Diagnosis and Management Viral Encephalitis in Pediatric Patients: An Overview

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Abstract:

Viral encephalitis is characterized by inflammation of the brain tissue caused by viral agents and often co-exists with viral meningitis. The progression involves viruses penetrating the host's body, initially outside the central nervous system (CNS), and then navigating to the brain and spinal cord either via the bloodstream or retracing along nerve endings. The younger demographic demonstrates a higher predisposition to viral encephalitis compared to their older counterparts. In Western regions, herpes simplex encephalitis (HSE) emerges as the predominant spontaneous form of this acute inflammation. To diagnose HSE, magnetic resonance imaging (MRI) remains a cornerstone tool, further enhanced by the polymerase chain reaction (PCR) assessment to detect the virus in cerebrospinal fluid, which is considered one of the most sensitive methods to detect Viral etiologies and unlike cultures it does not require 1 to 28 days for virus detection. An integrative diagnosis melds insights from clinical, laboratory, neuroimaging, and electrophysiologic sources. Distinguishing encephalitis from other encephalopathies necessitates key markers, such as the onset of fever, cerebrospinal fluid (CSF) pleocytosis, or MRI/EEG anomalies indicative of encephalitis. The clinical presentation often includes neuropsychiatric signs, like behavioral shifts, hallucinations, and cognitive decline. PCR stands out for its ability to detect challenging microorganisms swiftly and economically. When viral encephalitis is suspected, primary interventions encompass supportive care, rectifying imbalances in electrolytes, and maintaining organ functions, along with the management of seizures. Initiating empirical acyclovir therapy at the onset of symptoms, even preceding test results, is recommended. Post-infection care, particularly for children, focuses on rehabilitation through diverse therapeutic interventions, which is vital to avoid post-discharge manifestation.

Introduction:

Viral encephalitis denotes inflammation of brain tissue provoked by viral microbes. This type of encephalitis is the prevailing one and frequently occurs simultaneously with viral meningitis. Viruses infiltrate the host's body beyond the central nervous system (CNS) and subsequently find their way to the spinal cord and brain through the bloodstream or by tracing a reverse path from nerve endings. [1-4]

Meningoencephalitis denotes the inflammation affecting both the brain and meninges. Encephalopathy, on the other hand, refers to a neurological condition displaying signs akin to encephalitis, albeit lacking actual brain inflammation. Encephalitis is commonly categorized as either primary or postinfectious/parainfectious. In primary encephalitis, the condition arises from the direct infiltration and replication of an infectious agent within the brain. Conversely, postinfectious/parainfectious encephalitis occurs subsequent to, or in conjunction with, a different non-central nervous system ailment or emerges following the administration of a vaccine or another form of intervention. [5]

The occurrence of viral encephalitis is more prevalent among the younger demographic when compared to the elderly, although external circumstances also exert a pivotal influence. Numerous instances of viral encephalitis often remain undetected due to limited diagnostic capabilities and mild symptomatology. Furthermore, empirical data reveals that a substantial number of patients develop substantial antibody levels against the viruses yet remain devoid of symptoms. [1]

Herpes simplex encephalitis (HSE) stands as the most prevalent sporadic instance of abrupt viral brain inflammation in Western societies. In cases of HSE, magnetic resonance imaging serves as the foremost investigative approach, while confirmation of the diagnosis can be accomplished through the polymerase chain reaction assessment for the virus within the cerebrospinal fluid. [6]

Typically, the diagnosis is established through a blend of clinical, laboratory, neuroimaging, and electrophysiologic discoveries. Various sets of criteria have been formulated, generally mandating encephalopathy, evident by a sustained alteration in consciousness or lasting personality shift (typically exceeding 24 hours). To differentiate encephalitis from alternative encephalopathy causes, crucial markers encompass the presence of fever, CSF pleocytosis, or MRI/EEG modifications consistent with encephalitis. While these definitions likely encompass most patients with clinically notable encephalitis, a portion may elude detection. For instance, localized forms of cerebral inflammation (e.g., unilateral brainstem involvement) could induce focal neurological impairments without impacting awareness or behavior. [7-14]

For the majority of viral encephalitis variations, targeted therapy remains tenuous. Elevated mortality and morbidity rates, along with enduring aftereffects in survivors, underscore the gravity of the condition. The emergence of atypical zoonotic encephalitis forms has raised notable public health concerns. Preventive measures, including vaccination and vector management, offer valuable strategies against specific arboviral and zoonotic encephalitis strains. Yet, a more robust antiviral therapeutic approach is imperative to effectively confront the challenges posed by acute viral encephalitis. [6]

In individuals undergoing evaluation for encephalitis, medical professionals typically advise conducting lumbar puncture, brain MRI, and electroencephalography. Standard practice includes testing for HSV-1/2 and enteroviruses, given their frequent association with encephalitis in children. Additional investigation into potential infectious causes, such as EBV, CMV, ADV, influenza, HHV-6,7, VZV, measles, Mycoplasma spp., and others, might be conducted based on the local disease patterns and clinical symptoms. Despite comprehensive testing efforts, the origin of encephalitis often remains difficult to ascertain. [15-19]

In Canada, instances of encephalitis in children with identified causes often involve infections such as chickenpox, enterovirus, herpes simplex, influenza, human herpesvirus 6, measles, Epstein Barr virus, or arbovirus. Mycoplasma and bacteria from cat scratch disease, Bartonella species, are also progressively recognized as significant contributors to encephalitis. Conditions that might imitate viral encephalitis encompass brain abscess, bacterial meningitis or sepsis, subacute bacterial endocarditis, tuberculosis, fungal infection, parasitic infection (Naegleria species, cysticercosis, toxoplasmosis), Rocky Mountain spotted fever, syphilis, and leptospirosis. [20]

Even after comprehensive exploration for infectious and immune-related factors, a significant proportion, ranging from 37% to 62% of individuals suffering from encephalitis remain without a confirmed underlying cause. Emerging laboratory methodologies like proteomics, transcriptomics, and metabolomics hold the potential to unravel immune reactions associated with encephalitis, potentially categorizing unidentified cases into distinct etiological categories. Furthermore, the quest for potential infectious agents through advanced next-generation sequencing techniques, coupled with the identification of novel antibodies using protein arrays and mass spectrometry, holds promise for diagnosing a greater number of patients in upcoming times. [21]

Viruses Transmitted by Mosquitoes or Ticks Arboviruses represent a significant cause of severe encephalitis on a global scale. The prevalence of specific arboviruses varies seasonally and is heavily influenced by geographical factors. Typically, the incidence of neuroinvasive disease and the subsequent complications, including death, tends to rise with increasing age. Presently, Japanese encephalitis virus stands as a major contributor to epidemic encephalitis worldwide, resulting in around 10,000 fatalities and 35,000–50,000 cases annually. [5]

Etiology and classification of encephalitis:

