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REVIEW: THE DIAGNOSIS AND MANAGEMENT RELATED TO ENCEPHALITIS

Yash Srivastav* and Akhandnath Prajapati

Department of Pharmacy Goel Institute of Pharmacy & Sciences (GIPS), Lucknow, Uttar Pradesh, India.

***Corresponding Author: Yash Srivastav**

Department of Pharmacy Goel Institute of Pharmacy & Sciences (GIPS), Lucknow, Uttar Pradesh, India.

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ABSTRACT

Encephalitis is a meningitis-related inflammation of the brain parenchyma typically brought on by bacteria or viruses. The ability of viruses to infect the central nervous system (CNS) varies greatly. For instance, the rabies virus invariably and only results in CNS disease, whereas encephalitis is a less frequent symptom of infections brought on by the herpes simplex or varicella zoster viruses. The word "encephalitis" is a combination of the phrases "enkephalon," which in Greek means "brain," and "itis," which in Latin means "related to inflammation." Encephalitis is the term used to describe inflammation of the brain. Adult viral encephalitis affects 1.4 individuals per 100,000 years, according to a Finnish study. The most often identified pathogens as the culprits were the herpes simplex virus (16%), varicella zoster virus (5%), mumps virus (4%), and influenza a virus (4%). The bulk of encephalitis epidemics among children in India have historically been attributed to Japanese encephalitis. Many encephalitis epidemics with significant mortality rates were undetected until the first case was discovered in Jamshedpur, central India, in 1954. This review article investigates the pathophysiology, aetiology, management issues, and histopathology of encephalitis.

KEYWORD: Encephalitis, Epidemiology, Causes, Histopathology and Pathogenesis, Diagnosis, Management.

INTRODUCTION

An inflammatory illness of the central nervous system (CNS) known as encephalitis is characterized by fever, altered cerebral spinal fluid (CSF) tests, seizures, and abnormal MRI results.[1] Encephalitis is a serious, perhaps fatal infection that can result from a wide range of poisons, viruses, bacteria, parasites, autoimmune reactions to immunizations, and more.[2] The terms "enkephalon" (which means brain in Greek) and "itis," which means related to inflammation in Latin, are combined to form the word "encephalitis." Inflammation of the brain is what encephalitis refers to.[3] Encephalitis, which can be brought on by an infection or an autoimmune reaction, is an inflammation of the brain parenchyma that results in neurologic impairment. The identification of the inflammation in samples of brain tissue serves as confirmation. However, as this is infrequently necessary, ancillary noninvasive procedures such as cerebrospinal fluid (CSF) analysis and indirect evidence of inflammation in clinical presentation are used.[4,5] More than 50% of all cases of encephalitis are caused by viral infections, which are the primary cause of this illness. Despite having well-known respiratory symptoms, human parainfluenza virus (HPIV) and respiratory syncytial virus (RSV) are rarely identified as the cause of encephalitis. Furthermore, the pathophysiological mechanisms causing systemic inflammation and brain damage as a result of these viruses' infection are not entirely known.[6] The ability of viruses to infect the central nervous system (CNS) varies greatly. For instance, the rabies virus invariably and exclusively causes CNS disease, but encephalitis is a less frequent symptom of infections with the herpes simplex or varicella zoster viruses. The degree of brain involvement and the course of the disease depends not only on the particular infection but also on the host's immune condition and a variety of environmental factors.[7] Arbovirus, non-polio enterovirus, and herpesviruses 1 and 2 (HSV-1 and HSV-2) are the most prevalent causes of viral encephalitis.1 The aetiologies of seasonal influenza, cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6 (HHV-6) are also pertinent.[8] About 50% of these cases have an unknown cause. Between 20 and 50 per cent of cases with a known aetiology are blamed on viruses. The majority of the remaining viral cases are caused by enteroviruses, arboviruses, varicella-zoster virus (VZV), and herpes simplex virus (HSV), accounting for 50 to 75% of all cases. Arbovirus encephalitis, which reflects the ecology of arboviral transmission, exhibits significant year-to-year variation in case counts, occurs seasonally, and varies in incidence according to geographic region. HSV encephalitis affects people of all ages and does not have a distinctive seasonal or geographic pattern.[9,10] When there is no pathogenic indication of brain inflammation, an encephalitis diagnosis can be made. from the CSF's or

the brain's inflammatory reaction aberrant neuroimaging findings that are consistent with parenchymal affection and potential substitute signs of inflammation in the brain. The estimated encephalitis incidence is broad variation and is influenced by age. Population, environment, and the presence of a natural host for the presence of an epidemic disease and the causal agent. The aetiology of encephalitis must be determined. challenging. Different definitions exist, and identifying Meningoencephalitis may cause encephalitis, although Encephalopathy or meningitis can be challenging.[11,13] There is little knowledge of the variables that influence encephalitis susceptibility. While HSV produces encephalitis in people of all ages, some viruses, like West Nile virus, tend to cause severe central nervous system disease in the elderly, while others, like the La Crosse virus, mostly affect youngsters with encephalitis. Age-related changes in innate and adaptive immunity, such as decreased expression of TLRs and RIG-I-like receptors, decreased phagocytic function, and decreased natural killer and cytotoxic T-cell activity, may increase susceptibility in older people. On the other hand, a characteristic associated with mice's sensitivity to the La Crosse virus suggests that children may have lower type I interferon signalling as compared to adults.[16,14] Acute viral encephalitis involves a variety of neurotropic viruses. Furthermore, encephalitis of varied severity is linked to new viruses every day, making it difficult to make a precise diagnosis.[17,18] Given the difficulties in detecting pathogens, the annual prevalence of viral encephalitis is probably underestimated, particularly in underdeveloped nations. Every year, at least 50,000 people are affected by Japanese encephalitis. According to a Finnish study, there are 1.4 instances of adult viral encephalitis for every 100,000 people per year. The herpes simplex virus (16%), varicella zoster virus (5%), mumps virus (4%), and influenza a virus (4%), were the most often identified pathogens as the culprits. Japanese encephalitis has historically been linked to the majority of encephalitis epidemics among children in India. With the first case being reported in Jamshedpur, central India, in 1954, many encephalitis outbreaks with high mortality rates went unreported.[19,22] Despite advances in encephalitis treatment, the significant mortality and morbidity of this condition warrants continued global concern. Whatever the aetiology, quick identification and application of focused and supportive therapy options can generally result in improved outcomes. This depends on accurate and prompt determination of the encephalitis's root cause and availability of efficient therapy.[23,24]

