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# Viral Acute Encephalitis: Recent Updates and Imminent Perspectives

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**Published Date:** March 15, 2018

## ABSTRACT

Acute encephalitis syndrome **(AES)** is categorized by an acute onset of fever and clinical manifestation such as high fever, headache, sensitivity to light, stiff neck and back, vomiting, confusion and, in severe cases, seizures, Mental confusion, disorientation, delirium, paralysis and coma. Viruses are mainly cause of AES while others infectious agent such as bacteria, fungus, parasites, spirochetes, chemical, leptospirosis and toxoplasmosis can cause AES. The causative agent of AES varies with seasonal and geographical distributions, and mainly affects Individual below 15 years. AES is a disease condition characterized be presence of fever, and altered consciousness with or without presence of seizures or a neurological deficit and inflammation of the brain parenchyma and is a significant cause of human morbidity and mortality. Viral encephalitis is the most frequent known cause of fatal sporadic encephalitis in humans. The clinical manifestations vary depending upon which portions of the central nervous system **(CNS)** are affected (although the clinical syndromes overlap to some extent), the pathogenetic agent, and various host factors. Diagnosis should be based on medical history, examination followed by analysis of cerebrospinal fluid for protein and glucose contents, cellular analysis and identification of the pathogen by polymerase chain reaction **(PCR)** and serology. Neuroimaging, preferably by magnetic resonance imaging, is an essential aspect of evaluation. All encephalitis cases must be

hospitalized with an access to intensive care units. Supportive therapy is an important basis of management. Specific, evidence-based, anti-viral therapy should be followed.

## INTRODUCTION

Acute Encephalitis Syndrome **(AES)** is a group of clinically similar neurologic manifestation caused by several different viruses, bacteria, fungus, parasites, spirochetes, chemical/ toxins etc [1]. There is seasonal and geographical variation in the causative organism [2]. The case fatality and morbidity are very high among various viral encephalitis in various parts of world [3]. For surveillance purposes, all the cases of Acute Encephalitis Cases to be reported under the heading of acute encephalitis [4]. Viral infection of the central nervous system **(CNS)** most often leads to meningitis, meningo encephalitis, or encephalitis, in descending order of frequency [5]. Most people who have mild cases of encephalitis make a full recovery within 2-4 weeks [6]. Prognosis for severe encephalitis depends on many factors, including Age of the patient worse outcomes for infants under age 12 months and adults over age 55, Immune status, Pre-existing neurological conditions and Virulence of the virus [7]. Encephalitis is a serious condition, so you should see a doctor if you or your child start having symptoms [8]. You are usually diagnosed and treated in a hospital at first [9]. After doing a physical exam, a doctor may take the steps to diagnose the condition. Blood tests are finds viruses in the blood [10]. Spinal tap (lumbar puncture) finds viruses in the fluid around the brain, spinal cord and neurological imaging [11]. Use insect repellent and wear long pants and long sleeves. The most effective bug sprays contain Picaridin [12]. Do not apply insect repellent to children under 2 years of age. Make sure your child is vaccinated against diseases such as the measles, mumps, and rubella **(MMR)** [13]. Eat a healthy diet to keep your immune system healthy. Medications used to treat viral encephalitis are include such as Acyclovir (Zovirax) treats encephalitis [14]. Anticonvulsant medications prevent and treat seizures that may happen with encephalitis. Most cases of encephalitis are mild and people make a full recovery [15].

## CAUSATIVE AGENTS OF AES

The various causes of acute infectious viral encephalitis are Herpes simplex type 1 **(HSV1)**, Herpes simplex type 2 **(HSV2)**, Enteroviruses (echovirus, parechovirus, coxsackievirus A and B, poliovirus, and the numbered enteroviruses EV), Varicella zoster virus **(VZV)**, Epstein-Barr virus **(EBV)**, Cytomegalovirus **(CMV)**, Human herpesvirus **(HSV6)**, Human immunodeficiency virus **(HIV)**, Arboviruses **(**LaCrosse virus, West Nile virus **(WNV)**, St. Louis encephalitis virus **(LEV)**, Eastern and Western equine encephalitis virus **(EEV/WEV)**, Japanese encephalitis virus **(JE)**. Rabies virus **(RV)**, Influenza virus **(IV)**, Measles virus, Mumps virus, Rubella virus, Murray Valley encephalitis virus **(MVEV)**, Nipah virus, Hendra virus, Tick-borne encephalitis virus, Powassan virus, Hepatitis E virus [16].

# METHODS CLINICAL FEATURES

## General Examination

Symptoms of encephalitis usually appear within 2 days to 2 weeks of exposure to the virus [14]. In milder cases. symptoms are included such fever, depressed or altered level of consciousness, lethargy, Behavioral and personality change, Sensitivity to light, emotional lability, seizure, ataxia, Memory loss, Stiff neck and back accompanied by fever and headache would indicate meningitis, Confusion, Speech, hearing, vision problems, Muscle weakness, Seizures, Partial paralysis, Loss of consciousness and Coma. Patients experiencing these types of symptoms should immediately take medical consultants shown in Figure 1 [18].

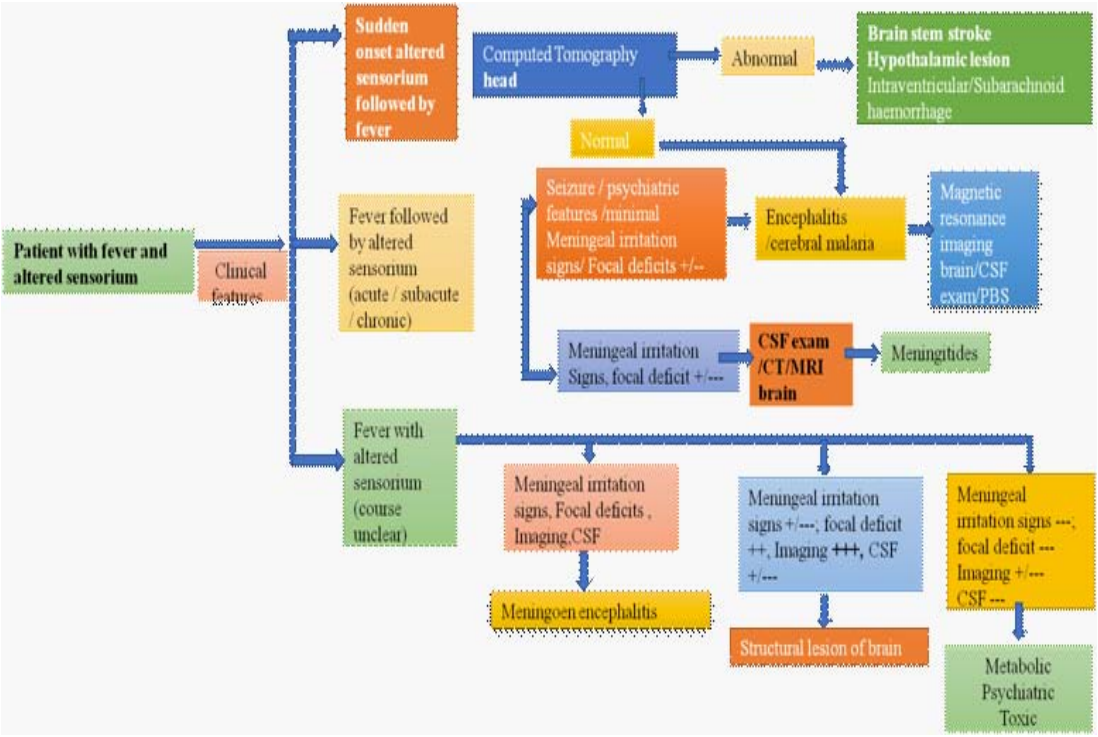


**Figure 1:** Clinical features of Patients With AES.

## Neurological Examination

Neurological signs in acute encephalitis identify focal abnormalities such as hemiparesis, aphasia, ataxia, brisk tendon reflexes and extensor plantar responses, cranial nerve deficits (oculomotor and facial), myoclonus and tremors, and partial seizures [19]. Magnetic resonance imaging **(MRI)** is the imaging modality of choice to investigate acute encephalitis and is recommended to be performed in all patients as soon as possible in whom diagnosis is uncertain CT (Computed Topography) or MRI scans can show the extent of the inflammation in the brain and help differentiate encephalitis from other conditions [20]. Electroencephalogram **(EEG)**,

which records brain waves, may reveal abnormalities in the temporal lobe that are indicative of AES [21].