Encephalitis can arise from diverse disease processes, yet it can generally be categorized into those linked to infection, whether directly or indirectly, and non-infectious origins. Direct infections of the central nervous system (CNS) can stem from a variety of viruses, bacteria (particularly intracellular types like Mycoplasma pneumoniae), parasites, and fungi. Indirectly related infections encompass an acute demyelinating process, often temporally associated with a preceding infection outside the CNS. This phenomenon can also follow vaccination and is termed acute disseminated encephalomyelitis (ADEM). Non-infectious triggers comprise antibody-mediated encephalitis, which might be paraneoplastic, such as limbic encephalitis linked to ovarian teratomas, or could present in isolation. Although initially reported in adults, these conditions are increasingly being identified in children. Most instances of viral encephalitis display

an acute onset, although specific pathogens, particularly in immunocompromised individuals, may present with sub-acute or chronic manifestations. [22]

Despite extensive investigation, the origins of numerous encephalitis cases remain elusive. Viruses constitute the predominant identified causative factor, being responsible for approximately 70% of confirmed encephalitis cases. In the United States, the primary culprits behind viral encephalitis are herpes simplex virus (HSV), West Nile virus, and the enteroviruses. Other viral agents contributing to the etiology encompass varicella-zoster virus, Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpesvirus type 6 and 7, measles virus, mumps virus, rubella virus, St. Louis virus, eastern equine virus, western equine virus, dengue virus, and rabies virus. [1]

The Herpes group of viruses, specifically Herpes simplex virus type 1 (HSV-1), is a prevalent cause of sporadic fatal encephalitis. This condition arises from the reactivation of latent infection; however, it can also be linked to primary infection or reinfection by a different HSV-1 strain. This form of encephalitis can affect individuals across all age groups. Among neonates, herpes encephalitis is predominantly attributed to disseminated HSV-2 infection acquired during childbirth. In contrast, encephalitis in older children is primarily associated with HSV-1. Except for the newborn period, HSV-2 seldom leads to encephalitis, except in cases of immunocompromised individuals. Nonetheless, aseptic meningitis resulting from HSV-2 is a relatively common condition connected with recurrent genital HSV-2 infections. [5] The HSV PCR test may yield inaccurate results, especially in children and early stages of the illness. If herpes simplex encephalitis is still under consideration despite negative results in the initial cerebrospinal fluid (CSF) test, a second CSF analysis should be conducted within 3 to 7 days. As VZV reactivation can happen without visible skin lesions (known as zoster sine herpete), it is advised to test for VZV in all suspected encephalitis cases, regardless of the presence of vesicular lesions. It's worth noting that while testing CSF for VZV PCR is recommended, its sensitivity might not be optimal. In fact, detecting CSF antibodies to VZV could potentially provide a more sensitive approach to diagnosing VZV encephalitis. [7]

Varicella, commonly known as chickenpox, is associated with varicella-zoster virus (VZV) encephalitis in approximately 0.3 cases per 1000. The initial VZV infection establishes latent infection within dorsal root ganglia. The reawakening of the virus causes shingles, and a small percentage, ranging from 0.5% to 5%, of shingles patients may develop encephalitis. Encephalitis may also arise from other herpes group viruses such as EBV, CMV, HHV-6, and HHV-7, albeit infrequently. Immunocompromised individuals are particularly susceptible to encephalitis triggered by these viruses due to the reactivation of latent viruses. In cases of primary EBV infection causing infectious mononucleosis, approximately 1% of instances will involve encephalitis during the illness. Although encephalitis is rare in primary CMV infections, it may occur in congenital infections. HHV-6 is a common cause of febrile convulsions in infants; however, it is an uncommon source of encephalitis. [5]

Epidemiology:

The occurrence of viral encephalitis ranges from 3.5 to 7.5 cases per 100,000 individuals, with the highest prevalence observed among both the young and elderly populations. The epidemiology of specific viral triggers of encephalitis has undergone changes over time. For instance, immunization efforts have led to a reduction in encephalitis cases attributed to mumps and measles. Conversely, instances of EBV and CMV encephalitis have become more frequent due to their occurrence among immunocompromised individuals, such as those with AIDS, transplant recipients, and patients undergoing chemotherapy. Additional significant epidemiological factors encompass the time of year, geographical location, as well as exposure to animals or insects. For instance, arboviruses (like eastern equine, western equine, St. Louis, Venezuelan equine, Zika, and West Nile viruses) cause infections during the warmer months when mosquitoes are active. St. Louis encephalitis is primarily concentrated in the Midwest and South regions, while tick-borne encephalitis predominantly occurs in the North-Central and Northeastern parts of the United States. [1, 23-25]

EV 71, a highly neurotropic strain of enterovirus (EV), has been acknowledged as an underlying agent responsible for swiftly progressing fatal rhombencephalitis in countries within Southeast Asia. In 1969, the initial identification and characterization of Enterovirus 71 occurred in cases of neurological disorders in California. In addition to provoking encephalitis, EV 71 has also been pinpointed as a causative factor in outbreaks of hand-foot-mouth disease coupled with encephalitis. A notably elevated fatality rate (19.3%) has been documented among children under 5 years of age in Taiwan. [26-29]

In Western countries, reported occurrence rates vary from 6.3 to 7.4 cases per 100 thousand individuals across all age groups (adults and children), and around 10.5–13.8 cases per 100 thousand among children. [30] In the context of the UK, this translates to an estimated 1–2 cases per year in a typical district general hospital and 8–10 cases in a larger tertiary children's hospital. In developed countries, the most frequently identified cause of encephalitis is herpes simplex virus (HSV), with an annual occurrence of approximately 1 in 250K to 500K individuals. [31] The incidence pattern across different age groups exhibits two distinct peaks, occurring during childhood and in the elderly. The majority of HSV encephalitis stems from HSV type 1, although about 10% is attributed to HSV type 2. HSV type 2 primarily affects immunocompromised adults and neonates, often leading to disseminated infection in the latter group. Varicella-zoster virus (VZV) also stands as a relatively common contributor to viral encephalitis, especially among immunocompromised individuals. Cytomegalovirus (CMV) predominantly occurs within this same immunocompromised cohort. While enteroviruses are more commonly associated with aseptic meningitis, they can also play a significant role in the development of encephalitis. Additionally, beyond infectious causes, immune-mediated conditions are increasingly being recognized as contributors to encephalitis, including acute disseminated encephalomyelitis (ADEM) and encephalitis linked to antibodies targeting the voltage-gated potassium channel complex or N-methyl-D-aspartate (NMDA) receptors. [22]

In a comprehensive study conducted in southern India, 4.7% of patients displaying signs of acute encephalitis syndrome (AES) tested positive for EV 75. A separate prospective study spanning two years in northern India, focusing on children with acute encephalitis, identified ECV 21 as the primary causative pathogen for encephalitis in roughly 51.8% of isolates. Following ECV 21 were ECV 1, CV B1, EV 75, CV B5, and ECV 19. Furthermore, a study conducted in Spain unveiled that 10.8% of isolates from patients with aseptic meningitis exhibited positivity for EV 75. [26, 32, 33]