Epidemiology

Due to its high morbidity and fatality rates as well as significant economic implications, encephalitis is a concern for public health around the world. Although incidence varies between research, it typically ranges from 3.5 to 7.4 per 100,000 patients and is greater in kids. Although both genders are impacted, the majority of research have found a slight male predominance. Unfortunately, there haven't been many population-based studies, the disease is underreported, and in many cases, the reason is still unknown. Data on the prevalence of various etiological agents are inconsistent. For instance, VZV was identified as the most often implicated agent (29% of cases) in a collaborative study conducted in Finland employing gene amplification to detect different viruses in CSF samples of 3231 patients with encephalitis, meningitis, and myelitis. HSV, enteroviruses, and influenza A virus each caused 11% and 7% of cases, respectively.[25,26] A recent investigation from Turku (Finland) on 144 consecutive adults with encephalitis or aseptic meningitis found that 72 patients had viral aetiology; of these, 46% were caused by enteroviruses, 31% by HSV-2, 11% by VZV, and 4% by HSV-1. The authors of the latter paper only looked at immunocompetent individuals; meningitis and encephalitis patients were evaluated separately; and the 5-year study period was long enough to minimise the impact of epidemics and seasonal variation. These factors may account for some of the differences. The most serious types of infections of the human brain are caused by HSV-1/2. Currently, it's thought that between 1 in 250,000 and 1 in 500,000 people get herpes simplex encephalitis (HSE) each year.[27,28] Similar to those in England and Sweden, the estimated incidence in the US is 1 in 300,000 people. HSE can affect patients of any age at any time of the year. A third of instances affect people between the ages of 6 months and 20 years, while about half of the patients are beyond 50. Genders (male and female) are equally impacted.[29,31] The illness is currently endemic in 171 districts across 19 States in India. In 2016, the National Vector Borne Diseases Control Programme (NVBDCP) received reports of 11,651 cases and 1301 deaths, with a CFR of around 11 per cent.[32]

Causes

Encephalitis can be brought on by autoimmune and infectious causes. Around the world, viruses like herpes, arbo, entero, and adenoviruses are frequently to blame for infective encephalitis. Herpes simplex virus (HSV) is most prevalent in high-resource environments, but Japanese encephalitis virus (JEV) is the primary cause of viral encephalitis in many Asian nations. Less frequent causes include bacterial, fungal, and parasitic diseases. 'Autoimmune encephalitis' refers to a broad group of causes of non-infectious encephalitis. In some cases of autoimmune encephalitis, specific autoantibodies that are directed against CNS antigen can be found in serum and CSF samples. N-methyl D-aspartate receptor (NMDAR) antibodies are linked to a frequent aetiology in young people. Leucine-rich glioma inactivated 1 (LGI1) antibodies are the most prevalent recognized autoantibody in people over 50,[26,33-35] However, current information indicates that this might apply to all instances of autoimmune encephalitis. Numerous new pathogenic autoantibodies have been described in the past ten years, and their frequency is rising. These include additional to these two autoantibodies. This is

most likely a result of improved awareness, testing, and understanding that such syndromes have long been misclassified. The association between NMDAR-antibody encephalitis and ovarian teratomas is one well-known example of how these autoimmune encephalitis's can constitute paraneoplastic disorders.[36-40] But even in this illness, about 30% of patients may have a malignancy.20 Furthermore, antibodies have been discovered in patients who appear to experience a 'relapse' of viral encephalitis, notably HSV encephalitis, where they seem to indicate a secondary autoimmune process following viral clearance from the CNS. Acute demyelinating encephalomyelitis (ADEM) is the second most common non-infectious cause of encephalitis. The term ADEM refers to a demyelinating condition brought on by an immunological response. This immunological response frequently happens following an illness or immunization and is most frequently observed in paediatric populations. Antibodies against the myelin oligodendrocyte glycoprotein seem to be frequently related with ADEM.[41-44]

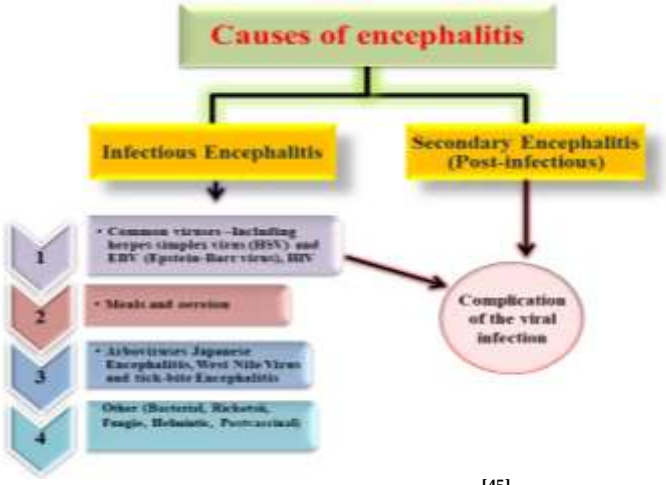

Fig. 1: Causes of encephalitis.[45]

Symptoms

Along with flu-like symptoms like a fever or a bad headache, it might also result in confounded thinking, seizures, or issues with the senses or mobility. Many encephalitis instances may go unnoticed because they have no symptoms at all or have mild flu-like symptoms. Even though they are relatively infrequent, severe encephalitis episodes can be fatal. The following indications may be present in more acute situations, which call for immediate medical attention: severe headache, fever, altered consciousness, agitation or confusion, personality changes, seizures, muscle weakness, hallucinations, double vision, a sense of foul odours, difficulties speaking or hearing, and loss of consciousness. Infants and young children may also show signs and symptoms such as bulging fontanels in the skull, nausea, vomiting, body stiffness, unceasing, inconsolable wailing that gets worse when the kid is taken up, and poor feeding. The prognosis is, however, typically worse in newborns under 1 year old and in people over 55. Because of severe cerebral edoema, young children may experience turbulent days.[46]

Fig. 2: Encephalitis Signs and Symptoms.

