the illness, directed at reducing intracranial pressure, and treating seizures that are a common accompaniment.

NON-HERPETIC VIRAL ENCEPHALITIDES

West Nile Virus Encephalitis

The most common epidemic viral encephalitis in the United States is now West Nile virus (WNV). WNV encephalitis was unknown in the United States until 1999. This is a mosquito-borne arbovirus, introduced presumably by infected animals, with birds being the principal intermediate host. Human disease is not transmissible from human to human, except in unusual circumstances like transplanted organs or blood transfusion. It is estimated that only 1% to 2% of patients infected with WNV develop central nervous system disease. Neuro-invasive disease manifestations include meningitis (25%–40%), encephalitis (55%–60%), or acute flaccid paralysis (5%–10%). Meningitis can occur in any age group, unlike encephalitis, which is more common in the elderly or immune suppressed. Acute flaccid myelitis (“poliomyelitis”) can occur in any age group.

The diagnosis is usually confirmed by identification of anti-WNV IgM in CSF in the acute setting of encephalitis symptoms often with impaired consciousness. Positive serum serology indicates exposure but not necessarily neuro-invasive disease. West Nile encephalitis cases show a high incidence of polymorphonuclear cell predominance in the CSF.[26]

Currently, there is no successful treatment for WNV encephalitis. However, some agents have been proposed and used, so far without generalized success. Two patients with serologic confirmation of WNV infection, who presented with deteriorating mental status and progression to coma, were treated with standard interferon alpha-2b within 72 hours of presentation.[27] Within 48 hours after initiation of therapy, both patients demonstrated rapid neurologic improvement. It remains unclear if the change in clinical status was due to interferon or to spontaneous improvement. Scattered reports of open-label interferon alpha used in other patients were regarded as unsuccessful.[28,29]

A large, multicenter, phase-2 trial of IVIg enriched with antibodies against WNV was conceived and organized by the Collaborative Antiviral Study Group. The study with 62 patients enrolled was published recently with negative results.[30]

Ribavirin has been tried in a few cases. It was not considered to be beneficial, and concern was raised that it might actually harmful and therefore not recommended by the Infectious Disease Society of America.[9]

Commercial pharmaceutical attempts have created synthetic anti-sense RNA as inhibitors of WNV replication. Those have not yet come to clinical trial.[31]

Eastern Equine Encephalitis Virus

Eastern equine encephalitis (EEE) is established in the United States, but outbreaks have fortunately been rare. The clinical manifestations can be quite severe, and the disease, transmitted by mosquitos, usually presents with fever, mental status changes, and seizures. This disease has a very high mortality (65% in some series). Focal cerebral signs are common, including increased intracranial pressure, and CSF white blood cell counts can exceed 1000 mm^3. It is typically diagnosed by positive EEE serology in the spinal fluid. Positive serum serology suggests recent exposure and is suspicious for the cause of the encephalitis.

There has been a recent outbreak in the United States. As of December 17, 2019, the Centers for Disease Control and Prevention has received reports of 38 confirmed cases of EEE virus disease for this year including 15 deaths.[32] Treatment is supportive. There have been attempts to treat the disease with IVIg, and 2 case reports have suggested some benefit.[33,34] However, there are no prospective trials.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

PML is a primary demyelinating disease of the central nervous system caused by infection with John Cunningham (JC) virus, which infects oligodendrocytes, killing those cells selectively and leading to focal demyelination, which spreads in a circumferential pattern to adjacent, uninfected cells. This disease does not present as typical encephalitis. It produces a subacute, focal neurologic deficit, more strokelike that progresses over time without fever, usually with normal spinal fluid cell count. It is a disease of immunosuppressed hosts, most commonly seen in association with AIDS or a lympho-reticular malignancy like lymphoma or chronic lymphocytic leukemia. It can occur in any immunosuppressed state with compromise of cell-mediated immunity. Thus, transplant patients and patients with exogenous immunosuppression, such as rheumatological conditions, are vulnerable. In the past 15 years, much attention has been focused on the occurrence of PML in patients with multiple sclerosis (MS) treated with immunosuppressive drugs, most prominently natalizumab. However, many of the MS disease-modifying agents carry a risk of PML.[35]

Treatment for PML has been disappointingly unsuccessful until recently, when there have been small series of open-label treatments of patients with immune-modifying drugs. Past medications included cytosine arabinoside (ARA-C), which was originally tried in the 1970s and 1980s as a PML treatment because of the antiviral effect of the nucleoside analog ARA-C interfering with DNA replication of JC virus. A small open-label series in non-AIDS patients suggested that approximately one-third had a nonfatal outcome, and some even had neurologic improvement.[36] However, a prospective trial in patients with AIDS was considered unsuccessfull.[37] There were delays in initiating ARA-C in the prospective trial that may have influenced the outcome.