Encephalitis resulting from measles, mumps, and rubella is uncommon in countries with successful universal childhood immunization programs. Encephalitis rates associated with these infections are as follows: measles, occurring at a rate of 0.74 per 1000 cases; mumps, at 3 per 1000 cases; and rubella, at 0.1–0.2 per 1000 cases. [5]

Pathophysiology:

Viruses infiltrate the host through a point external to the central nervous system (CNS) and commence replication. Subsequently, most viruses access the spinal cord and brain via the bloodstream. Nevertheless, certain viruses, such as HSV, rabies, and herpes zoster virus, deviate from this pattern. They progress to the CNS through retrograde transmission from nerve endings. Upon entering the brain, both the virus itself and the ensuing inflammatory response from the host disrupt neural cell functionality. Gross examination typically reveals cerebral edema, vascular congestion, and hemorrhaging. Infiltration by leukocytes or microglial cells is also a frequent characteristic. Notably, in cases of EEE and JE, the level of tissue necrosis can be notably extensive. [1]

In most cases, the central nervous system (CNS) becomes affected after the pathogen spreads through the bloodstream. The pathogen can directly invade the brain tissue through either the choroid plexus or the endothelial cells. Infections caused by herpes simplex and rabies viruses follow transmission along nerve fibers. Certain viruses exhibit a preference for specific types of brain cells; for instance, the polio virus tends to target motor cells, rabies virus has an affinity for limbic cells, and mumps virus shows a preference for ependymal cells. [34]

Encephalitis and meningitis represent intertwined syndromes. Both viral and non-viral intrusions into the brain result in varying degrees of inflammation affecting both the meninges and the brain tissue itself. Due to this overlap, many medical practitioners opt for the term "meningoencephalitis". In terms of clinical manifestations, there exists a spectrum of presentations, yet two primary patterns tend to emerge. When the illness primarily showcases notable sensory changes, it is referred to as "encephalitis". Conversely, when the emphasis is on meningeal irritation, it is termed "meningitis". The descriptor "aseptic meningitis" is employed when the presentation is characterized by self-restricted meningitis and minimal to no sensory alterations. [35]

The entry of EV into the human host takes place through either the gastrointestinal (GI) or respiratory tract. The surfaces of GI tract cells act as viral receptors, initiating the initial replication process in the local GI lymphatic tissue. Subsequently, the virus disseminates into the bloodstream, resulting in minor viremia around the third day following infection. This is followed by a second

viremic episode occurring between days 3 and 7, during which the virus infiltrates various organ systems. This dual viremic pattern aligns with the biphasic prodromal illness characteristic. [26] The passage of virus particles from the bloodstream to the central nervous system (CNS) is typically confined by the blood-brain barrier (BBB), a specialized and selective barrier separating the brain's blood vessels from its cellular components. Nonetheless, the integrity of the BBB can be compromised through either direct infection of brain microvascular endothelial cells (BMECs), which form the BBB, or by the action of locally produced cytokines within the CNS during viral infections. For instance, PV has been observed to infiltrate the CNS by exploiting the BBB. Recent research has also indicated that the attachment of PV to the cell surface of BMECs and its subsequent invasion into the CNS through the BBB is facilitated by the mouse transferrin receptor 1. Additionally, enteroviruses have the capacity to access the CNS through immune cells circulating in the periphery, which harbor intracellular viruses. This method is often referred to as the "Trojan horse" route. [36-38]

During the major viremic phase of EV or even later, the infection can extend to involve the central nervous system (CNS), targeting the motor neurons within the anterior horn cells of the spinal cord. This progression can also affect other regions of the CNS such as the motor cortex, cerebellum, thalamus, hypothalamus, midbrain, and medulla, ultimately causing neuronal death and paralysis. Neuropathy arises due to direct cellular damage. The immune response to enteroviral infections leads to the production of antibodies within the initial 7–10 days, primarily occurring in the GI tract's lymphatic system before the virus reaches the CNS tissue. [26]

There is also evidence indicating that EV-A71 has the ability to infect leukocytes by binding to hPSGL1, a membrane proteinfound on leukocytes. Additionally, specific enteroviruses have been observed to access the CNS through peripheral nerves using retrograde axonal transport and trans-synaptic propagation. Retrograde axonal transport is a crucial process within neurons, facilitating the movement of various components like synaptic vesicles, proteins, lipids, and organelles, including mitochondria, lysosomes, autophagosomes, and endosomes, to and from the cell body. Notably, certain neurotropic viruses can exploit retrograde axonal transport to infiltrate the CNS. For instance, studies have demonstrated that intramuscularly administered PV is internalized via endocytosis at neuromuscular junctions. The viral particles taken up through endocytosis in the axon terminal are subsequently transported in the retrograde direction towards the cell body through dynein-mediated vesicular transport, all without initiating uncoating. [36, 39, 40]

Acute viral encephalitis primarily affects the grey matter, whereas ADEM is characterized by demyelination and mainly targets the white matter of the brain. Pathologically, in cases of acute encephalitis, notable findings include pronounced inflammation of cortical vessels' capillaries and endothelial cells (referred to as 'eptomeningitis'), along with lymphocytic infiltration surrounding blood vessels (referred to as 'cuffing'). As the disease advances, either increased astrocytosis and gliosis or demyelination due to immune responses may occur. [34]

Infants maintain their immunity acquired through the placenta for the initial 4-6 months of life. Fatal cases of EV 71 are mostly concentrated in children under the age of 3. The central nervous system, especially the brainstem, is the primary target. These young patients experience rapid onset of heightened sympathetic activity, along with the development of pulmonary edema (PE) and/or pulmonary hemorrhage, leading to cardiopulmonary collapse. The predominant cause of mortality in these children is overwhelming PE. The surge in systemic inflammatory agents associated with PE seems to result from continuous sympathetic stimulation, stemming from direct brainstem damage by the virus. Higher occurrences of leukocytosis and thrombocytosis were noted in PE cases. Marked elevation in plasma levels of interleukin (IL)-10, IL-13, and interferon (IFN)-g has been detected in PE patients. Individuals with PE also exhibited reduced counts of circulating CD4+ T cells, CD8+ T cells, and natural killer (NK) cells. [26, 41,42]

Clinical Presentation & Patient History: Enteroviral encephalitis manifests with a broad spectrum of symptoms, either individually or in various combinations: elevated body temperature, head pain, fatigue, reduced alertness, sleepiness, altered cognitive state, unconsciousness, enlargement of the spleen, enlargement of the liver, sudden onset of weak muscles lacking tone, decreased reflex response or rapid deep tendon reflexes, positive indications of meningeal inflammation, and indications of dysfunction in the brain stem such as unsteady movement, involuntary muscle contractions, rapid, repetitive movements, issues with eye movement (uncontrolled eye movement,

misaligned eyes, or difficulty moving the eyes), and paralysis of muscles related to the mouth and throat (difficulty swallowing, speech issues, voice problems, and facial muscle weakness). [26]