## INVESTIGATIONS

According to WHO guideline AES cases characterized as Acute onset of fever mild to high grade, not more than 5-7 days duration [22]. Change in mental status with/ without new onset of seizures excluding febrile seizures, include irritability, somnolence or abnormal behaviour greater than that seen with usual febrile illness [23]. Screening laboratories are performed such as CBC (Cuboidal blood count), glucose, electrolytes, creatinine, ammonia, blood pH, blood cultures, LFTs (Liver function test), urinalysis, urine drug screen and save a sample of acute serum [24].

CSF examination along with serological tests plays a key role in diagnosing and identifying etiology of encephalitis and excluding conditions like pyogenic meningitis and subarachnoid haemorrhage [25]. Laboratory diagnosis is generally performed by testing the CSF or serum sample to detect virus specific IgM antibodies. IgM antibodies are usually after onset of illness and persist. Sample collected within 6-10 days of illness onset may not have detectable antibodies and so Real Time PCR and antibody testing on a convalescent sample becomes important. For patients with positive IgM antibodies, further neutralizing antibody identification should be performed [26]. In severe cases, conventional PCR or real time PCR, histopathological investigations and virus culture. If necessary, brain tissue sample samples are used for examination and testing for the presence of the virus [27]. Tissue is prepared using staining techniques and observe under an electron microscope [28].

## ETIOLOGY/CAUSES OF VIRAL AES

People recovering from serious cases may have complications ranging from fatigue and trouble concentrating to tremors and personality changes [27]. Life-threatening emergency, requiring prompt intervention. Physical finding is Also observed such as Vital signs and general trauma examination, Neurologic examination, particularly for focal findings [29]. The evolution of the clinical etiology is depending on the virus, the age, and the immune status of the patient as shown in Figure 2.

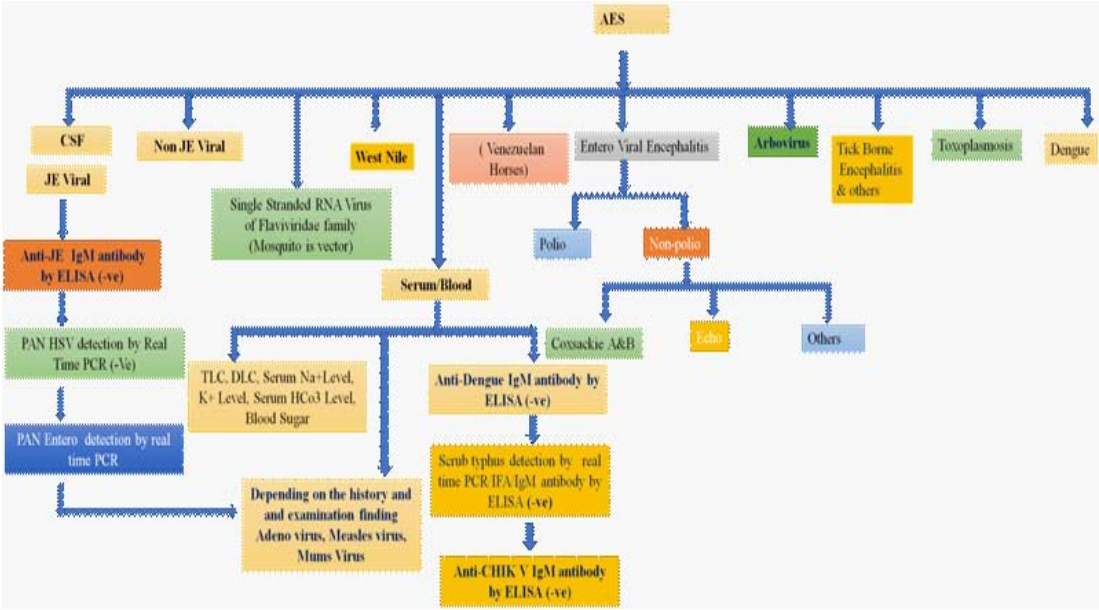


**Figure 2:** Representation of Etiology of AES.

## TREATMENT

Specific treatment must be targeted to the suspected or identified aetiological agent [28]. Antiviral therapy acyclovir is an analogue of 2'-deoxyguanosine and is selectively inhibits viral replication [27]. It exerts its antiviral effect after being metabolised to acyclovir triphosphate [26]. The standard dose of acyclovir for HSE is 10mg/kg three times daily (30mg/kg/day) for 14 days [28]. The dose for neonatal HSE is 60mg/kg/day. The duration of treatment is 21 days for immunosuppressed patients. Acyclovir is effective against encephalitis due to HSV-1, HSV-2, and VZV [29]. Acyclovir is not completely innocuous and can precipitate a toxic encephalopathy that can confound the diagnosis of acute encephalitis if this has not been made before the treatment was initiated [30]. Although acyclovir resistance has been reported in mucocutaneous HSV among AIDS patients, 44 the development of acyclovir resistance in HSV has not yet been reported and it is only a theoretical possibility at present [27].

The clinical response of cytomegalovirus encephalitis to antiviral drugs is not known and anecdotal experience suggests it is not dramatic [23]. Acyclovir is ineffective in cytomegalovirus encephalitis. Combination therapy with ganciclovir (5mg/kg intravenously twice daily) with or without foscarnet (60mg/kg every eight hours or 90mg/kg every 12 hours) is currently recommended [30].

## MANAGEMENT OF ACUTE ENCEPHALITIS SYNDROME

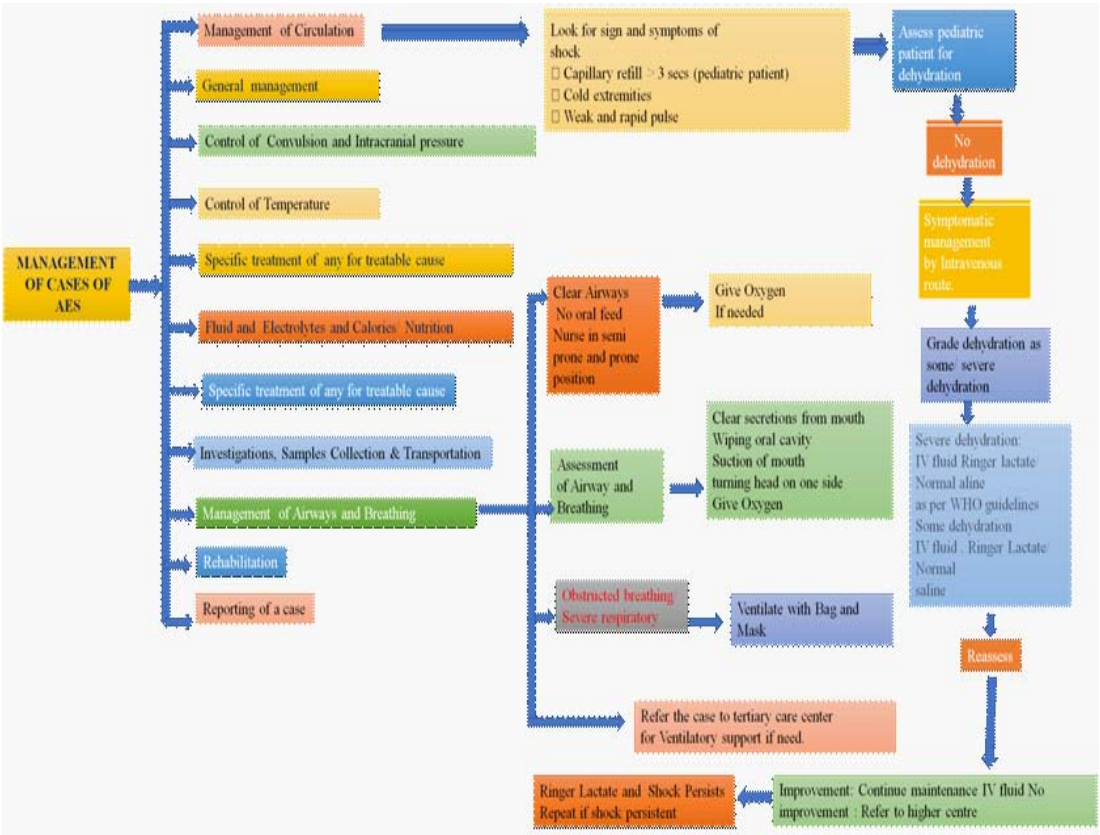


**Figure 3:** Schismatic representation of Management of cases of AES.

Management of Acute Encephalitis Syndrome including to reduce severe morbidity and mortality are shown in Figure 3. It is important to identify early warning signs and refer patients to health facility and educate the health workers about the first line if management at the grassroots level [10]. All cases of acute encephalitis must be hospitalized and should have access to intensive care unit equipped with mechanical ventilators [11]. Isolation for patients with community acquired acute infective encephalitis is not required; rabies encephalitis, however, is an exception [15]. Consideration of isolation should also be given for severely immune suppressed patients, patients with an exanthemata's encephalitis, and those with a potentially contagious viral haemorrhagic fever [18].