Histopathology

Viruses can enter the CNS via the neuronal or hematogenous pathways. The latter is the more frequent and is connected to changes in the blood-brain barrier in illnesses transmitted by arthropods. Following viral replication in the skin after an insect bite in TBE, the reticuloendothelial system is invaded, resulting in transitory viraemia. The CNS and other organs become infected as a result of secondary viremia. A notable pathological sign in acute viral encephalitis is the infiltration of mononuclear inflammatory cells in the Wirchow-Robin gaps and in the meninges surrounding the artery walls (perivascular cuffing). As the disease progresses, significant histological features include neuronophagia, which is a cluster of microglial cells encircling a dead neuron, as well as Astro cytosis proliferation and hypertrophy of microglial cells with formation of microglial aggregates (microglial nodules). Although intranuclear inclusions predominate, the intracytoplasmic Negri body in rabies is the only pathognomonic inclusion. Infected cells balloon, and the HSV that is replicating causes intranuclear eosinophilic amorphous or droplet-like entities with chromatin margination nuclear membrane (Cowdry type A inclusions) and a distinct halo around them. HSV, VZV, and CMV all include intranuclear type A inclusions, however electron microscopy and immunohistochemistry in situ hybridization techniques provide a better understanding of the viral particles. Mononuclear cells begin to swarm into the diseased tissue. Most primarily in the temporal lobes and typically asymmetrically in adults, HSE is linked to acute inflammation, congestion, and bleeding. Meninges covering the temporal lobes may be clogged, and nearby limbic regions are also implicated. Frank necrosis of the affected brain parts occurs around two weeks later.[47-49] Intraneuronal access to the CNS frequently occurs in HSV infections and rabies (limbic system). Once the virus has entered the brain, it may stay contained to a small number of cells or spread to other tissues through extracellular gaps or cell-to-cell contact; after that, HSV may stay dormant within the central nervous system (CNS). The pathophysiology of HSE in children older than 3 months, adolescents, and adults has been extensively studied, but it is still not entirely clear. Both primary and recurrent HSV infections can result in encephalitis (in around one-third of cases, usually in people under the age of 18). Only 10% of patients have a history of recurrent herpes labialis in the two thirds of cases that develop in the presence of pre-existing antibodies. Patients who already have antibodies may develop HSE as a result of HSV reactivation.[50,52] It's interesting to note that when the genomic DNA from peripheral (labial) and CNS isolates is examined by restriction analysis, distinct isolates—which are typically identical—are retrieved. The olfactory and trigeminal nerves have both been suggested as preferred pathways for HSV entry to the CNS during primary infection. By using electron microscopy on some HSE patients, HSV particles have been seen along the olfactory pathway. Animal models lend credence to the idea that the olfactory tract serves as an entrance point into the central nervous system, leading infection to concentrate in brain areas similar to the human medial temporal structures. There is no evidence of reactivation within the brain. Although it has been suggested that this event occurs in the olfactory bulb trigeminal ganglion and is then transmitted neuronally to the central nervous system.[53-57]

Pathogenesis

The breakthrough of the CNS's protective barriers is the initial step towards VE. The two methods listed below are the main ways that viruses can enter the central nervous system (CNS).[58-60] By directly harming endothelial cells and opening a pathway via the junctions, through the blood supply. Or by passing through anatomical features with weaker defenses, such as the choroid plexus and circumventricular organs. Alternatively, with the aid of infected hematopoietic cells (also known as "Trojan horses").[61-65] by contaminating motor or sensory nerves in the periphery. Monocytes infiltrate the infected CNS region after viral invasion and change into the necessary cell types, such as dendritic cell, macrophage, and microglial cells. The presence of $Ly6C^{hi}$ monocytes in the CNS inflammation is thought to be a pathognomonic sign of VE. By aiding in antigen presentation and T cell stimulation, these altered cells work to restrict and depopulate viral components. Reactive oxygen species and other inflammatory mediators are also produced with its assistance. Damage to nerve cells caused by a pathogenic component that has reached the central nervous system leads to disease and the appearance of clinical symptoms. HSV-induced encephalitis is caused by the apoptosis of nerve cells.[65-66]