Children experiencing encephalitis may display indications of widespread disorder, such as alterations in behavior or character, reduced awareness, generalized seizures, or localized symptoms including focal seizures, weakness on one side of the body, movement irregularities, impairments in cranial nerves, and difficulties with coordination. Certain children might initially exhibit mild symptoms but then suddenly deteriorate into a comatose state followed by abrupt fatality. In other cases, the onset of the illness could be marked by high fever, intense seizures accompanied by unusual movements, and periods of hallucination alternating with brief moments of lucidity. These children might recover with minimal lasting effects. [5] Neurologists should possess a comprehensive understanding of the various factors that can imitate encephalitis. Some instances encompass vascular disorders, systemic infections without direct CNS involvement, inflammation, toxic substances, or disruptions in metabolic processes. It is imperative to conduct thorough investigations into such conditions for all individuals suspected of having encephalitis. Given the wide array of factors that either cause or mimic encephalitis, obtaining a detailed medical history is of utmost importance. Essential historical aspects encompass recent illnesses, contacts with sick individuals, uncommon exposures (including those related to work, vectors, and animals), outdoor activities, and substances ingested. It is vital to inquire about travel history, both recent and distant, as agents like rabies or malaria can manifest symptoms long after initial exposure. [1] Frequently, the initial signs indicate an acute systemic ailment featuring fever, headaches, or in infants, episodes of crying, abdominal discomfort, queasiness, and vomiting. As the temperature rises, signs of central nervous system involvement emerge, including a decline in mental sharpness progressing to stupor, peculiar movements, seizures, stiffness in the neck, and localized symptoms which could remain stable, advance, or fluctuate. [5]

In cases of encephalitis, there is consistently an evident presence of leptomeningeal inflammation, and the clinical indications encompass a combination of diffuse and localized cerebral pathology as well as signs of meningitis (fever, headache, and signs of meningeal irritation). The extent of altered consciousness serves as a measure of acute encephalitis severity and can vary from drowsiness to a state of coma. Seizures, both focal and generalized, are frequently observed. Unlike aseptic viral meningitis, encephalitis often exhibits predominant neuropsychiatric symptoms, including conditions like anomia, hallucinations, psychosis, alterations in personality, and restlessness. Acute encephalitis is a critical neurological situation, and prompt initiation of suitable treatment based on the likely clinical diagnosis is essential as soon as feasible. [6]

The diagnosis of viral encephalitis heavily relies on a comprehensive assessment of medical history and physical examination. Essential aspects of the patient's background include factors like immune status, exposure to animals or insects, travel history, vaccination records, geographical location, and the time of year. Fever, headache, seizures, and changes in mental state are the most prevalent signs and symptoms. Furthermore, neuropsychiatric indications like alterations in behavior, hallucinations, and cognitive decline are frequently observed. Patients might also exhibit other symptoms or examination findings specific to a particular virus. For instance, herpes zoster encephalitis is associated with skin rash and vesicles, while EBV is often linked to lymphadenopathy and splenomegaly. HSV encephalitis usually affects the temporal and frontal lobes, leading to psychiatric symptoms, memory issues, and aphasia. Conversely, some arboviruses predominantly target the basal ganglia, resulting in motor symptoms like choreoathetosis and parkinsonian movements. [1]

Enteroviral encephalitis displays a diverse array of symptoms, either individually or in combination, encompassing fever, headache, lethargy, drowsiness, altered mental state, coma, enlarged spleen and liver, sudden onset of weak muscles, reduced reflexes or heightened deep tendon reflexes, positive indications of meningeal irritation, and signs of brainstem dysfunction seen in rhombencephalitis like unsteady movement, shaking, myoclonic muscle jerks, issues with eye movement control (such as nystagmus, strabismus, or gaze impairment), and impaired functions of the bulbar region (resulting in difficulties with swallowing, speech, and facial movement). When compared to other forms of viral encephalitis, enteroviral-associated encephalitis (EVAE) exhibits notably elevated occurrences of personality shifts, skin rashes, and diarrhea. However, research indicates that neck stiffness is less commonly observed in cases of EVAE. [26]

During the physical examination, it's important to observe general indicators such as heart rate, respiratory rate, blood pressure, and the presence of meningismus, while also assessing other systems like the skin, lymph nodes, and signs of potential trauma. A thorough examination of the fundus with indirect ophthalmoscopy could provide insights into conditions like shaken baby syndrome or vasculitis. Neurological manifestations vary based on the specific brain region affected, and these findings might be prominent in different parts of the brain or even in non-CNS areas. [34]

Enteroviral encephalitis has the potential to cause symptoms resembling neonatal sepsis in newborns, as well as viral myocarditis, and it has been linked to instances of dilated cardiomyopathy. Reports indicate the destruction of beta cells and the presence of acute and chronic inflammatory infiltrations in islets from individuals affected by CV B infections, which can result in the onset of juvenile diabetes mellitus and diabetic ketoacidosis following flu-like symptoms and encephalitis. [26]

Specific neurological observations encompass mental status, the Glasgow Coma Score, the level of consciousness (ranging from alert to stupor or coma with decorticate or decerebrate posturing), the presence of photophobia, language impairment (aphasia), abnormalities in cranial nerves (such as ophthalmoplegia, facial paralysis, and ptosis), deep tendon reflexes, and motor deficits like hemiparesis, as well as sensory and cerebellar issues like ataxia. These findings should be detailed regarding their normalcy or abnormality, symmetry, and whether they are focal. [34]

Koplik spots, appearing as blue-white dots on the buccal mucosa, generally precede the measles rash. This rash is a maculopapular eruption that originates from the neck, progressing to involve the face before spreading centrifugally to the limbs and trunk. The period of highest infectivity for measles, when transmission risk is greatest, spans 4 days before rash onset and 4 days after. While the initial measles infection typically presents with fever, coryza, and a maculopapular rash, concerns arise when the virus infiltrates neurons, leading to neurological symptoms. Neurological and respiratory complications have emerged as significant and frequent causes of measles-related mortality. These complications are particularly common among children under 5 years old, adults, and certain immunocompromised individuals. Additionally, diarrhea and otitis media are two recognized complications associated with measles. [43]

Changes in cognitive state can vary from mild drowsiness and lethargy to pronounced irritability and profound coma. In infants, signs can be as vague as drowsiness, irritability, a high-pitched cry, generalized hyper-reflexia, or a full/bulging fontanelle, along with symptoms like feeding difficulties and vomiting. Some manifestations arise due to increased intracranial pressure. Indicators of elevated intracranial pressure rather than direct brain infection encompass papilledema, unusual breathing patterns, posturing (flexor or extensor), ophthalmoplegia or irregular pupils, and bradycardia. [34]