## EMERGENT ISSUES OF ACUTE ENCEPHALITIS SYNDROME

In spite of a major economic and epidemiological transitions being underway, infectious diseases continue to remain a major public health problem such as endemic diseases, recent epidemics of emerging infections [21]. While existing environmental, climatic and socio-economic

factors contribute to the risk, the impact can be worse with weak health systems, inadequate resources and poor preparedness and response mechanisms [24]. Neurologists are often consulted or directly care for patients with encephalitis admitted to the hospital and must be able to discriminate between encephalitis and the many conditions that mimic it [28]. Moreover, neurologists must be familiar with the myriad causes of encephalitis in order to develop a practical approach to diagnostic testing and treatment [30].

An understanding of recent advances in management, particularly with respect to autoimmune etiology and critical care approaches, is equally important [18]. Here, we summarize a general approach to the care of adult patients with encephalitis [11]. The diagnostic approach provided above may require days to weeks to ascertain a specific etiologic basis for treatment [28]. At the time of presentation, it is important to consider empiric management for common aetiologies of encephalitis [25]. No specific therapy is available for most forms of viral encephalitis [23]. Mortality and morbidity may be high and long-term sequelae are known among survivors [13]. The emergence of unusual forms of zoonotic encephalitis has posed an important public health problem [3]. Vaccination and vector control measures are useful preventive strategies in certain arboviral and zoonotic encephalitis [8]. However, we need better antiviral therapy to meet the challenge of acute viral encephalitis more effectively [9].

## COMPLICATIONS AND OUTCOME OF ACUTE VIRAL ENCEPHALITIS

AES typically affects children and young adults [1]. Older adults are affected in epidemics. Dengue haemorrhagic fevercan lead to encephalitis or encephalopathy, transverse myelitis, and mononeuropathy or polyneuropathy similar to that in Guillain-Barre syndrome [20]. The haemorrhagic form may also cause hepatic failure leading to a Reye syndrome–like illness [10]. Enteroviral 71 encephalitis has a high mortality and can present with herpangina or enteroviral hand, foot, and mouth disease [13]. Complications include myocarditis and acute flaccid paralysis and chronic meningoencephalitis in patients who are immunocompromised [21]. Mumps encephalitis typically starts 3-10 days after parotitis and usually resolves without sequelae, except for occasional hydrocephalus due to ependymal cell involvement [24]. Rabies virus usually incubates for 20-60 days but is capable of incubating for years [29]. Hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion **(SIADH)** may be frequent in St Louis encephalitis [22]. Dehydration, respiratory complications, nosocomial infections, and decubitus ulcers may also occur [19]. Focal neurologic deficits (eg, opisthotonos, pareses, tremors, ataxia, hypotonia, diplopia), accentuated reflexes, and extensor plantar responses may be observed [20]. Abnormal movements and, rarely, tremor may be seen [7]. Increased intracranial pressure **(ICP)** can also lead to papilledema and cranial nerve VI palsy [6]. JE can cause marked extrapyramidal manifestations, tremor, choreoathetosis, head nodding, and rigidity [24]. Flaccid paralysis, especially involving the lower extremities, has been described as being due to damage to the anterior horn cells [3]. Parkinsonism can be a sequela of JE, and von Economo encephalitis

(encephalitis lethargica) is considered to be a sequela of influenza encephalitis [25]. Enterovirus 71 can cause rhombencephalitis with myoclonus, tremor, ataxia, cranial nerve involvement, neurogenic pulmonary edema, and coma [20]. Nipah virus, AES encephalitis presentation, produces cerebellar and brainstem signs, as well as segmental myoclonus, significant hypertension, and tachycardia [8,13,23,29].

## CONCLUSIONS

Encephalitis results in considerable morbidity and mortality in the worldwide. The availability of antiviral therapy has led to early initiation of the treatment with substantial improvement in the clinical outcome. Some viral encephalitis may be prevented by immunisation (for example, mumps, measles, rubella, Japanese encephalitis, and rabies). Adequate vector control and environmental sanitation are essential to prevent large outbreaks of arboviral encephalitis. Cluster outbreaks of emergence of zoonotic encephalitis continue should be monitor regularly to signal an important public health principle that any new outbreaks of unusual and fatal diseases in animals may herald related events, maybe new infections, in humans.

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