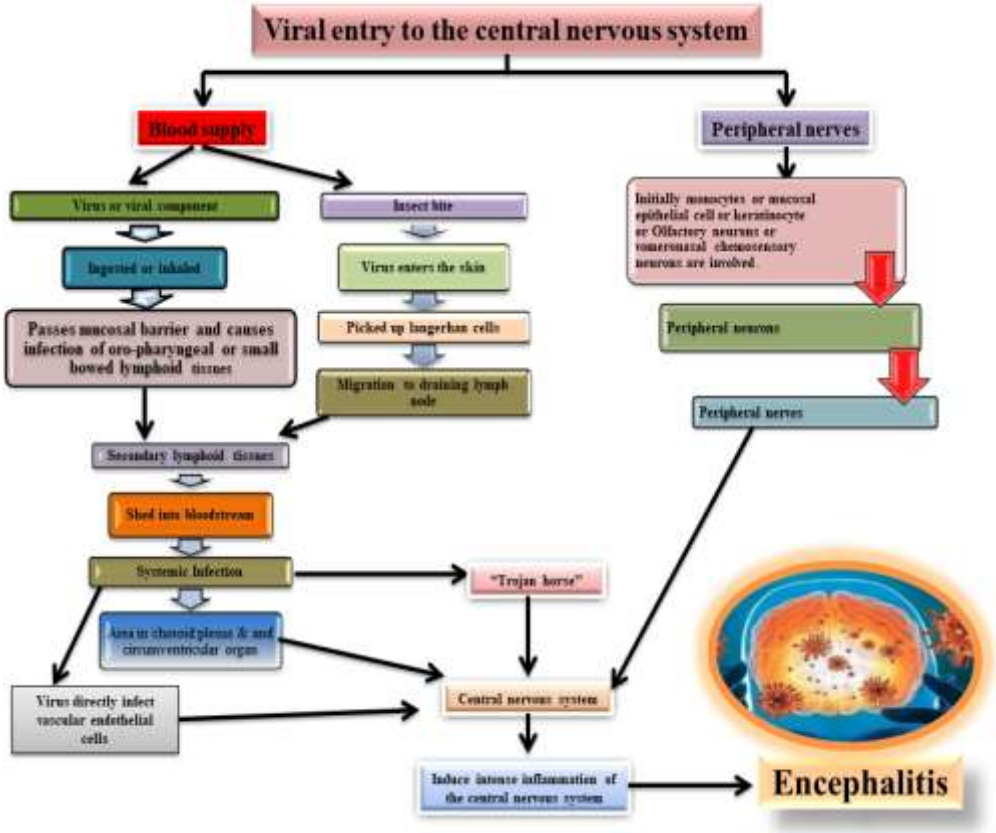

Fig. 3: Viral encephalitis pathogenesis.[67]

Diagnosis

The important step in proving CNS inflammation is to acquire and test CSF via an LP. When focal neurological symptoms, papilledema, seizures, or a GCS 13 are present, neuroimaging is only recommended before LP since these indications signal obstructive increased intracranial pressure. However, neuroimaging is not a need for LP The CSF often exhibits a mostly lymphocytic pleocytosis in viral encephalitis. In these samples, the CSF: blood glucose ratio is normally normal, and protein levels may be slightly raised or normal. It's crucial to send CSF samples for viral PCR as soon as possible. In cases of HSV and varicella zoster, delaying the LP and consequently the CSF viral PCR might cause diagnostic ambiguity as the viral load drops. This is especially true after acyclovir has been started. At these postponed timepoints, repeat LPs to collect CSF and serum for antiviral antibody testing may be helpful in making a diagnosis. In all instances, especially those with an identifiable phenotype of autoimmune encephalitis, autoantibody testing should be taken into consideration.[38] Cell-based assays and immunohistochemistry for neuronal surface antibodies are among the diagnostic procedures used to identify autoimmune encephalitis. According to mounting research, live cell-based assays work best in these conditions and in-house fixed cell-based assays outperform their commercially available counterparts.[68,69] Brain imaging is advised to check for encephalitis-related abnormalities and rule out other diseases such lesions that take up too much area. The preferred method for assessing encephalitis-related alterations is MRI, particularly with diffusion weighted imaging (DWI) sequences. The most well-known infection, HSV encephalitis, which causes bilateral but asymmetrical inflammation of the temporal and frontal lobes71, causes particular alterations that can be observed on neuroimaging. Although MRI results from autoimmune encephalitis might show a variety of abnormalities, bilateral and symmetrical limbic system inflammation is the most typical sign.[70,71] Bilateral white matter lesions that can be supra- and infratentorial and affect the brainstem and spinal cord are frequently visible on MRI in cases with suspected ADEM. Body imaging techniques like positron emission tomography and whole-body CT imaging must also be taken into account in the case of autoimmune encephalitis in order to rule out any underlying malignancies. Due to its ability to detect encephalopathy, which is unusual in main psychiatric diagnosis, or subclinical seizures, the electroencephalogram can be helpful in the investigation of encephalitis. In high-income environments, autoimmune encephalitis may indeed play a significant role in the development of non-convulsive status epilepticus. In instance, the pathognomy severe delta brush appearance in NMDAR-antibody encephalitis is one of the distinctive patterns that have been described in autoimmune encephalitis.[4,72,73]

Management or treatment

In extreme circumstances, the general management must be in a high dependency or critical care facility and

serves mostly as a supportive role. Anticonvulsants administered intravenously are necessary for the efficient management of focal and generalized seizures. Steroids or intravenous mannitol must be used to treat elevated intracranial pressure. Surgical decompression may be life-saving when there is a fast rise in intracranial pressure and clinical deterioration that is not responding to medicinal intervention. Other consequences must be identified early and treated effectively, including secondary bacterial infections, aspiration pneumonia, respiratory failure, heart irregularities, and fluid and electrolyte imbalance. An antiviral therapy with promise can be used to treat herpesvirus-related encephalitis. Patients with HSE who receive acyclovir (within 48 hours of the beginning of symptoms) at a dose of 10 mg/kg bw intravenously three times daily for 14 days (21 days in immunocompromised hosts) see a reduction in mortality and severe long-term neurological effects.[29,30] Nevertheless, mortality is still significant (14%, rising to 25.4% by the end of the first year following therapy in Sweden over an 11-year period), particularly in patients with Glasgow coma scores below. The best outcomes are seen in patients under 30 and with a Glasgow coma score above 10. Herpesvirus resistance is uncommon and typically does not correlate with clinical outcome in immunocompetent people. When a biphasic course or relapses occur, high dose steroids may be beneficial in some paediatric patients.[74-76] The effectiveness of consistently administering acyclovir to children who are immunologically competent in treating VZV encephalitis has not been established. Patients who report with neurological impairments that have a delay after start (> 7 days) can get IV methylprednisolone as these are likely to be cases of ADEM. There is no effective treatment for EBV encephalitis (antiviral medications, immunoglobulins, and steroids are useless). A few cases of HHV-6 encephalitis have apparently responded well to several antivirals (ganciclovir, foscarnet, and cidofovir), but no published clinical trials have been conducted. There is currently no treatment for enteroviral encephalitis, although the broad-spectrum ant picornavirus medication pleconaril may become available in the future.[77-78] Various antiviral and immunomodulatory medications have occasionally been tried to treat SSPE, with mixed outcomes. A multicenter research assessing oral inosiplex (isoprinosine) alone or in combination with intraventricular IFN-α2b therapy found encouraging outcomes with a 6-month follow-up. But additional research is required to validate these findings. The majority of treatment for rabies encephalitis is palliative because it progresses and is fatal. Although sporadic cases of symptomatic patients have survived, all of those patients got either pre- or post-exposure prophylaxis, and none had a positive rabies virus test result.[77,79-83] Immunotherapy, such as high-dose steroid therapy with or without intravenous immunoglobulin (IvIg) and/or plasmapheresis, is the first line of treatment for autoimmune conditions. Rituximab and/or cyclophosphamide are second-line therapeutic options. A trial (EncephIg) is currently looking into the benefits of adjunctive IvIg in patients receiving high-dose steroids. Additionally, a clinical trial for LGI1-antibody encephalitis intends to evaluate the usefulness of lowering IgG levels by inhibiting the FcRn molecule, which generally recycles IgG. A CD19 monoclonal antibody is additionally being tested in patients with NMDAR-antibody encephalitis in an effort to enhance outcomes. The care of encephalitis's long-term sequelae, which come from damage and injury to the brain, is an important part of treatment. Long-term repercussions include emotional, behavioural, physical, and cognitive problems affect a lot of people. Social consequences, such as the inability to drive and the loss of employment or education owing to a handicap, are frequently disabling in some of these disorders.[84-85] Since most viral infections of the central nervous system do not have a specific medicinal therapy, supportive care is the mainstay of treatment for viral encephalitis. HSV encephalitis is an extremely significant exception to this. Acyclovir has been demonstrated to considerably reduce mortality and morbidity when administered early in the course of HSV encephalitis, as well as to lessen the degree of long-term behavioural and cognitive impairment. Therefore, it is advised that doctors begin administering acyclovir to all patients who have a suspicion of having encephalitis. 10 mg/kg intravenously (IV) every eight hours for 14 to 21 days is the recommended dose. Nucleoside analogues are used for other herpesviruses as well, albeit they are not as efficient as they are with HSV. The recommended treatment for varicella-zoster virus is acyclovir 10 to 15 mg/kg IV every eight hours for 10 to 14 days, with possibly additional corticosteroids in immunocompetent patients. Ganciclovir 5 mg/kg IV every 12 hours and foscarnet 60 mg/kg IV every 8 hours or 90 mg/kg IV every 12 hours for 21 days are the recommended treatments for CMV encephalitis. Serial intracranial pressure (ICP) monitoring is a crucial part of treating patients with viral encephalitis. ICP elevation is linked to a bad prognosis. In order to lower elevated ICP, prednisolone and mannitol can be used, albeit there is little information on their effectiveness in viral encephalitis. Valproic acid or phenytoin may be required to treat seizures. Benzodiazepines might be necessary for status epilepticus. Antipsychotics may be required for a brief period of time in order to treat behavioural changes.[86-88]