There are also some specific features for specific viruses, such as:

- Japanese encephalitis (JE) can result in extrapyramidal symptoms that resemble those seen in Parkinson's disease.
- Enterovirus 71 has the potential to induce tremors, myoclonus, ataxia, pulmonary edema, and cranial nerve impairments.
- Nipah virus has been demonstrated to generate indications of brainstem and cerebellar involvement, hypertension, and localized myoclonus.
- Microcephaly is a characteristic feature of Zika virus infection. [1]

Diagnostic Studies:

Identifying a specific underlying cause can enable targeted and effective treatments for certain treatable factors, minimizing unnecessary diagnostic procedures or empiric treatments. Different levels of evidence can establish a potential cause of encephalitis. For well-established causes, confirming the presence of an etiologic agent in brain tissue or cerebrospinal fluid (such as HSV DNA) or the production of intrathecal antibodies (as seen with pathogens where PCR is not the primary method, like West Nile virus IgM antibodies) is considered a confirmed cause. [44]

Identifying the cause is seldom achievable through clinical evaluation alone, except when linked to a rash-inducing condition like varicella or measles. The Collaborative Antiviral Study Group from the National Institute of Allergy and Infectious Diseases (NAIAD) reported no significant variations in the initial clinical indicators and symptoms between patients with

confirmed herpes simplex encephalitis and those lacking this infection. [34,45]

Situations like serologic evidence (such as serum Bartonella henselae IgM antibodies) without PCR confirmation for an established cause that might be directly detectable in CSF, or detection of a not yet firmly established cause through PCR in brain tissue or CSF (like HHV-6 DNA), can be categorized as a probable cause. Instances of suggestive serologic evidence or finding a well-established pathogen outside the central nervous system (such as influenza RNA in respiratory samples) are deemed possible causes. To prevent misinterpretation, it is crucial that the clinical presentation and epidemiological context align with the detected etiology at all levels of causation. [44]

The International Encephalitis Consortium has proposed a guideline for investigating potential causes of encephalitis. Below are the key elements for investigating viral etiologies: [46,47]

1. During a lumbar puncture, ensure at least 5 mL of cerebrospinal fluid is collected, and any unused fluid should be frozen for further testing.
2. Analyze cerebrospinal fluid for leukocyte count with differentiation, protein levels, lactate, and glucose levels.
3. Conduct HSV-1/2 testing (polymerase chain reaction [PCR]) on cerebrospinal fluid (consider HSV CSF IgG and IgM if available).
4. Perform enterovirus testing (PCR) (throat swab and stool tests are more sensitive than CSF).
5. Conduct EBV serology (VCA IgG and IgM, EBNA IgG).
6. Collect acute serum and obtain convalescent serum 10-14 days later for paired antibody testing.

For patients showing signs of extra-CNS involvement, additional tests are advised (e.g., skin lesion biopsy, bronchoalveolar lavage or endobronchial biopsy for those with lung issues, throat swab PCR/culture for upper respiratory symptoms, stool culture for diarrhea).

PCR versus culture methods: Polymerase chain reaction (PCR) is highly suitable for detecting delicate microorganisms that may pose challenges for cultivation. This technique allows for rapid and cost-effective analysis, with results available within 24 hours, a significant improvement compared to the lengthy 1 to 28 days needed for traditional culture. Unlike conventional culture methods, which might lose sensitivity after patients receive even small doses of antiviral medications, CSF PCR remains effective even following short antiviral treatment or passive immunization. This enables the swift initiation of empirical therapy upon initial suspicion of meningitis or encephalitis, without jeopardizing definitive diagnostic assessments. PCR is also more advantageous than serologic testing, which often necessitates 2 to 4 weeks post-acute infection for meaningful elevation in antibody levels and is limited for viruses with high baseline seroprevalence rates. Unlike serologic testing, CSF PCR provides positive results during the acute infection phase when virus replication is at its peak. Lastly, CSF PCR is considerably less invasive compared to brain biopsy, which previously served as the "gold standard" for diagnosing numerous CNS herpesvirus infections. [48]

Patients with viral encephalitis may exhibit elevated opening pressure during lumbar puncture. Typically, they present with lymphocytic pleocytosis, slightly elevated protein levels, and normal glucose levels. While brain MRI may appear normal in many cases, specific findings are likely, especially in HSV encephalitis cases. EEG abnormalities are observed in over 80% of viral encephalitis patients, characterized by diffuse high amplitude slow waves and/or focal epileptiform activity. Continuous EEG monitoring may be necessary to detect non-convulsive status epilepticus. [46]

Only minimal quantities of specimen are needed for CSF PCR testing; nonetheless, the sensitivity of PCR assays is linked to the volume of the specimen examined. While most assays can be conducted using a minimum of 30 µl of the sample, opting for 100 to 200 µl could yield more favorable outcomes. Ideally, PCR is performed on freshly collected CSF samples; nevertheless, positive outcomes have been achieved from preserved specimens that have been frozen for extended periods. Generally, RNA viruses in CSF samples exhibit lower stability compared to DNA viruses. Although the decline in sensitivity over prolonged storage hasn't been extensively explored, there is no significant reduction in yield with short-term storage at 4 or −20°C. For extended archival storage, samples should be stored at −70°C, and multiple freeze-thaw cycles should be avoided. [48]

The utilization of polymerase chain reaction (PCR) has significantly enhanced our capacity to detect encephalitis triggered by herpes viruses and

enteroviruses. CSF PCR testing for HSV conducted between day 2 and 10 of the illness demonstrates an overall sensitivity and specificity exceeding 95% for diagnosing HSV encephalitis in immunocompetent adults. Even though HSV PCR might yield negative results in the initial days of illness, a subsequent CSF sample taken 2 to 7 days later frequently yields positive HSV results, even if aciclovir treatment has been initiated. [22, 49-51]

Before undergoing PCR, nucleic acids present in CSF must be made accessible. Although basic techniques like exposure to high temperatures or repeated freeze-thaw cycles have been employed to release nucleic acids, nucleic acid extraction and purification methods such as phenol-chloroform or spin column-based (Qiagen) techniques offer the advantage of providing pure nucleic acid for entry into the amplification process. These methods also eliminate potential inhibitors of PCR amplification and substances that might degrade nucleic acids, thus enhancing yield. [48]

Neuroimaging: Brain imaging is now a standard procedure in patients suspected of having acute encephalitis and is typically performed before other specific investigations. Magnetic resonance imaging (MRI) is the preferred method for cranial imaging in cases of acute encephalitis, although a computed tomogram (CT) may be obtained quickly and easily for restless patients. Distinctive changes observed in neuroimaging could provide indications of the particular infective causes. For instance, frontotemporal alterations may suggest herpes simplex encephalitis (HSE), and thalamic hemorrhage may be indicative of Japanese encephalitis.[6] CT may reveal areas of decreased density in the temporal lobes in cases where herpes simplex virus (HSV) is implicated. These specific lesions typically become visible approximately 3 to 5 days following the onset of infection. [1] Magnetic resonance imaging is superior to computed tomography in visualizing small hemorrhagic changes and characteristic lesions in the limbic system associated with HSE. Administration of Gd-DTPA may reveal meningeal and gyral enhancement in HSE cases. In Eastern equine encephalitis, magnetic resonance imaging reveals disseminated lesions in the brainstem and basal ganglia. [6]