The serologic monitoring of patients of JC virus in patients with MS considering treatment with disease-modifying therapy is based on antibodies in the blood, and the decision to select specific therapy for MS is beyond the scope of this discussion. The diagnosis of PML in MS, however, is similar to the diagnosis of PML in patients

with other immunosuppressive illness and relies on JC virus PCR detection in the spinal fluid. That assay is only approximately 70% sensitive.

Treatment of patients with MS who developed PML after taking natalizumab requires specific discussion. When natalizumab was initially released, a higher incidence of PML was recognized than had been noted in clinical trials of the drug. The drug was suspended from use and then reintroduced with safety-monitoring requirements.[36] However, management of the PML, once diagnosed in the context of natalizumab-associated therapy or other immune-modifying therapy for MS, should lead to specific treatment. Management of PML has routinely used plasma exchange (PLEX) to hasten clearance of natalizumab from the bloodstream. The patient's immune system is allowed to reconstitute and clear JC virus from the brain. PLEX has no known role in affecting virus clearing from the brain. However, exacerbation of symptoms and inflammation of lesions on MRI with clinical worsening have occurred indicative of immune reconstitution inflammatory syndrome (IRIS). IRIS seems to be more common and more severe in patients with natalizumab-associated PML than in patients with HIV-associated PML. If IRIS occurs, the treatment is to use high-dose IV methylprednisolone typically 1000 mg IV each day for 5 days and then a tapering dose of oral prednisone usually over 3 to 4 weeks, typically starting with 60 mg per day.

There has been some doubt expressed about whether plasmapheresis (PLEX) removes natalizumab from the body more quickly or, indeed, has any effect on the outcome of PML[37] One study looked at outcomes of patients with MS and natalizumab (NTZ)-associated progressive multifocal leukoencephalopathy in 193 international and 34 Italian NTZ-PML cases. PLEX did not improve the survival or clinical outcomes of Italian or international patients with MS and NTZ-PML,[37] This point is still being debated, but most experts would still recommend plasma exchange in the initial phase of treatment. The newer therapies discussed later in this article, which enhance immunity through the PD-1 pathway, should not be applied to patients with MS. These PD-1 inhibitor drugs are known to exacerbate MS.

AIDS-related PML is typically initially treated with optimizing antiretroviral therapy and attempts to clear virus from the brain by enhancing the patient's immune system with combined antiretroviral therapy (cART). Some other immune reconstitution strategies (see later in this article) have been suggested for patients with AIDS whose immune restoration is refractory to antiretroviral therapy.

For transplant recipients, immunosuppressive therapy can be tapered or discontinued temporarily until there is immune reconstitution and clearing of the virus from the brain. The possibility of organ rejection is a risk. In the case of patients on immunosuppressive therapy for autoimmune disease, the therapy can be discontinued for 2 to 3 months, allowing the patient's own immune system to reconstitute and help to clear the virus. These 2 situations require close clinical reexamination and monitoring with MRI scan to watch for neurologic worsening secondary to IRIS. Repeat spinal fluid PCR for JC virus may also help to guide therapy.

Immune-enhancing drugs like the PD-1 inhibitor pembrolizumab have been suggested as a novel therapy to restore immunity and treat PML. Pembrolizumab has shown promise in patients with leukemia, lymphoma-associated PML, or other conditions in which there is no other ability to reverse immune suppression.[38] This drug works through the PD-1 blockade and attempts to "reinvigorate" anti–JC virus immune activity. In a recent study, 8 adults with PML were administered pembrolizumab, 2 mg per kilogram of body weight every 4 to 6 weeks.[38] Five patients had clinical improvement or stabilization of PML accompanied by a reduction in the JC viral load in the CSF by PCR analysis. The other 3 patients had no meaningful change in outcome. At least 2 other cases have shown no clinical benefit when treated in this

fashion.[39,40] The factors determining response to pembrolizumab may be due to exhausted T cells.[40,41] It was concluded that more study of immune checkpoint inhibitors in the treatment of PML is warranted.