Fig. 4: Possibilities for encephalitis therapy.

Challenges with diagnostic

Numerous neurodiagnostic methods are available, some of which have just lately been created to concentrate on thorough investigation of meningitis encephalitis, further increasing the likelihood of an etiological diagnosis. It is advised to perform a lumbar puncture to determine the opening pressure and to analyse the CSF for microbiological evidence, molecular assays like PCR, and immunological testing for antibodies. The timing of sample collection in relation to the onset of infection and the length of symptoms, the availability and accessibility of particular tests, as well as the clinicians' experience in interpreting negative results, may all have an impact on the early and effective detection of pathogens. The CSF often exhibits a pleocytosis that is primarily lymphocytic in viral encephalitis, and protein levels may be slightly increased or normal. Getting CSF gramme stain and culture, CSF HSV PCR, CSF VZV PCR, and CSF Enterovirus PCR is advised. If HSV encephalitis with symptoms suggestive of the virus is suspected and a CSF PCR test is initially negative, a repeat test is recommended in 3–7 days.[4] Paraneoplastic and autoimmune factors should be taken into account when imaging and CSF are unable to identify the underlying cause. It is ideal to test for both serum and CSF levels of anti-neuronal autoantibodies, such as those against NMDAR, LGI1, AMPAR, GAD65, GABA-A, and GABA B, keeping in mind that the absence of an antibody does not always rule out the presence of the disease. To rule out hidden cancers and systemic infections, more imaging should be taken into consideration. Traditional neuroimaging methods include computed tomography (CT) or the more effective brain magnetic resonance imaging (MRI), which may identify the affected areas and reveal a probable pathogen as well as measure the severity of the involvement and the existence of edoema, haemorrhage, or herniation. The most suitable MRI sequences are T2-weighted images, FLAIR, diffusion-weighted imaging (DWI), and post-gadolinium sequences. Lack of adequate information on specific areas of involvement may cause a delay in the diagnosis of the illness. 90% of abnormalities in HSV encephalitis can be seen in the medial and inferior temporal lobes, where there is cytotoxic and vasogenic edoema. In contrast, T2 hyper intensities with restricted diffusion are seen in the basal ganglia, thalamus, temporal cortex, and cerebellum in VZV encephalitis. The evaluation of autoimmune causes and the evaluation of brain physiology are both possible with fluorodeoxyglucose-positron emission tomography (FDG- PET) studies. It has been advised to perform a continuous electroencephalogram (c-EEG) on critically ill patients who have persistent altered mental status for at least 24 hours with unexplained aetiologies despite treatment. Compared to traditional EEG, it detects 95% of nonconvulsive seizures in patients.[89,90] As determined by a retrospective study, following diagnostic guidelines has a significant impact. Despite high rates of compliance with performing tests like brain CTs, blood cultures, and CSF microbiology, evaluation of other available tests was inconsistently carried out, which resulted in underutilization of resources.[91] These cutting-edge technologies are, however, not readily accessible and may only be used in tertiary facilities where there are few specialists trained in interpreting the results. Over the last ten years, innovative emerging methodologies have been introduced, enabling thorough examination. These include the metagenomic Next Generation Sequencing (NGS) and the molecular-based assay BioFire FilmArray® Meningitis/Encephalitis (ME) panel. In particular for infections that cause meningitis and encephalitis, the FilmArray® ME panel enables for numerous CSF PCR assays, detecting fourteen different microorganisms with excellent sensitivity and specificity and a quick turnaround.[92] There are restrictions, though, as not all pathogens are represented in the panel and are still unavailable in the majority of medical settings. By isolating and sequencing RNA or DNA in samples like fluids and tissue, metagenomic NGS offers a more thorough method of detection for viruses, bacteria, parasitic, and fungal infections. The non-human pathogen is then identified by comparison to known

genetic sequences stored in a database. The possibility of false positive results because of sample contamination can result in incorrectly diagnosing a cause, even if it provides an objective approach to pathogen identification and excludes out co-infections. Additionally, as the approach depends so largely on nucleic acids, it might not be suitable for identifying pathogens with short half-lives or low pathogen loads.[93,94]

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CONCLUSION AND FUTURE DIRECTION

Our review articles' initial portion provides a thorough overview of encephalitis, encompassing its aetiology, pathophysiology, histology, diagnosis, management (combination therapy), symptoms, and outcomes. Despite the fact that pharmaceutical therapies take some time to work and don't have any negative side effects, our research indicates that they complete the body's repair. To learn more about how to treat encephalitis, further randomised controlled research must be conducted. We plan to continue encephalitis research in the future. Further study incorporating counselling will be carried out in our country or state with the aid of our colleagues in order to assess patients' physical and mental health and supply more detailed knowledge about encephalitis and its improved therapy.

Table 1: Current status of clinical trials on encephalitis.

Drug	Mode of administration	Disease	Enrollment	Allocation/Intervention model/Masking	Official Title of the study	Status	Clinical trial	Year
Japanese encephalitis chimeric virus vaccine (JE-CV)	Interventional	Encephalitis	300	Randomized/ Parallel Assignment/Quadruple (ParticipantCare ProviderInvestigatorOutcomes Assessor)	A Controlled Study of the Immunogenicity and Safety of Japanese Encephalitis Chimeric Virus Vaccine (JE-CV) in Comparison With SA14-14-2 Vaccine in Infants and Toddlers in Thailand	Phase-3	NCT01092507	2015
None, non-interventional study	Observational [Patient Registry]	Encephalitis	596	NA	EURopean Study on Encephalitis in Intensive CAre	NA	NCT03144570	2021
Blood sample/ JE-CV administered in Study JEC02	Interventional	Encephalitis	596	Randomized/ Parallel Assignment/Quadruple	Long-term Follow-up of Immunogenicity of a Single Dose of JE-CV in Toddlers in Thailand and the Philippines	Phase-3	NCT01001988	2017
ChimeriVax-JE, Japanese Encephalitis vaccine/ 0.9% Saline	Interventional	Encephalitis	2004	Randomized/ Parallel Assignment/Quadruple (ParticipantCare ProviderInvestigatorOutcomes Assessor)	Randomised, Double Blind, Multicentre, Placebo Controlled Phase III Study of the Safety and Tolerability Following Administration of Live Attenuated JE Vaccine (ChimeriVax™-JE)	Phase-3	NCT00314132	2012
0.5ml experimental vaccine on day 0,7 Vero cell-derived inactivated Japanese Encephalitis vaccine	Interventional	Encephalitis	900	Randomized/ Parallel Assignment/Double (ParticipantInvestigator)	A Single-centre Phase III Clinical Trial for Vero Cell-derived Inactivated Japanese Encephalitis Vaccine Produced by Shandong Hengye Biotech Co., Ltd. in Healthy Chinese Infants Aged 6-11	Phase-3	NCT02367664	2016

					Months, Aimed to Evaluate Immunogenicity and Safety			
IC51 Japanese Encephalitis/ Havrix ®720/ Prevnar	Interventional	Encephalitis	1869	Randomized/ Parallel Assignment/ None (Open Label)	Safety and Immunogenicity of the Japanese Encephalitis Vaccine IC51 (IXIARO®) in a Pediatric Population. Open Label, Randomized, Active Controlled, Phase 3 Study	Phase-3	NCT01041573	2021
Live attenuated Japanese encephalitis virus, then ChimeriVax diluent	Interventional	Encephalitis	202	Randomized/Crossover Assignment/Quadruple	Randomised, Double-blind, Phase 2 Study of the Safety, Immunogenicity and Duration of Immunity of ChimeriVax™-JE, Live Attenuated Vaccine in Healthy Adults	Phase-2	NCT00981175	2012
IC51/ IC51/ IC51	Interventional	Encephalitis	100	Non-Randomized/ Parallel Assignment/ None (Open Label)	Immunogenicity and Safety of the Japanese Encephalitis Vaccine IC51 (IXIARO®, JESPECT®) in a Pediatric Population in Non-endemic Countries. Uncontrolled, Open-label Phase 3 Study	Phase-3	NCT01047839	2020
Nivolumab	Observational	Encephalitis	486	Case-Only	Case Series Analyses of the Risk Factors and Outcomes of Immune-Mediated Encephalitis Following Exposure to Nivolumab	NA	NCT02856451	2022
Proleukin	Interventional	Encephalitis	10	N/A/ Single Group Assignment/ None (Open Label)	Effect of IL-2 in Refractory Autoimmune Encephalitis Patients: A Pilot Study	Phase-1&2	NCT02714959	2021
Valacyclovir/ Placebo	Interventional	Encephalitis	91	Randomized/ Parallel Assignment/Double (ParticipantInvestigator)	A Phase III Double-Blind, Placebo-Controlled Trial of Long Term Therapy of Herpes Simplex Encephalitis (HSE): An Evaluation of Valacyclovir (CASG-204)	Phase-3	NCT00031486	2012
Inactivated Hepatitis A vaccine	Interventional	Encephalitis	50	N/A/Single Group Assignment/ None (Open Label)	Immunogenicity of a Live Attenuated Chimeric Japanese Encephalitis Vaccine (IMOJEV) as	Phase-4	NCT02526550	2016