MRI is the most effective imaging technique for detecting features consistent with herpes simplex virus (HSV) encephalitis, particularly involvement of the temporal and frontal lobes. [52,] MRI findings in cases of enterovirus encephalitis can vary, ranging from normal results to hyperintensities observed at specific brain regions like the posterior brainstem, medulla oblongata, and thalami. Notably, brainstem hyperintensities, particularly in the vicinity of the fourth ventricle, have been documented in cases of enterovirus-71 encephalitis, often accompanied by tremor and myoclonus. [15]

Cerebrospinal fluid (CSF) analysis is crucial, encompassing assessments of pressure, cell counts, glucose, and protein levels. Polymerase chain reaction (PCR) assessments for HSV-1, HSV-2, and enteroviruses should be included in CSF evaluation. Depending on the patient's medical history and clinical indications, supplementary assessments like serological tests for arboviruses and HIV may be conducted. [1, 53]

Management:

When suspicion arises of viral encephalitis, initial steps involve administering supportive care and addressing any disturbances in electrolyte levels, autonomic function, as well as kidney and liver function. Additionally, it is crucial to manage seizures and non-convulsive status epilepticus. [46]

Herpes simplex virus (HSV) encephalitis stands as the predominant origin of viral encephalitis. Timely administration of treatment significantly influences both crucial outcomes and functional predictions. Therefore, it is advisable to commence empirical **acyclovir** therapy promptly upon the manifestation of encephalitis indicators and symptoms, even prior to obtaining the results of CSF HSV PCR testing. [54]

Acyclovir exhibits antiviral properties against HSV and closely related viruses, which are typically the prevailing culprits behind viral encephalitis.

The recommended dosing regimen involves administering either:

- 500 mg/m2 every eight hours for children aged 3 months to 18 years.
- 10 mg/kg/dose every eight hours for children older than 12 years. [46]

Adjustments in dosing are necessary if there is a history of renal impairment.

In cases of children less than 3 months the dosing regimen entails 20mg/kg/dose every 8 hours. This treatment approach should be maintained until HSV testing yields negative results. Furthermore, it is advisable to consider continuing acyclovir treatment

while conducting additional CSF testing or brain biopsy, particularly for cases with a high degree of clinical suspicion and no identifiable alternative cause. [44]

Ribavirin has demonstrated its ability to hinder the replication of various EV strains. Nonetheless, the presence of ribavirin might compel the virus in question into a state of "error catastrophe," inducing a non-infectious quasi-species swarm marked by significant variability, potentially leading to lethal mutagenesis. Both in laboratory settings and live organisms, ribavirin has exhibited inhibitory effects on the replication of EV 71. In a study conducted by Li et al., mice treated with ribavirin displayed reduced rates of mortality, morbidity, and paralysis upon exposure to EV 71. Ribavirin is already employed for managing viral infections in humans, and promising outcomes from animal trials against EV 71 suggest its potential for addressing enteroviral infections in humans. [26, 55]

For other viral agents other than HSV the antiviral of choice are as follow:

Varicella-Zoster Virus (VZV): Acyclovir is also effective against VZV, given at the same dosage as for HSV encephalitis. [56]

Enteroviruses: There's no specific antiviral treatment, but pleconaril has shown some promise, especially for severe neonatal cases. [57]

Arboviruses: Specific antiviral therapy doesn't exist for most arboviral encephalitides, and management is largely supportive.

Supportive Care: Given the absence of specific antiviral treatments for many etiologies of encephalitis, supportive care is the backbone of management. This includes:

1. Airway Management: Protecting the airway is crucial, especially in children with altered levels of consciousness or seizures. [58]
2. Seizure Control: Seizures are common and need prompt management. First-line antiepileptic drugs (AEDs) like levetiracetam, phenytoin, or benzodiazepines can be administered as per seizure type and clinical presentation. [59]
3. Control of Intracranial Pressure (ICP): Elevated ICP can result from cerebral edema. Osmotic agents, like mannitol or hypertonic saline, can be used to manage elevated ICP. [60] Head positioning, sedation, and in extreme cases, surgical interventions might be required.
4. Fever Management: Antipyretics can be used to control fever. Physical cooling methods might be employed for refractory cases.
5. Hydration and Nutrition: Ensuring adequate hydration is crucial. However, overhydration should be avoided as it can exacerbate cerebral edema. Nutritional needs should be met through enteral or parenteral routes, considering the child's metabolic demands. [61]

Immunomodulatory Therapies: In certain cases, where autoimmune reactions are believed to exacerbate the disease, therapies like steroids, intravenous immunoglobulins (IVIG), and plasmapheresis might be beneficial. [62]

Rehabilitation: Post-acute care and rehabilitation play pivotal roles, especially for children who experience neurological sequelae post-infection. This can include physical therapy, occupational therapy, speech therapy, and neuropsychological support. [63]

Prevention and Prophylaxis: While not directly a management strategy for active disease, vaccination for preventable causes, like Japanese encephalitis or mumps, is crucial. For children exposed to certain viruses (e.g., rabies), post-exposure prophylaxis might be life-saving. [64]

Monitoring and Follow-Up: Regular neurological assessments are vital during the acute phase. Post-discharge, monitoring for cognitive, motor, or behavioral sequelae should be arranged, and appropriate therapeutic interventions initiated as required. [65]

Given the strain and anxiety associated with encephalitic illnesses, families benefit significantly from counseling. Ensuring they're equipped with knowledge about the disease, its prognosis, and potential complications can aid in home-based care and reduce parental anxiety.

Conclusion:

While encephalitis symptoms may overlap with other conditions such as encephalopathy and meningitis, diagnostic tools are useful to rule out any differential diagnosis and to get to the precise etiology of the disease which will help in effective treatment for the disease, these methods include CSF analysis, Neurological imaging such as CT and MRI, and most importantly

PCR which is considered the golden standard for diagnosis of viral Encephalitis and start appropriate therapy.

Early identification is further augmented by the strategic use of therapeutic agents like acyclovir, which has proven efficacy in curbing the progression of the disease. Concurrently, the provision of comprehensive supportive care ensures stabilization of the patient's condition and mitigates potential complications. It's imperative to understand that while acute management is critical, long-term outcomes are significantly influenced by post-infection rehabilitation, particularly in younger demographics. Emphasizing the confluence of diagnostic precision, timely therapeutic intervention, and meticulous supportive care can pave the way for optimized patient outcomes in the realm of viral encephalitis management.

References:

1. Said S, Kang M. Viral Encephalitis. [Updated 2022 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470162/
2. Im JH, Baek J, Durey A, Kwon HY, Chung MH, Lee JS. Current Status of Tick-Borne Diseases in South Korea. Vector Borne Zoonotic Dis. 2019 Apr;19(4):225-233.
3. Kadambari S, Harvala H, Simmonds P, Pollard AJ, Sadarangani M. Strategies to improve detection and management of human parechovirus infection in young infants. Lancet Infect Dis. 2019 Feb;19(2):e51-e58.
4. Blom K, Cuapio A, Sandberg JT, Varnaite R, Michaëlsson J, Björkström NK, Sandberg JK, Klingström J, Lindquist L, Gredmark Russ S, Ljunggren HG. Cell-Mediated Immune Responses and Immunopathogenesis of Human Tick-Borne Encephalitis Virus-Infection. Front Immunol. 2018;9:2174.
5. Cherry JD. Recognition and management of encephalitis in children. Adv Exp Med Biol. 2009;634:53-60. doi:10.1007/978-0-387-79838-7_5.
6. Chaudhuri, A., & Kennedy, P. G. (2002). Diagnosis and treatment of viral encephalitis. Postgraduate medical journal, 78(924), 575–583. https://doi.org/10.1136/pmj.78.924.575
7. Venkatesan A, Geocadin RG. Diagnosis and management of acute encephalitis: A practical approach. Neurol Clin Pract. 2014;4(3):206-215. doi:10.1212/CPJ.0000000000000036.
8. Granerod J, Ambrose HE, Davies NW, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis. 2010;10:835–844.
9. 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.
10. Ball R, Halsey N, Braun MM, et al. Development of case definitions for acute encephalopathy, encephalitis, and multiple sclerosis reports to the vaccine: adverse event reporting system. J Clin Epidemiol. 2002;55:819–824.
11. Glaser CA, Honarmand S, Anderson LJ, et al. Beyond viruses: clinical profiles and etiologies associated with encephalitis. Clin Infect Dis. 2006;43:1565–1577.
12. Sejvar JJ, Kohl KS, Bilynsky R, et al. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25:5771–5792.
13. Mailles A, Stahl JP. Infectious encephalitis in France in 2007: a national prospective study. Clin Infect Dis. 2009;49:1838–1847.
14. 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;57:1114–1128.
15. Vergadi E, Zacharioudaki M, Raissaki M, Galanakis E. Challenges in the Diagnosis of Viral Encephalitis in Children: The Case of Two Siblings. Infect Dis Rep. 2022;14(1):106-111. Published 2022 Feb 11. doi:10.3390/idr14010014
16. Messacar K, Fischer M, Dominguez SR, Tyler KL, Abzug MJ. Encephalitis in US Children. Infect Dis Clin N Am. 2018;32:145-162. doi:10.1016/j.idc.2017.10.007.
17. Sadarangani M, Willis L, Kadambari S, Gormley S, Young Z, Beckley R, Gantlett K, Orf K, Blakey S, Martin NG, et al. Childhood meningitis in the conjugate vaccine era: A prospective cohort study. Arch Dis Child.

2014;100:292-294. doi:10.1136/archdischild-2014-306813.

18. Ekambaram M, Nabower A, Rajbhandari P, Eisenberg J, Goodrich N, Ampofo K, Gollehon NS, Martin KC, Lyden E, Snowden J. Evaluation of Discordant Results Between FilmArray Meningitis/Encephalitis Panel and Conventional Testing in Pediatric Patients: A Multisite Retrospective Cohort Study. J Pediatr Infect Dis Soc. 2022;10:piab126. doi:10.1093/jpids/piab126.
19. Schwartz KL, Richardson SE, Ward KN, Donaldson C, MacGregor D, Banwell B, Mahant S, Bitnun A. Delayed Primary HHV-7 Infection and Neurologic Disease. Pediatrics. 2014;133:e1541-e1547. doi:10.1542/peds.2013-3344.
20. Ellul M, Solomon T. Acute encephalitis - diagnosis and management. Clin Med (Lond). 2018;18(2):155-159. doi:10.7861/clinmedicine.18-2-155
21. Encephalitis. Paediatr Child Health. 1998;3(1):47-52. doi:10.1093/pch/3.1.47
22. Kneen R, Michael BD, Menson E, et al. Management of suspected viral encephalitis in children - Association of British Neurologists and British Paediatric Allergy, Immunology and Infection Group national guidelines. J Infect. 2012;64(5):449-477. doi:10.1016/j.jinf.2011.11.013
23. Baldwin KJ, Cummings CL. Herpesvirus Infections of the Nervous System. Continuum (Minneap Minn). 2018 Oct;24(5, Neuroinfectious Disease):1349-1369.
24. Phipps P, Johnson N, McElhinney LM, Roberts H. West Nile virus season in Europe. Vet Rec. 2018 Aug 18;183(7):224.
25. Ben Abid F, Abukhattab M, Ghazouani H, Khalil O, Gohar A, Al Soub H, Al Maslamani M, Al Khal A, Al Masalamani E, Al Dhahry S, Hashim S, Howadi F, Butt AA. Epidemiology and clinical outcomes of viral central nervous system infections. Int J Infect Dis. 2018 Aug;73:85-90.
26. Jain S, Patel B, Bhatt GC. Enteroviral encephalitis in children: clinical features, pathophysiology, and treatment advances. Pathog Glob Health. 2014;108(5):216-222. doi:10.1179/2047773214Y.0000000145
27. Wang JR, Tuan YC, Tsai HP, Yan JJ, Liu CC, Su IJ. Change of major genotype of Enterovirus 71 in outbreaks of hand-foot-and-mouth disease in Taiwan between 1998 and 2000. J Clin Microbiol. 2002;40:10–5. doi: 10.1128/JCM.40.1.10-15.2002.
28. Huang CC, Liu CC, Chang YC, Chen CY, Wang ST, Yeh TF. Neurologic complications in children with enterovirus 71 infection. N Engl J Med. 1999;341:936–42. doi: 10.1056/NEJM199909233411301.
29. Ferrari S, Toniolo A, Monaco S, Luciani F, Cainelli F, Baj A, et al. Viral encephalitis: etiology, clinical features diagnosis and management. Open Infect Dis J. 2009;3:1–12. doi: 10.2174/1874279300903010001.
30. Jmor F, Emsley HCA, Fischer M, Solomon T, Lewthwaite P. The incidence of acute encephalitis syndrome in Western industrialised and tropical countries. Virol J. 2008;5:1.
31. Whitley RJ, Kimberlin DW. Herpes simplex encephalitis: children and adolescents. Semin In Ped Infect Dis. 2005;16:17-23.
32. Lewthwaite P, Desai A, Perera D, Ooi MH, Last A, Kumar R. Enterovirus 75 encephalitis in children, Southern India. Emerg Infect Dis. 2010;16:1780–2. doi: 10.3201/eid1611.100758.
33. Avellón A, Rubio G, Palacios G, Casas I, Rabella N, Reina G, et al. Enterovirus 75 and aseptic meningitis, Spain, 2005. Emerg Infect Dis. 2006;12:1609–11. doi: 10.3201/eid1210.060320.
34. Ford-Jones EL, Macgregor D, Richardson S, Jamieson F, Blaser S, Artsob H. Acute childhood encephalitis and meningoencephalitis: Diagnosis and management. Paediatr Child Health. 1998;3(1):33-40. doi:10.1093/pch/3.1.33.
35. Kumar R. Understanding and managing acute encephalitis. F1000Res. 2020;9:F1000 Faculty Rev-60. Published 2020 Jan 29. doi:10.12688/f1000research.20634.1
36. Chen BS, Lee HC, Lee KM, Gong YN, Shih SR. Enterovirus and Encephalitis. Front Microbiol. 2020;11:261. Published 2020 Feb 20. doi:10.3389/fmicb.2020.00261.
37. Rhoades RE, Tabor-Godwin JM, Tsueng G, Feuer R. Enterovirus infections of the central nervous system. Virology. 2011;411:288-305. doi:10.1016/j.virol.2010.12.014.

38. Huang HI, Shih SR. Neurotropic Enterovirus infections in the central nervous system. Viruses. 2015;7:6051-6066. doi:10.3390/v7112920.
39. hka S, Matsuda N, Tohyama K, Oda T, Morikawa M, Kuge S, et al. Receptor (CD155)-dependent endocytosis of poliovirus and retrograde axonal transport of the endosome. J Virol. 2004;78(13):7186-7198. doi: 10.1128/jvi.78.13.7186-7198.2004.
40. Ohka S, Sakai M, Bohnert S, Igarashi H, Deinhardt K, Schiavo G, et al. Receptor-dependent and -independent axonal retrograde transport of poliovirus in motor neurons. J Virol. 2009;83:4995-5004. doi: 10.1128/JVI.02225-08.
41. Wang SM, Lei HY, Huang KJ, Wu JM, Wang JR, Yu CK, et al. Pathogenesis of brainstem encephalitis due to Enterovirus 71 in pediatric patients: involvement of cytokines and activation of cellular immunity in cases with pulmonary edema. Journal of Infectious Diseases. 2003;188:564–70.
42. Avellón A, Rubio G, Palacios G, Casas I, Rabella N, Reina G, et al. Enterovirus 75 and aseptic meningitis, Spain, 2005. Emerging Infectious Diseases. 2006;12:1609–11.
43. Diwan MN, Samad S, Mushtaq R, Aamir A, Allahuddin Z, Ullah I, Ullah Afridi R, Ambreen A, Khan A, Ehsan N, Ehsan Khattak Z, Ventriglio A, De Berardis D. Measles Induced Encephalitis: Recent Interventions to Overcome the Obstacles Encountered in the Management Amidst the COVID-19 Pandemic. Diseases. 2022;10(4):104. https://doi.org/10.3390/diseases10040104.
44. Messacar K, Fischer M, Dominguez SR, Tyler KL, Abzug MJ. Encephalitis in US Children. Infect Dis Clin North Am. 2018;32(1):145-162. doi:10.1016/j.idc.2017.10.007.
45. Marrie TJ, Purdy RA, Johnston BL, et al. Encephalomyeloradiculopathy of infectious or parainfectious etiology – a new entity? Clin Infect Dis. 1995;20:945–53.
46. Klein da Costa B, Sato DK. Viral encephalitis: a practical review on diagnostic approach and treatment. Jornal de Pediatria. 2020;96(Suppl 1):12-19. ISSN 0021-7557. https://doi.org/10.1016/j.jped.2019.07.006.
47. Venkatesan A, Tunkel AR, Bloch KC, Lauring AS, Sejvar J, Bitnun A, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis. 2013;57:1114-28.
48. DeBiasi RL, Tyler KL. Molecular Methods for Diagnosis of Viral Encephalitis. Clinical Microbiology Reviews. 2004;17(4):903-925. doi: 10.1128/cmr.17.4.903-925.2004.
49. Read SJ, Jeffery KJM, Bangham CRM. Aseptic meningitis and encephalitis: the role of PCR in the diagnostic laboratory. J Clin Microbiol. 1997;35:691-696.
50. Tyler KL. Update on herpes simplex encephalitis. Rev Neurol Dis. 2004;1:169-178.
51. Weil AA, Glaser CA, Amad Z, Forghani B. Patients with suspected herpes simplex encephalitis: rethinking an initial negative polymerase chain reaction result. Clin Infect Dis. 2002;34:1154-1157.
52. Jayaraman K, Rangasami R, Chandrasekharan A. Magnetic Resonance Imaging Findings in Viral Encephalitis: A Pictorial Essay. Journal of Neuroscience in Rural Practice. 2018 Oct-Dec;9(4):556-560.
53. Leahy CB, Mathur S, Majeed T. The clinical approach to managing herpes simplex virus encephalitis. British Journal of Hospital Medicine (London). 2018 Oct 02;79(10):556-559.
54. Fillatre P, Crabol Y, Morand P, et al. Infectious encephalitis: Management without etiological diagnosis 48hours after onset. Med Mal Infect. 2017;47(3):236-251. doi:10.1016/j.medmal.2017.02.004.
55. Li ZH, Li CM, Ling P, Shen FH, Chen SH, Liu CC, et al. Ribavirin diminishes mortality in mice infected with enterovirus 71 through its suppressive effect on viral replication. J Infect Dis. 2008;197:854–7.
56. Gilden D, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. Lancet Neurol. 2009;8(8):731-740.
57. Abzug MJ. Presentation, diagnosis, and management of enterovirus infections in neonates. Paediatr Drugs. 2004;6(1):1-10.
58. Singhi P. Infectious causes of seizures and epilepsy in the developing world. Dev Med Child Neurol. 2011;53(7):600-609.

59. Patel AK, Patterson JL. Current concepts in management of viral encephalitis. Curr Treat Options Neurol. 2013;15(4):415-427.
60. 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):303-327.
61. Misra UK, Kalita J. Overview: Japanese encephalitis. Prog Neurobiol. 2010;91(2):108-120.
62. Leypoldt F, Armangue T, Dalmau J. Autoimmune encephalopathies. Ann N Y Acad Sci. 2015;1338:94-114.
63. Kneen R, Michael BD, Menson E, et al. Management of suspected viral encephalitis in children - Association of British Neurologists and British Paediatric Allergy, Immunology and Infection Group National Guidelines. J Infect. 2012;64(5):449-477.
64. World Health Organization. Vaccines and vaccination against yellow fever: WHO Position Paper – June 2013. Weekly Epidemiological Record. 2015;88(27):269-283.
65. Hargrave DR, Webb DW. Long term outcome following childhood encephalitis. Arch Dis Child. 1997;77(2):162-164.