Allogeneic BK virus-sensitized T cells have also been proposed as a treatment strategy for PML patients with no ability to reverse their immune-suppressed status, given the strong antigenic overlap between JC virus and BK virus.[42] In a small series, 3 PML-immunosuppressed patients, each with a different kind of immunosuppression, were treated with partially expanded ex vivo, HLA-matched, third-party–produced, cryopreserved BK virus–specific T cells. One patient was undergoing a conditioning regimen for cord-blood transplantation. Another had a myeloproliferative neoplasm treated with rituximab, and the third had AIDS. T-cell infusion in 2 of the patients, led to alleviation of the clinical signs and imaging features of PML, and clearing of JC virus from the cerebrospinal fluid. The other patient had a reduction in JC viral load and stabilization of symptoms that persisted until her death 8 months later. Two of the patients had IRIS and required treatment of IRIS as part of their therapy.

SUMMARY

Therapy for viral encephalitis remains largely supportive in many circumstances. Specific inroads have been achieved in selected virus infections. Strategies to develop immune therapy or more specific viral-targeted therapy appear promising. When dealing with encephalitis, questions about penetration of the central nervous system will remain. Perhaps the lessons learned in the treatment of COVID-19 will translate to future trials of viral encephalitis due to other viruses.

DISCLOSURE

The author has nothing to disclose.

REFERENCES

1. Vora NM, Holman RC, Mehal JM, et al. Burden of encephalitis-associated hospitalizations in the United States, 1998-2010. Neurology 2014;82(5):443–51.
2. Singh TD, Fugate JE, Rabinstein AA. The spectrum of acute encephalitis: causes, management, and predictors of outcome. Neurology 2015;84(4):359–66.
3. Carteaux G, Maquart M, Bedet A, et al. Zika virus associated with meningoencephalitis. N Engl J Med 2016;374(16):1595–6.
4. Gerardin P, Couderc T, Bintner M, et al. Chikungunya virus-associated encephalitis: a cohort study on La Reunion Island, 2005-2009. Neurology 2016;86(1):94–102.
5. Leber AL, Everhart K, Balada-Llasat JM, et al. Multicenter evaluation of BioFire FilmArray meningitis/encephalitis panel for detection of bacteria, viruses, and yeast in cerebrospinal fluid specimens. J Clin Microbiol 2016;54(9):2251–61.
6. Britton PN, Eastwood K, Paterson B, et al. Consensus guidelines for the investigation and management of encephalitis in adults and children in Australia and New Zealand. Intern Med J 2015;45(5):563–76.
7. Steiner I, Budka H, Chaudhuri A, et al. Viral meningoencephalitis: a review of diagnostic methods and guidelines for management. Eur J Neurol 2010;17(8).999-e57.
8. Venkatesan A, Tunkel AR, Bloch KC, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis 2013;57(8):1114–28.

9. Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2008;47(3):303–27.
10. Whitley RJ, Kimberlin DW. Herpes simplex encephalitis: children and adolescents. Semin Pediatr Infect Dis 2005;16(1):17–23.
11. Chow FC, Glaser CA, Sheriff H, et al. Use of clinical and neuroimaging characteristics to distinguish temporal lobe herpes simplex encephalitis from its mimics. Clin Infect Dis 2015;60(9):1377–83.
12. Skoldenberg B, Forsgren M, Alestig K, et al. Acyclovir versus vidarabine in herpes simplex encephalitis. Randomised multicentre study in consecutive Swedish patients. Lancet 1984;2(8405):707–11.
13. Whitley RJ, Alford CA, Hirsch MS, et al. Vidarabine versus acyclovir therapy in herpes simplex encephalitis. N Engl J Med 1986;314(3):144–9.
14. Gnann JW Jr, Skoldenberg B, Hart J, et al. Herpes simplex encephalitis: lack of clinical benefit of long-term valacyclovir therapy. Clin Infect Dis 2015;61(5):683–91.
15. Martinez-Torres F, Menon S, Pritsch M, et al. Protocol for German trial of Acyclovir and corticosteroids in Herpes-simplex-virus-encephalitis (GACHE): a multicenter, multinational, randomized, double-blind, placebo-controlled German, Austrian and Dutch trial [ISRCTN45122933]. BMC Neurol 2008;8:40.
16. Solomon T, Hart IJ, Beeching NJ. Viral encephalitis: a clinician's guide. Pract Neurol 2007;7(5):288–305.
17. Stahl JP. Dexamethasone in herpes simplex virus encephalitis open label randomized controlled trial with an observer-blinded evaluation at 6 months. Grenoble, France Liverpool, UK: University Hospital, Grenoble; 2017.
18. Skoldenberg B, Aurelius E, Hjalmarsson A, et al. Incidence and pathogenesis of clinical relapse after herpes simplex encephalitis in adults. J Neurol 2006;253(2):163–70.
19. De Tiege X, Rozenberg F, Des Portes V, et al. Herpes simplex encephalitis relapses in children: differentiation of two neurologic entities. Neurology 2003;61(2):241–3.
20. Armangue T, Leypoldt F, Malaga I, et al. Herpes simplex virus encephalitis is a trigger of brain autoimmunity. Ann Neurol 2014;75(2):317–23.
21. Leypoldt F, Titulaer MJ, Aguilar E, et al. Herpes simplex virus-1 encephalitis can trigger anti-NMDA receptor encephalitis: case report. Neurology 2013;81(18):1637–9.
22. Armangue T, Spatola M, Vlagea A, et al. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. Lancet Neurol 2018;17(9):760–72.
23. De Broucker T, Mailles A, Chabrier S, et al. Acute varicella zoster encephalitis without evidence of primary vasculopathy in a case-series of 20 patients. Clin Microbiol Infect 2012;18(8):808–19.
24. Anduze-Faris BM, Fillet AM, Gozlan J, et al. Induction and maintenance therapy of cytomegalovirus central nervous system infection in HIV-infected patients. AIDS 2000;14(5):517–24.
25. Bhanushali MJ, Kranick SM, Freeman AF, et al. Human herpes 6 virus encephalitis complicating allogeneic hematopoietic stem cell transplantation. Neurology 2013;80(16):1494–500.

26. Tyler KL, Pape J, Goody RJ, et al. CSF findings in 250 patients with serologically confirmed West Nile virus meningitis and encephalitis. Neurology 2006;66(3):361–5.
27. Kalil AC, Devetten MP, Singh S, et al. Use of interferon-alpha in patients with West Nile encephalitis: report of 2 cases. Clin Infect Dis 2005;40(5):764–6.
28. Chan-Tack KM, Forrest G. Failure of interferon alpha-2b in a patient with West Nile virus meningoencephalitis and acute flaccid paralysis. Scand J Infect Dis 2005;37(11–12):944–6.
29. Penn RG, Guarner J, Sejvar JJ, et al. Persistent neuroinvasive West Nile virus infection in an immunocompromised patient. Clin Infect Dis 2006;42(5):680–3.
30. Gnann JW Jr, Agrawal A, Hart J, et al. Lack of Efficacy of High-Titered Immunoglobulin in Patients with West Nile Virus Central Nervous System Disease. Emerg Infect Dis 2019;25(11):2064–73.
31. Deas TS, Bennett CJ, Jones SA, et al. In vitro resistance selection and in vivo efficacy of morpholino oligomers against West Nile virus. Antimicrob Agents Chemother 2007;51(7):2470–82.
32. Eastern equine encephalitis. Atlanta (GA): Centers for Disease Control; 2019. Available at: https://www.cdc.gov/easternequineencephalitis/index.html. Accessed October 4, 2020.
33. Mukerji SS, Lam AD, Wilson MR. Eastern equine encephalitis treated with intravenous immunoglobulins. Neurohospitalist 2016;6(1):29–31.
34. Wendell LC, Potter NS, Roth JL, et al. Successful management of severe neuroinvasive eastern equine encephalitis. Neurocrit Care 2013;19(1):111–5.
35. Grebenciucova E, Berger JR. Progressive multifocal leukoencephalopathy. Neurol Clin 2018;36(4):739–50.
36. Clifford DB, De Luca A, Simpson DM, et al. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. Lancet Neurol 2010;9(4):438–46.
37. Landi D, De Rossi N, Zagaglia S, et al. No evidence of beneficial effects of plasmapheresis in natalizumab-associated PML. Neurology 2017;88(12):1144–52.
38. Cortese I, Muranski P, Enose-Akahata Y, et al. Pembrolizumab treatment for progressive multifocal leukoencephalopathy. N Engl J Med 2019;380(17):1597–605.
39. Kupper C, Heinrich J, Kamm K, et al. Pembrolizumab for progressive multifocal leukoencephalopathy due to primary immunodeficiency. Neurol Neuroimmunol Neuroinflamm 2019;6(6):e628.
40. Pawlitzki M, Schneider-Hohendorf T, Rolfes L, et al. Ineffective treatment of PML with pembrolizumab: Exhausted memory T-cell subsets as a clue? Neurol Neuroimmunol Neuroinflamm 2019;6(6):e627.
41. Du Pasquier RA. Pembrolizumab as a treatment for PML? Waiting for Godot. Neurol Neuroimmunol Neuroinflamm 2019;6(6):e629.
42. Muftuoglu M, Olson A, Marin D, et al. Allogeneic BK virus-specific T cells for progressive multifocal leukoencephalopathy. N Engl J Med 2018;379(15):1443–51.