					a Booster Dose After a Primary Vaccination With CD.JEVAX in Thai Children			
AVI-4065 Injection	Interventional	Encephalitis	12	Non-Randomized/ Single Group Assignment/ None (Open Label)	Pharmacokinetic Study of AVI-4065 in Cerebral Spinal Fluid Among Healthy Adult Males Following Subcutaneous Administration	Phase-1	NCT00381433	2009
Live attenuated Japanese encephalitis vaccine SA14-14-2	Interventional	Encephalitis	17	N/A/Single Group Assignment/ None (Open Label)	A Prospective, Open Label Study of Human T Cell Responses to Live Attenuated Japanese Encephalitis Vaccine SA14-14-2	Phase-4	NCT01656200	2019
IBW or adjBW for HSV for safe and effective therapy.	Observational	Encephalitis	50	Other	Impact of Dosing Weight on Clinical Outcomes in Obese Patients Receiving Acyclovir for HSV Encephalitis (ID-OPRAH)	NA	NCT05127395	2023
Long-term outcome	Observational	Encephalitis	70	Cohort	Long-term Follow up of Patient With Anti-GABAbr Antibodies Associated-encephalitis.	NA	NCT05741619	2023
Retrospective evaluation of specific brain MRI features	Observational	Encephalitis	50	Cohort	Investigating the Prognostic Role of Brain MRI in Anti-LGI1 Encephalitis	NA	NCT05825690	2023
JEVAX/ JECEVAX	Interventional	Encephalitis	220	Randomized/ Parallel Assignment/ Quadruple (ParticipantCare ProviderInvestigatorOutcomes Assessor)	Evaluate the Safety of a Vero Cell - Derived Inactivated Japanese Encephalitis Vaccine (JECEVAX) Produced by The Company for Vaccine and Biological Production No.1 in Vietnamese Children Aged 9-24 Months	Phase-2	NCT03204227	2018
Live attenuated Japanese encephalitis chimeric virus vaccine	Interventional	Encephalitis	250	Non-Randomized/ Parallel Assignment/ None (Open Label)	Immunogenicity and Safety of a Single Primary Dose of a Live Attenuated Japanese Encephalitis Chimeric Virus Vaccine (IMOJEV®) Given to Healthy Subjects in Vietnam	Phase-3	NCT02492165	2022
NA	Observational	Encephalitis	600	Other	An Observational, Retrospective, Clinical Performance Study Testing Residual Specimens of Cerebrospinal Fluid	NA	NCT05092438	2021

					Obtained by Lumbar Puncture From Meningitis/Encephalitis Subjects Using the QIAstat-Dx® Meningitis/Encephalitis Panel			
Intravenous immunoglobulin [ImmunoRel™ (batch 20081217)]	Interventional	Encephalitis	22	Randomized/Parallel Assignment/ Triple (Care ProviderInvestigatorOutcomes Assessor)	A Randomized Double Blind Placebo Controlled Trial to Assess the Safety and Efficacy of Intravenous Immunoglobulin (IVIG) in Children With Japanese Encephalitis in Nepal	Phase-2	NCT01856205	2013
Fundamental research	Observational	Encephalitis	253	Cohort	Mechanisms of Auto-immune Encephalitis	NA	NCT02905136	2020
Stem cell transplantation	Interventional	Encephalitis	22	N/A/ Single Group Assignment/ None (Open Label)	The Outcomes of Autologous Bone Marrow-derived Mononuclear Cell Transplantation In-patient With Neurological Sequelae Due to Encephalitis or Meningitis at Vinmec International Hospital	Phase-1&2	NCT04080921	2019
Primary and booster immunizations with MB-JEV	Interventional	Encephalitis	120	Non-Randomized/ Parallel Assignment/ None (Open Label)	Ability of the New Vero-cell-derived Inactivated Japanese Encephalitis Vaccine (IXIARO) to Elicit a Booster Response in Travellers Previously Vaccinated With Traditional Mouse-brain Derived Vaccine (JE-MB)	Phase-3	NCT01386827	20111
Rituximab	Interventional	Encephalitis	10	N/A/ Single Group Assignment/ None (Open Label)	A Pilot Study of the Use of Rituximab in the Treatment of Chronic Focal Encephalitis	Phase-1	NCT00259805	2013
JEVAX/ JECEVAX-1	Interventional	Encephalitis	200	Randomized/ Parallel Assignment/Quadruple (ParticipantCare ProviderInvestigatorOutcomes Assessor)	Safety and Immunogenicity of an Inactivated Japanese Encephalitis Vaccine (JECEVAX) in Vietnamese Children	Phase-2	NCT02816554	2016
NA	Observational	Encephalitis	50	Other	Post-marketing Surveillance Study for a Live Attenuated Japanese Encephalitis Chimeric Virus	NA	NCT02933710	2022

					Vaccine (IMOJEV®) in Republic of Korea			
JEVAX/ JECEVAX	Interventional	Encephalitis	655	Randomized/ Parallel Assignment/Quadruple (ParticipantCare ProviderInvestigatorOutcomes Assessor)	Evaluate the Safety and Immunogenicity of a Vero Cell - Derived Inactivated Japanese Encephalitis Vaccine (JECEVAX) Produced by VABIOTECH (Vietnam) in Vietnamese Children Aged 9-24 Months	Phase-3	NCT03282370	2018
IXIARO/ IXIARO	Interventional	Encephalitis	300	Randomized/ Parallel Assignment/ None (Open Label)	Long-Term Immunity and Safety With or Without a Booster Dose Following Primary Vaccination With the Japanese Encephalitis Vaccine IC51 (IXIARO®) in a Pediatric Population in a JEV-Endemic Country. Open-Label, Randomized, Phase 3 Study	Phase-3	NCT01296360	2014
Japanese Encephalitis purified inactivated vaccine	Observational	Encephalitis	3258	Cohort	Longterm Immunogenicity of the Japanese Encephalitis Vaccine IC51. An Uncontrolled Phase 3 Follow-up Study	NA	NCT00596102	2014
IMOJEV	Interventional	Encephalitis	18	Non-Randomized/Parallel Assignment/ None (Open Label)	Flavivirus Cross-priming Potential of Live Attenuated Japanese Encephalitis (JE) Vaccine IMOJEV in Flavivirus naïve and Flavivirus Experienced Participants	NA	NCT03920111	2022
Japanese Encephalitis purified inactivated vaccine (IC51)/ Placebo	Interventional	Encephalitis	2675	Randomized/ Parallel Assignment/Double (ParticipantInvestigator)	Safety and Tolerability of the Japanese Encephalitis Vaccine IC51. Double Blind, Randomized, Placebo Controlled Phase 3 Study	Phase-3	NCT00605085	2012
Live Attenuated Japanese Encephalitis SA-14-14-2 Vaccine	Interventional	Encephalitis	561	N/A/ Single Group Assignment/ None (Open Label)	Assessment of Long Term Immunogenicity of Japanese Encephalitis Live Attenuated SA-14-14-2 Vaccine in Previously Vaccinated Bangladeshi Children and Antibody Response and Safety	Phase-4	NCT02514746	2020

					to a Booster Dose			
IC51	Interventional	Encephalitis	639	Randomized/ Parallel Assignment/Double (ParticipantInvestigator)	Comparison of Three Batches of the Japanese Encephalitis Vaccine IC51. Double Blind, Randomized, Controlled Phase 3 Study.	Phase-3	NCT00594958	2016
IC51	Interventional	Encephalitis	374	Randomized/ Parallel Assignment/ Single (Participant)	Phase 3 Study to Compare a Rapid Immunization Regime With the Standard Regime of IC51 as Vaccine for Japanese Encephalitis	Phase-3	NCT00595790	2014
IC51/ JE-VAX	Interventional	Encephalitis	867	Randomized/ Parallel Assignment/ Single (Participant)	Observer Blinded, Randomized Phase 3 Study to Investigate the Non-Inferiority of IC51 vs. JE-VAX as Vaccines for Japanese Encephalitis in Healthy Subjects	Phase-3	NCT00604708	2016
Vaccine produced in existing facility	Interventional	Encephalitis	818	Randomized/Parallel Assignment/ Quadruple (Participant Care ProviderInvestigatorOutcomes Assessor)	A Clinical Trial in Healthy Infants to Assess Lot-to-lot Consistency of Japanese Encephalitis Live Attenuated SA 14-14-2 Vaccine and Non-inferiority With Respect to an Earlier Product.	Phase-4	NCT01567865	218
Japanese Encephalitis purified inactivated vaccine	Interventional	Encephalitis	389	Randomized/ Parallel Assignment/Double (ParticipantInvestigator)	Comparison of Three Commercial Batches of the Japanese Encephalitis Vaccine IC51. Double Blind, Randomized, Controlled Phase 3 Study.	Phase-3	NCT00595465	2014
IC51	Interventional	Encephalitis	349	N/A/ Single Group Assignment/ None (Open Label)	Long Term Persistence and Effect of a Booster Dose of the Japanese Encephalitis Vaccine IC51	Phase-3	NCT00595270	2014
IC51	Interventional	Encephalitis	198	N/A/ Single Group Assignment/ None (Open Label)	Effect of a Booster Dose of the Japanese Encephalitis Vaccine IC51 on Long Term Immunogenicity. An Uncontrolled, Open-label Phase 3 Study.	Phase-3	NCT00595309	2014
IMOJEV	Interventional	Encephalitis	119	N/A/ Single Group Assignment/ None (Open Label)	Immunogenicity and Safety Exploration of a Booster Dose of a Live Attenuated Japanese Encephalitis	Phase-3	NCT01900444	2022

					Chimeric Virus Vaccine (IMOJEV®) Given One Year After Primary Immunization in Healthy Children in South Korea			
Live attenuated Japanese encephalitis virus	Interventional	Encephalitis	128	Randomized/ Parallel Assignment/ Quadruple	Randomised, Double-blind, Placebo Controlled Phase II, Dose-ranging Study of the Safety, Tolerability and Immunogenicity of Live Attenuated ChimeriVax™-JE Vaccine (Lyophilised)	Phase-2	NCT00981630	2012
Immunoglobulin G	Interventional	Encephalitis	23	N/A/ Single Group Assignment/ None (Open Label)	A Phase 2a, Prospective, Open-label, Single-arm, Single Center, Proof of Concept Study to Evaluate the Safety and Efficacy of IGIV 10% in Patients With Autoimmune Encephalitis	Phase-2	NCT04175522	2020
Live, Attenuated Japanese Encephalitis SA 14-14-2 Vaccine	Interventional	Encephalitis	278	N/A/ Single Group Assignment/ None (Open Label)	Assessment of the Immunogenicity and Safety of Japanese Encephalitis Live Attenuated SA 14-14-2 Vaccine in Children in Sri Lanka	Phase-4	NCT00463684	2019
Live, Attenuated Japanese Encephalitis SA 14-14-2 Vaccine (LJEV)	Interventional	Encephalitis	305	Non-Randomized/ Single Group Assignment/ None (Open Label)	Assessment of the Immunogenicity and Safety of Japanese Encephalitis Live Attenuated SA 14-14-2 Vaccine in Children in Sri Lanka	Phase-4	NCT00463476	2020
Japanese encephalitis vaccine	Interventional	Encephalitis	94	N/A/ Single Group Assignment/ None (Open Label)	A Multi-center, Open, phase4 Study to Assess the Long-term Immunogenicity and Safety of Fourth Administration of BR JEV and to Investigate on Vaccine Interchangeability in Children Aged 6 Years Who Received 3 Doses With ENCEVAC or JEV-GCC	Phase-4	NCT02532569	2017
ChimeriVax™-JE/ JE-VAX	Interventional	Encephalitis	820	Randomized/ Parallel Assignment/ Quadruple	A Multicentre, Randomized, Double-blind, Phase III Study of The Comparative Immunogenicity, Safety and	Phase-3	NCT00314145	2012

					Tolerability of Two Japanese Encephalitis Vaccines (ChimeriVax™-JE and JE-VAX®)			
IXIARO®	Interventional	Encephalitis	200	Non-Randomized/ Single Group Assignment/ None (Open Label)	An Open-label, Uncontrolled Phase 4 Study to Assess the Safety and Immunogenicity of the Japanese Encephalitis (JE) Vaccine Ixiaro® (IC51) in an Elderly Population	Phase-4	NCT01158599	2012
A live attenuated chimeric JE vaccine	Interventional	Encephalitis	50	N/A/ Single Group Assignment/ None (Open Label)	Immunogenicity of a Japanese Encephalitis Chimeric Virus Vaccine (JE-CV) as a Booster Dose After a Primary Vaccination With SA14-14-2 Vaccine in Thai Children	NA	NCT02602652	2016

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