Changing Spectrum of Acute Encephalitis Syndrome in India and a Syndromic Approach

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Abstract

Acute encephalitis syndrome (AES) refers to an acute onset of fever and clinical neurological manifestation that includes mental confusion, disorientation, delirium, or coma, which may occur because of infectious or non-infectious causes. Cerebrospinal fluid (CSF) pleocytosis generally favors infectious etiology, and a normal CSF favors an encephalopathy or non-infectious AES. Among the infectious AES, viral, bacterial, rickettsial, fungal, and parasitic causes are the commonest. Geographical and seasonal clustering and other epidemiological characteristics are important in clinical decision making. Clinical markers like eschar, skin rash, myalgia, hepatosplenomegaly, thrombocytopenia, liver and kidney dysfunction, elevated serum CK, fronto-temporal or thalamic involvement on MRI, and anterior horn cell involvement are invaluable clues for the etiological diagnosis. Categorizing the AES cases into neurologic [Herpes simplex encephalitis (HSE), Japanese encephalitis (JE), and West Nile encephalitis (WNE)] and systemic (scrub typhus, malaria, dengue, and Chikungunya) helps in rational utilization of diagnostic and management resources. In neurological AES, cranial CT/MRI revealing frontotemporal lesion is consistent with HSE, and thalamic and basal ganglia lesions are consistent with JE. Cerebrospinal fluid nucleic acid detection test or IgM antibody for JE and HSE are confirmatory. Presence of frontotemporal involvement on MRI indicates acyclovir treatment pending virological confirmation. In systemic AES, CT/MRI, PCR for HSE and JE, and acyclovir therapy may not be useful, rather treatable etiologies such as malaria, scrub typhus, and leptospirosis should be looked for. If smear or antigen for malaria is positive, should receive antimalarial, if negative doxycycline and ceftriaxone should be started pending serological confirmation of scrub typhus, leptospira, or dengue. A syndromic approach of AES based on the prevalent infection in a geographical region may be developed, which may be cost-effective.

Keywords: Dengue, encephalitis, Japanese encephalitis, herpes simplex encephalitis, malaria, scrub typhus

Introduction

World Health Organization (WHO) defines acute encephalitis syndrome (AES) as an illness in a person of any age at any time of year characterized by acute onset of fever with alternation in consciousness ranging from stupor to coma and/or new onset convulsion excluding simple febrile seizure.[1] This definition has been used for surveillance of Japanese encephalitis (JE). In 2013, International Encephalitis Consortium (IEC) has provided a consensus definition for presumed infectious or autoimmune encephalitis.[2] This definition includes the following:

1. **Major criteria**: Neurological dysfunction manifesting with altered mental status for more than 24 hours without an alternative cause.
2. **Minor criteria**
    1. Fever >38°C
    2. New focal neurological findings.
    3. Cerebrospinal fluid (CSF) pleocytosis >5 cells/mm^3
    4. Cranial imaging showing brain parenchymal changes
    5. Electroencephalography findings consistent with encephalitis.

Definite AES

Definite AES is diagnosed if there is microbiological evidence of organism, laboratory evidences of autoimmune encephalitis, or pathological changes on biopsy.

Probable or confirmed AES

Presence of major criteria with 3 or more minor criteria are considered as probable or confirmed AES, and presence of major and two minor criteria as possible AES.[2]

Both WHO and IEC probable/possible AES definition do not differentiate between non-infectious and infectious etiologies. