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REVIEW

Viral Meningitis and Encephalitis Update

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Abstract

Purpose of Review This review describes advances in the diagnosis, treatment, and prevention of non-bacterial meningitis and encephalitis, with a focus on emerging viral causes of central nervous system (CNS) infection.

Recent Findings The Infectious Diseases Society of America recently published new guidelines for the management of encephalitis. Multiple articles have been published detailing emerging etiologies in human CNS infections, including analyses of neurological complications in the ongoing COVID-19 pandemic. Finally, several novel viral detection methods have been described, which may improve the detection of the specific etiologies of CNS infections (Hongyan et al. Front Neurol 14,[1]).

Summary Meningitis and encephalitis remain important causes of morbidity and mortality. They are as a whole uncommon, yet timely diagnosis, treatment, and disposition are still critical to improve patient outcomes. In clinical practice the exact cause of encephalitis is frequently unidentified, making supportive care often the only available treatment. Emergency physicians, neurologists, infectious disease doctors, and intensive care unit specialists will benefit from reviewing this discussion on emerging pathogens, as well as from reviewing advances in virology, immunology, and the imaging of inflammatory CNS conditions.

Keywords Encephalitis · Meningitis · Viral meningitis · Aseptic meningoencephalitis · Emerging viral infections

Introduction

Meningitis and encephalitis are common neurological emergencies worldwide, with significant morbidity and mortality [2–4].

Encephalitis is a defined neurological syndrome, with an acute or subacute course. Its pathogenesis involves a primarily brain parenchymal inflammatory process causing sustained neurologic dysfunction, manifested clinically by some combination of delirium, altered sensorium, epilepsy, and focal neurological deficits. Severe cases of encephalitis are complicated by coma and cardiopulmonary dysfunction. Fever, hypothermia, cerebrospinal fluid pleocytosis, or specific abnormalities on brain MRI or electroencephalogram may be present [5•, 6, 7•]. Rhombencephalitis denotes inflammation in the brainstem and cerebellum, which can manifest as an onset of ataxia and cranial nerve abnormalities, followed by hemodynamic instability and respiratory failure. Importantly, to diagnose encephalitis, there must be evidence of primary brain inflammation, not just encephalopathy. Encephalopathy per se can complicate many serious systemic infectious and inflammatory conditions, can result from local or systemic circulatory issues, or it can be a sign of degenerative brain disorders. The International Encephalitis Consortium has proposed the following diagnostic criteria for encephalitis: the presence of encephalopathy for at least twenty-four hours plus any two of the following: 1) fever; 2) seizures; 3) focal neurological findings; 4) CSF (cerebrospinal fluid) pleocytosis; 5) characteristic brain MRI or electroencephalogram (EEG) findings.

The cause of encephalitis is unknown in over half the cases despite extensive diagnostic workup [6, 8]. Autoimmune etiology is diagnosed in twenty percent of all cases of encephalitis, and in developed countries it is more common than any single infectious cause [5, 9]. Autoimmune encephalitis can follow viral encephalitis or vaccinations, be paraneoplastic or cryptogenic [7•, 9–11, 12•]. A constellation of neuropsychiatric manifestations

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called Kluver-Bucy syndrome (bilateral temporal lobe dysfunction- see Table 1) rarely develops and is classically associated with herpes simplex encephalitis (see description below). New onset of seizures, including atypical febrile seizures in children [13•], especially if signs of infection are present, should raise suspicion of acute encephalitis.

Meningitis is defined as inflammation of the three protective neuromembranes that can clinically manifest as meningeal irritation signs. Bacterial meningitis is a well-known life-threatening reportable disease [14, 15]. Fortunately, incidence of bacterial meningitis has been decreasing due to effective immunizations targeting common causes [14]. Currently, viruses are the most common cause of infectious meningitis in children and adults [1, 16]. Once meningitis is suspected based on symptoms and clinical signs of acute infection and meningeal irritation, it is prudent to initially suspect and treat the patient for acute bacterial meningitis, which is immediately life-threatening.

Aseptic meningitis is a somewhat misleading term for meningeal inflammation from causes other than pus-producing bacteria [14]. Those causes include infectious agents, such as "atypical" bacteria (*Borrelia burgdorferi*, *Leptospira spp*., *Mycobacteria,* or *Treponema pallidum*), fungi (such as *Cryptococcus neoformans*), or a free-living ameba (*Naegleria fowleri*). Noninfectious meningitis can have an autoimmune cause triggered by certain medications [14], may be due to autoimmune diseases such as systemic lupus erythematosus, or can result from malignant invasion of the meninges [15]. The gold standard to diagnose (or exclude) meningitis is cerebrospinal fluid analysis and culture obtained from a lumbar puncture [4]. Cerebrospinal fluid examination also plays a central role in evaluating patients with suspected encephalitis [5•]. A reasonable suspicion of bacterial meningitis, herpes encephalitis, varicella-zoster (VZV) encephalitis or brain abscess should prompt administration of antibacterial or antiviral therapy without delay. Supportive measures and diagnostic tests, including neuroimaging and, so long as no contraindications to the procedure exist, an expeditious performance of a lumbar puncture. Meningoencephalitis is diagnosed when meningeal irritation develops following a clinical picture of encephalitis, or when encephalitis develops complicating meningitis. Importantly, in a patient presenting with fever, headache, and altered mental status, initial differentiation between meningitis and encephalitis may be impossible [12•]. Transverse myelitis is defined by inflammation of the spinal cord itself, which can be triggered either by viral invasion or by an autoimmune process [3]. It presents with acute or subacute symmetric motor and sensory deficits in extremities, usually in combination with neurogenic bowel and bladder dysfunction which can progress to respiratory muscle dysfunction, but without meningeal signs or encephalopathy. Several neurotropic viruses, such as Powassan virus, Epstein-Barr virus, and tick-borne encephalitis virus, cause encephalomyelitis, presenting with brain inflammation accompanied by flaccid paresis or paralysis of the extremities. Tick-borne encephalitis virus can also cause encephaloradiculitis, where pain in radicular distribution is a prominent symptom.

Blood-Brain Barrier (BBB) and Blood-CSF Barrier

Blood-brain barrier (BBB) disruption is thought to be the main mechanism of neurotropic viral invasion of brain parenchima [17]. BBB consists of specialized endothelial cells, glia, and extracellular matrix, and blocks entry of most large molecules. Four principal mechanisms of virus migration through the BBB are described. Once viremia develops, viruses can either directly infect brain microvascular endothelium cells, or pass through them via transcytosis in endocytic vesicles [2]. Alternatively, viral infection of monocytes or macrophages that can translocate across the BBB (in a process called diapedesis) denotes the "Trojan Horse" mechanism [2, 17], assisted via inflammatory cytokine production by viruses. Notably, West Nile virus and HIV use this mechanism [17]. Some viruses enter the CNS via sensory, motor, or olfactory neurons, using specialized proteins for neuronal transport [2]. COVID-19 and Rabies virus are two notable viruses which use this mechanism. Lastly, Nipah virus can directly infect glia cells that form part of the BBB [17]. For a pathogen to infect the meninges, it must defeat the blood-CNS barrier formed by tight junctions of the arachnoid membrane and the choroid plexus' endothelial cells. That occurs in a manner similar to viruses passing through the BBB, using the mechanisms detailed above.

Table 1 Kluver-Bucy syndrome manifestations (adopted from National Libraryof Medicine by Joe M. Das and Waquar Siddiqui)

1. Hyperorality: compulsion to examine objects by mouth, pica, bulimia
2. Hypermetamorphosis: compulsive tendency to explore and touch the immediate environment, and overreaction to visual stimuli
3. Hypersexuality
4. Placidity: flat affect, loss of normal fear
5. Visual agnosia: inability to recognize familiar objects
6. Amnesia

CSF Analyses and Molecular Diagnostics of Viral CNS Infections

Timely performance of lumbar puncture and CSF analyses are critical to both the diagnosis of meningitis or encephalitis and to establishing the specific etiology of CNS infection. In immunocompetent patients without focal neurological abnormalities, prior neurosurgery, recent trauma, or papilledema, lumbar puncture can be done without performing head CT first [15]. CSF that is not clear, has increased opening pressure, has a WBC count above 500 cells/mL with greater than 80% of neutrophils, has a glucose CSF/blood ratio less than 0.4, and has CSF protein above 1g/L, or visible microorganisms, suggests bacterial meningitis [14]. CSF lactic acid above 4.2 mmol/L is also strongly associated with bacterial infection [14]. On the other hand, CSF pleocytosis of less than 300 cells/mL with lymphocytic predominance, clear fluid with normal opening pressure, normal or only slightly decreased CSF glucose, and normal CSF protein all suggest viral etiology [4]. Increased red blood cell count in a non-traumatic tap is associated with HSV encephalitis [8]. It is important to note that with immunological dysfunction, or if CSF is obtained early in the course of the illness, bacterial meningitis can initially present with low white blood count CSF pleocytosis, while viral CNS infections can show either neutrophilic predominance or no increase in WBC counts in the CSF at all [14, 15, 18].

Many laboratories now offer molecular techniques, such as various methods for polymerase chain reaction, that have better sensitivity and give results faster than viral culture, which was used before [19]. There are now two rapid multiplex PCR-based panel tests on the market that allow for the detection of multiple viral, bacterial, and fungal pathogens in CSF from a single sample [20]. This has the potential to allow timelier discontinuation of unnecessary antibacterial agents, and to permit focusing on supportive measures and antiviral therapy where available. While published reviews report near-perfect specificity and high sensitivity [1, 20] with the use of these tests, caution should be observed in relying solely on them in clinical practice given their novelty [19].

Viral Meningitis

Viral meningitis is the most common infection of the CNS [1], and numerous viruses can cause this syndrome. Recent progress in identifying viruses in biological samples allows for more precise and rapid etiological diagnosis and more specific treatment [1, 20]. Various subtypes of human non-polio enteroviruses, especially coxsackieviruses A and B, along with echoviruses are the most common causative agents in viral meningitis in children and adults. Their incidence peaks in summer and autumn [14]. Herpes simplex virus and varicella virus are also common culprits [14]. The initial presentation is similar to bacterial meningitis [14], with fever, headache, and neck stiffness in immunocompetent patients. Those at extremes of age, or with abnormal immune systems may present with subtle altered mental status and without fever or neck stiffness [15]. Septic shock, focal seizures, status epilepticus, or disseminated intravascular coagulation strongly suggest bacterial etiology when present. Several clinical signs described over the years such as Kernig, Brudzinski, and jolt headache accentuation, are helpful when present but do not rule out the disease if absent, and do not help in distinguishing viral from bacterial disease [21•]. Management of viral meningitis is supportive, focusing on headache and fever control, and when necessary, management of seizures. An important exception is HSV or varicella zoster (VZV) CNS infections, where acyclovir is recommended [18] although it is not as clearly beneficial as it is in encephalitis caused by these agents [22]. Morbidity and mortality are low in viral meningitis [3, 22].

Viral Encephalitis

Any patient presenting with acute or subacute onset of confusional state (encephalopathy) should be evaluated for having developed infectious or autoimmune brain inflammation (encephalitis) [23]. Encephalopathy is a common presenting complaint in the Emergency Department, among hospital floor patients, and in ICUs [5•]. The differential diagnosis is extremely broad, as the human brain requires a tight homeostasis for appropriate functioning. It is important to attempt to consider and differentiate psychiatric causes, especially psychosis, mania, and catatonia, from organic brain diseases such as CNS infections, seizures including non-convulsive status epilepticus, drug withdrawal, and brain trauma.

Documented incidence of hospitalization for encephalitis in the United States is approximately seven per one hundred thousand [8] with roughly a third of those cases having proven viral etiologies [7•]. However, the causes remain unknown in most patients [24••]. HSV is the leading viral cause of acute encephalitis in the US, while enteroviruses predominate in China [3]. Japanese Encephalitis virus is the most common cause worldwide [10]. The outcomes of viral encephalitis, unlike viral meningitis, are frequently poor, with death and severe disability in survivors very common [5•, 7•, 25], febrile

seizures accompanying acute fever spikes, brain hypoperfusion from shock, or hypoxia or hypercarbia in respiratory failure.

Strictly neurotropic viruses, such as rabies or Japanese encephalitis virus, only cause CNS disease. Herpes viruses, while neurotropic [4], do cause overt neurological infections in a minority of infected patients. Lastly, many viruses with respiratory or gastrointestinal system tropism only very rarely cause encephalitis [10, 25]. It is unclear what host factors make apparently immunocompetent persons susceptible to the development of viral encephalitis, although age-related variations in innate and acquired immunity, including T-cell activity and humoral immunity, likely play a role [8]. Some viruses tend to cause more severe disease in the elderly (such as West Nile virus), while the population most at risk for developing viral encephalitis from any cause are children less than one-year old [16]. For example, La Crosse virus and California encephalitis virus predominately affect children [8].

A CT scan of the head is usually the first imaging study performed in workup of acute encephalopathy and can rule in space occupying lesions and intracranial hemorrhage. MRI imaging of the CNS plays an important role in diagnosing encephalitis and differentiating various types of encephalitis where certain patterns are observed [12•, 26]. As MRI takes time to obtain images, and patient cooperation is required, careful consideration should be given to appropriate sedation, monitoring, and airway management in these patients. Importantly, early in the clinical course MRI may not show any changes in a patient with encephalitis [5•, 9, 27].

Once acute encephalitis is suspected, acyclovir should be administered intravenously without delay, especially as HSV encephalitis outcomes are directly affected by timely administration of this antiviral. Administration of acyclovir is recommended in cases of VZV CNS infection as well [28]. Parenteral administration is recommended as oral bioavailability of acyclovir is poor. Oral valacyclovir (acyclovir prodrug) administration produces higher concentrations of acyclovir in plasma, but CSF clinical evidence on its use is scant [18]. Acyclovir can cause renal insufficiency (preventable by assuring adequate hydration status of the patient) and accumulates in the CNS in patients with renal insufficiency potentially causing altered mental status. Ganciclovir and valganciclovir are alternative options for HSV treatment, while foscarnet and cidofovir are active against both HSV and VZV, including against the rare acyclovir-resistant strains. All of these are significantly more toxic than acyclovir. Patients should be closely monitored, as respiratory failure can develop early, especially in cases of brainstem encephalitis.

Another priority is to consider the possibility of autoimmune etiology, especially anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis, which is a common cause of encephalitis in developed countries. Psychiatric prodrome is seen in 70% of cases [9] and MRI shows abnormalities early in a minority of patients [12•]. Early immunotherapy, with either corticosteroids or IVIG, improves outcomes [9]. Autoimmune encephalitis can develop following viral encephalitis and can have a relapsing course [11].

The prognosis of encephalitis remains poor [8, 29] and is broadly worse in patients where no etiology is found [7•].

Prevention of Viral CNS Infections

High morbidity and mortality of certain types of viral encephalitis, combined with a lack of specific therapies, make preventive measures very important if available. In cases of encephalitis complicating measles, mumps, or varicella-zoster virus disease, or in Japanese encephalitis, effective vaccines exist for pre-exposure prophylaxis, making both primary infection and its complications unlikely. Analyses of CNS varicella disease before and after vaccination showed a 60% reduction of this disease in Germany [8]. In Nepal, a Japanese encephalitis vaccination campaign reduced case incidence by 78% [8] after five years.

There are effective pre- and postexposure vaccines for the prevention of rabies encephalitis. As rabies is almost always fatal [30] and common in many mammals around the world, including stray dogs, strict adherence to postexposure prophylaxis with administration of immunoglobulin and vaccine is very important. Rabies can occur up to a year after exposure and has been described in patients after incomplete postexposure prophylaxis was given [31•].

For most mosquito or tick-borne arboviruses that cause encephalitis, reducing exposure to arthropod vectors is the only known way to reduce the risk of developing the disease. This can include the use of mosquito nets, wearing garments to make ticks more visible, frequently checking for ticks, and application of insect and tick repellants. Visitors can avoid endemic areas in seasons when arthropod vectors are particularly active, such as in Eurasian mixed forest and taiga in the spring and early summer.

Emerging Viral Causes of Meningitis and Encephalitis

COVID-19

SARS-CoV-2 virus infection symptoms are highly variable, and most infected people remain asymptomatic or only develop mild symptoms. In symptomatic patients the respiratory and digestive systems involvement predominate.

Multiple neurological complications have been reported in COVID-19 cases, including severe headaches, ischemic and hemorrhagic strokes, and delirium [32]. At least one series documents COVID-19 to be the most common viral cause of encephalitis in a hospital in Africa in the year 2021 [33]. Initially, olfactory nerve dysfunction without overt rhinitis was observed so commonly that screening tests were developed to detect COVID-19 infection by detecting anosmia, even though the exact mechanism of its development was not conclusively elucidated [32]. At the time of this writing, the Omicron variant is the predominant type, and it appears to cause anosmia and ageusia much less often than earlier variants. Acute encephalitis can complicate severe COVID-19 [34], and at times may be the only clinical manifestation of this viral infection [35]. Cases of hemorrhagic encephalitis which closely mimic HSV encephalitis in both CSF and in MRI of the brain findings have also been reported [36, 37]. As with other cases of encephalopathy complicating a severe systemic infectious disease, MRI findings can be helpful to distinguish encephalitis from CNS complications of severe sepsis, and several distinct neuroradiological patterns are now described [37]. Similarly to other respiratory viruses, COVID-19 infection in children can rarely be manifested by cytokine storm, with the development of a multiorgan inflammatory state and acute encephalitis [38]. One series from NEJM described an observational series where CSF analyses failed to detect COVID-19, despite clinical and MRI findings highly suggestive of encephalitis [39].

Powassan Virus [4, 8, 12•, 24••, 40]

Powassan virus (PWV) is an RNA arbovirus from the *Flaviviridae* family which causes viral encephalitis in humans, with the number of cases increasing in the US over the past decade. This zoonotic infection's primary reservoir is in small mammals, and it can spread to humans via the bites of several tick species, primarily *Ixodes scapularis* (the deer tick or black-legged tick). This tick is present in the Upper Midwest, Northeastern, and Southeastern states, along with southeastern Canada, with the area expanding dramatically over the past three decades. This tick is a vector for the pathogens that cause Lyme disease and Anaplasmosis in addition to PWV and may be involved in the development of α-gal syndrome (red meat and milk allergy). Most cases of PWV encephalitis occur in late spring and early summer. It is not known as to why some patients develop encephalitis while most patients infected with PWV remain asymptomatic or only mildly symptomatic. After an incubation period of one to five weeks, an acute febrile illness develops. Within days to weeks, it becomes complicated by encephalopathy with signs of cerebellar dysfunction, followed in severe cases by coma and flaccid paralyses. MRI of the brain findings are nonspecific and may be normal early in the disease course. If the MRI is positive, inflammation is seen in basal ganglia and the thalamic region. The diagnosis is made by measuring IgM titers or PCR detection of the virus in CSF, and it is a nationally notifiable disease. The treatment is supportive, with a reported fatality rate of 10% and neurological sequela in about half of the survivors. Prognosis is worse in patients over the age of fifty.

Nipah Virus [6, 10, 24••, 41]

Nipah virus (NV) is a zoonotic virus with documented person-to-person spread, both in households of infected people and in healthcare settings, raising concerns for a potential epidemic. It is a member of the family *Paramyxoviridae*, along with measles virus, mumps virus, and parainfluenza virus. NV can infect pigs and humans, with flying foxes serving as a natural reservoir. Different flying fox species are found in Asia, Africa, Australia, and some Pacific Ocean islands. Consumption of food contaminated by infected animals, such as raw date palm sap, or close contact with infected bats or pigs can result in virus transmission to people. The first outbreak of NV encephalitis occurred in 1999 in Malaysia and Singapore, affecting people who were caring for infected pigs, with three hundred cases and one hundred deaths. Multiple outbreaks have been reported since then, mostly in India and Bangladesh, but also in the Philippines. After an incubation period of four to fourteen days, an acute febrile illness develops that lasts up to two weeks, often with prominent upper respiratory symptoms. Some patients go on to develop acute encephalitis, with brainstem and upper cervical spinal cord involvement. Coma can develop early, with mortality of the neurologic disease of up to seventy-five percent. Molecular tests exist to detect the viral material obtained in nasal or throat swabs, or from CSF; there are also assays for antibody detection in plasma or CSF. MRI of the brain, when positive, shows multiple hyperintense (without contrast) white matter lesions. There is currently no vaccine available for NV disease prevention. There are case reports of IVIG therapy in NV encephalitis and the use of remdesivir and ribavirin, but the mainstay of treatment is supportive care. A monoclonal therapy drug is under development.

Tick-borne Encephalitis Virus [8, 12•, 18, 19, 24••, 42]

Tick-borne encephalitis (TBE) is a zoonosis caused by a tick-borne encephalitis virus (TBEV), a flavivirus, occurring across Eurasia, from Western Europe and Scandinavia to the Japanese island of Hokkaido. There are three subtypes of the virus, with the European subtype causing a milder disease than the Siberian and Far Eastern subtypes. Small rodents

serve as the main reservoir of this virus in nature. It spreads via *Ixodes spp*. ticks and infects humans and livestock, especially goats. People become infected mainly through tick bites, with a minority of cases reported after consuming unpasteurized milk or milk products; there is no person-to-person spread except for rare cases through breastfeeding. The peak incidence of the disease is in the spring and early summer, and it is called tick-borne spring-summer encephalitis in some countries. TBE is not a notifiable condition in many countries where it is endemic, making true incidence hard to ascertain, but overall reported cases have increased over the past several decades with new endemic foci emerging in Belgium and the Netherlands. No viral transmission has been reported in North America so far, but with increasing tourism the chances of US clinicians encountering this disease in a returning traveler are increasing, as the incubation period ranges from two to twenty-eight days (usually one to two weeks).

Many patients with TBE do not recall a tick bite. The majority of TBEV disease is thought to be minimally symptomatic or asymptomatic, based on serological surveillance in endemic areas. The disease typically (but not always) follows a biphasic course. Initially, patients develop acute febrile illness with muscle aches and headaches, but without signs of CNS inflammation. This lasts up to a week, followed by defervescence and clinical improvement for two to ten days. Some patients progress to the second phase, which is heralded by recurrence of high fever, and with CNS involvement. This can range from meningitis, more common in children, to meningoencephalitis, radiculitis, and myelitis. Common symptoms include ataxia, radicular distribution of pain in the extremities, followed by the development of paresis, with upper extremities more commonly affected. In severe cases there are signs of brainstem encephalitis with cranial nerve abnormalities, autonomic instability, and coma. Diagnosis requires clinical suspicion for the disease, based on travel and activities history. Laboratory abnormalities, including leukopenia, thrombocytopenia, and liver function test abnormalities, are nonspecific and only seen in a minority of the patients. In the first phase of the illness, viral material can be detected in serum with PCR technology, while in the second phase IgM and IgG antibodies are usually present in the serum. CSF analysis shows changes typical for viral meningitis, although pleocytosis as high as 1000 cells/mL has been observed and can be confused with bacterial meningitis initially. The detection of the virus or IgM antibodies in CSF is diagnostic. Brain MRI can show basal ganglia and thalamic involvement, but the changes are only observed in a minority of cases and are not specific to TBE. Importantly, the same *Ixodes* ticks that transmit TBE can carry *Anaplasma phagocytophilum* and *Borrelia burgdorferi*, which can cause granulocytic anaplasmosis and Lyme borreliosis respectively with CNS complications and requiring antibiotic administration for treatment. Patients may also be coinfected with TBEV and a bacterial pathogen. Supportive treatment is a mainstay of care for TBE, with case reports of IVIG use for treatment. Prognosis is worse in adults compared to children and worsens with advanced age. It is also worse in monophasic disease, or in cases of simultaneous co-infection. The fatality rate ranges from two percent for the European subtype of TBEV to twenty to forty percent for the Siberian subtype, and disability affects up to fifty percent of survivors, ranging from persistent paresis to neuropsychiatric abnormalities. Survivors of this disease develop lifelong immunity. Several effective vaccines are available for pre-exposure prophylaxis. Usual measures of tick avoidance and detection can reduce the risk of exposure to TBEV.

Eastern Equine Encephalitis (EEE) [12•, 27, 43]

The eastern equine encephalitis virus (EEEV) is a mosquito-borne flavivirus from the *Togaviridae* family that is transmitted to humans by the *Aedes, Coquillettidia,* and *Culex* genera of mosquitos from infected birds. While most patients affected do not develop CNS inflammation, it can cause severe encephalitis with a mortality of thirty to forty percent in those affected and neurological sequela in many survivors. Those younger than fifteen and older than fifty years old appear to be most at risk. Most human cases in the US are reported in the Northeastern and Gulf states, but recently new cases were found in the Great Lakes and Appalachian regions, and the number of reported cases has been rising sharply. It is considered a potential bioterrorism agent and can be transmitted through organ transplantation. In symptomatic cases, after an incubation period of four to ten days, patients develop a nonspecific acute febrile illness, followed by meningoencephalitis with seizures, thalamic, and brainstem involvement signs. Blood chemistry may show hyponatremia, especially in severe cases. CSF analysis can show pleocytosis, with neutrophilic predominance and a normal CSF/plasma glucose ratio. Etiological diagnosis requires detection of anti-EEEV specific IgM antibodies in serum or in CSF specimens with the ELISA technique, which then must be confirmed using Plaque Reduction Neutralization Tests (PRNT) to detect false positive results. Both tests require specialized laboratories or sending the specimen to the CDC for analyses. Similarly to West Nile virus, PCR technology for direct detection of the EEE virus is not well developed, and viral culture is only done on autopsy specimens. MRI of the brain shows a characteristic pattern of basal ganglia and thalamic T2 hyperintensities. However, a similar pattern can be observed in rabies encephalitis and in prion disease. The treatment is supportive, and prevention requires measures to avoid mosquito bites, as no vaccines are available for use in humans.

Chikungunya Virus [12•, 44, 45]

Chikungunya virus is an alphavirus from the family *Togaviridae* transmitted via *Aedes* mosquito bites, and vertically from mother to fetus causing Chikungunya Virus disease (CHVD). Eastern equine encephalitis virus, western equine encephalitis virus, and Venezuelan equine encephalitis virus are other members of that family transmitted via mosquito bite with the potential to cause acute encephalitis. Four major subtypes of CHVD are known, and all but one are potentially neuroinvasive. There was a large outbreak of CHVD in La Reunion, an island in the Indian Ocean which is a major tourist destination, in 2005–2006. In the Americas humans are the main reservoir for this pathogen, while in Africa wild primates also play a role. The first cases in the Americas were reported in 2013, with local transmission in the US identified in 2014 (in Puerto Rico, the U.S. Virgin Islands, Florida, and Texas), and in 2015 this emerging disease became a nationally notifiable condition in the US [45]. Most cases of CHVD manifest as self-limited acute febrile illness, marked with severe arthralgias and myalgias, which are a hallmark of the symptomatic disease. The word *chikungunya* means "to become contorted" in the Kimakonde language of southern Tanzania, where the disease was first identified in 1952. Maculopapular rash, conjunctivitis, and lassitude are other commonly reported symptoms. Acute encephalitis is one of the neurological complications of CHVD and is more common in patients over fifty, those with diabetes, cardiovascular disease, and impaired cellular immunity. CHVD encephalitis is often complicated by severe renal failure requiring renal replacement therapy. The white blood cell count can show leukopenia typical for acute viral infections. Brain MRI can be normal or demonstrate multiple stroke-like lesions in white matter [12•]. PCR techniques exist to detect viral material in CSF, and anti-Chikungunya virus antibodies can be detected in serum and CSF. Treatment is supportive, and the disease appears to induce durable immunity against future episodes in survivors.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Hongyan Xu, Peng Chen, et el. Progress in etiological diagnosis of viral meningitis. Front Neurol. 2023;14:1193834. https://doi.org/10.3389/fneur.2023.1193834
2. Bohmwald K, Gálvez NM, et al. Neurologic alterations due to respiratory virus infections. Front Cell Neurosci. 2018;12:386. https://doi.org/10.3389/fncel.2018.00386. Published 26/10/2018
3. Abid FB, Abukhattab M, et al. Epidemiology and clinical outcomes of viral central nervous system infections. Int J Infect Dis. 2018;73:85–90.
4. Kaitlin M. Bowers V, Mudrakola V. Neuroinfections: presentation, diagnosis, and treatment of meningitis and encephalitis. EMJ Neurology. 2020;8(1):93–102.
5.• Ellul M, Solomon T. Acute encephalitis - diagnosis and management. Clin Med (Lond). 2018;18(2):155–159. https://doi.org/10.7861/clinmedicine.18-2-155. PMID: 29626021; PMCID: PMC6303463. **This article provides a nice overview of different etiologies and early management of acute encephalitis**.
6. Wagner JN, Leibetseder A, Troescher A, Panholzer J, von Oertzen TJ. Efficacy and safety of intravenous immunoglobulins for the treatment of viral encephalitis: a systematic literature review. J Neurol. 2022;269(2):712–24.
7.• Bakal JA, Rivera R, Charlton C, Plitt S, Power C. Evolving etiologies, comorbidities, survival, and costs of care in adult encephalitis. J NeuroVirol. 2023;17. **This article provides data that shows that encepahalitis, while a rare disease, is an important cause of prolonged neurological morbidity with associated high financial burden**.
8. Tyler KL. Acute Viral Encephalitis. J Med. 2018;379:557–66. https://doi.org/10.1056/NEJMra1708714.
9. Dutra LA, Abrantes F, Toso FF, Pedroso JL, Barsottini OGP, Hoftberger R. Autoimmune encephalitis: a review of diagnosis and treatment. Arq Neuropsiquiatr. 2018;76(1):41–49. https://doi.org/10.1590/0004-282X20170176. PMID: 29364393.
10. Kumar R. Understanding and managing acute encephalitis. F1000Res. 2020;9:F1000 Faculty Rev-60. https://doi.org/10.12688/f1000research.20634.1. PMID: 32047620; PMCID: PMC6993835.

11. Armangue T, Moris G, Cantarín-Extremera V, et al. Autoimmune post-herpes simplex encephalitis of adults and teenagers. Neurology. 2015;85:1736–43.
12.• Bertrand A, Leclercq D, Martinez-Almoyna L, Girard N, Stahl JP, De-Broucker T. MR imaging of adult acute infectious encephalitis. Med Mal Infect. 2017;47:195–205. **This article reinforces the importance of MRI imaging in both establishing the diagnosis of acute infectious encephalitis as well as providing clues for narrowing the differential to a specific infectious agent**.
13.• Kajiwara K, Koga H. Risk factors for acute encephalitis and early seizure recurrence in complex febrile seizures. Eur J Pediatr. 2022;181(8):3103–10. **This article reminds a clinician of danger of premature closure in children presenting with a febrile seizure**.
14. Kohil A, Jemmieh S, Smatti MK, et al. Viral meningitis: an overview. Arch Virol. 2021;166:355–345.
15. Meningitis SD. Pediatr Rev. 2015;36(12):514–24.
16. Li Qi, Wang R, Hui Xu, Zhang L, Yiliang Fu, Tian J, Liu M, Feng G, Zeng Y, Chen X, Xie Z. Epidemiology and disease burden of hospitalized children with viral central nervous system infections in China, 2016 to 2020. Pediatr Neurol. 2023;138:38–44.
17. Al-Obaidi MJ, Bahadoran A, Wang SM. Disruption of the blood brain barrier is vital property of neurotropic viral infection of the central nervous system. Acta Virologica. 2018;62(1):16–27.
18. Bookstaver PB, Mohorn PL, Shah A, et al. Management of viral central nervous system infections: a primer for clinicians. J Cent Nerv Syst Dis. 2017; volume 9 1-12
19. Yong HYF, Pastula DM, Kapadia RK. Diagnosing viral encephalitis and emerging concepts. Curr Opin Neurol. 2023;36(3):175–84.
20. Humisto A, Antikainen J, Holma T, Jarva H, Toivonen A, Loginov R, Mannonen L, Tesic V. Evaluation of the novel CE-IVD-marked multiplex PCR QIAstat-Dx meningitis/encephalitis panel. Microbiol Spectr. 2023;11:3.
21.• Nakao JH, et al. Jolt accentuation of headache and other clinical signs: poor predictors of meningitis in adults. Am J Emerg Med. 2014;32(1):24–8. **This article reinforces the difficulty of relying on clinical signs to rule in meningitis**.
22. Griffiths MJ, et al. Management of acute meningitis. Clin Med. 2018;18(2):164–9.
23. Sigfrid L, Perfect C, Rojek A, et al. A systematic review of clinical guidelines on the management of acute, community-acquired CNS infections. BMC Med. 2019;17:170. https://doi.org/10.1186/s12916-019-1387-5.
24.•• Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, Hartman BJ, Kaplan SL, Scheld WM, Whitley RJ. The management of encephalitis: clinical practice guidelines by the infectious diseases society of America. Clin Infect Dis. 2008;47(3):303–27. https://doi.org/10.1086/589747. PMID: 18582201. **This paper from Infectious Diseases Society of America is a great up to date review for clinician on diagnosis and management of encephalitis with tips on determining etiology, using neuroimaging, and choosing appropriate interventions**.
25. Kyung Yeon Lee. Rotavirus infection-associated central nervous system complications: clinicoradiological features and potential mechanisms. Clin Exp Pediatr. 2022;65(10):483–93.
26. Bhat MD, Priyadarshini P, Prasad C, Kulanthaivelu K. Neuroimaging findings in rabies encephalitis. J Neuroimaging. 2021;31(3):609–614. Wiley. https://doi.org/10.1111/jon.12833.
27. Montalvo M, Ayoub D, McGary M, Byrd K, Mahmoud L, Mermel L, Thompson B, Wendell L. Eastern equine encephalitis. Neurol Clin Prac. 2021;11(5):e714–21.
28. Grahn A, Studahl M. Varicella-zoster virus infections of the central nervous system-prognosis, diagnostics and treatment. J Infect. 2015;71:281–93.
29. Cooper J, Kierans C, Defres S, et al. Care beyond the hospital ward: understanding the socio-medical trajectory of herpes simplex virus encephalitis. BMC Health Serv Res. 2017;17:646.
30. Chaudhary SC, Khandelwal A, Tandon R, et al. Rabies encephalitis. BMJ Case Rep CP. 2021;14:e239249.
31.• Karande S, Muranjan M, Mani RS, et al. Atypical rabies encephalitis in a six-year-old boy: clinical, radiological, and laboratory findings. Int J Infect Dis. 2015;36:1–3. **This article presents a case of rabies that developed due to incorrectly administered post exposure prophylaxis. This reinforses the importance of obtaining detailed history in a patient presenting after an exposure concerning for transmission of rabies virus**.
32. Al-Ramadan A, Rabab'h O, Shah J, Gharaibeh A. Acute and post-acute neurological complications of COVID-19. Neurol Int. 2021;13(1):102–19.
33. Kahwagi J, Seye AO, et al. Surveillance of viral encephalitis in the context of COVID-19: A one-year observational study among hospitalized patients in dakar. Senegal Viruses. 2022;14(5):871.
34. Haider A, Siddiqa A, Ali N, Dhallu M. COVID-19 and the brain: acute encephalitis as a clinical manifestation. Cureus. 2020;12:e10784. https://doi.org/10.7759/cureus.10784.
35. Etemadifar M, Salari M, Murgai AA, Hajiahmadi S. Fulminant encephalitis as a sole manifestation of COVID-19. Neurol Sci. 2020;41:3027–9. https://doi.org/10.1007/s10072-020-04712-y.
36. Handa R, Nanda S, et al. SARS-CoV-2-associated haemorrhagic encephalitis mimicking Herpes encephalitis. J Neurovirol. 2022;28(2):322–5.
37. Kremer S, Lersy F, de Sèze J, et al. Brain MRI findings in severe COVID-19: a retrospective observational study. Radiology. 2020;297:242–51. https://doi.org/10.1148/radiol.2020202222.
38. Santos PC, Holloway AJ, Custer JW, Alves T, Simon L. Encephalitis and cytokine storm secondary to respiratory viruses in children: Two case reports. Front Pediatr. 2023;10.
39. Helms J, Kremer S, Merdji H, et al. Neurologic features in severe SARS-CoV-2 infection. N Engl J Med. 2020;382:2268–2270. Haider A, Siddiqa A, Ali N, Dhallu M. COVID-19 and the brain: acute encephalitis as a clinical manifestation. Cureus. 2020;12:e10784. https://doi.org/10.7759/cureus.1078.
40. https://www.cdc.gov/powassan/index.html.
41. https://www.cdc.gov/vhf/nipah/.
42. Riccardi N, Antonello RM, et al. Tick-borne encephalitis in Europe: a brief update on epidemiology, diagnosis, prevention, and treatment. Eur J Intern Med. 2019;62:1–6. https://doi.org/10.1016/j.ejim.2019.01.004. PMID: 30678880.
43. (EEE) virus. https://www.cdc.gov/easternequineencephalitis/transmission/index.html.
44. Hopkins HK, Traverse EM, Barr KL. Chikungunya encephalitis: an inconsistently reported headache and cause of death in patients with pre-existing conditions. Curr Trop Med Rep. 2022;9(3):73–91.
45. https://www.cdc.gov/chikungunya/geo/chikungunya-in-the-us.html.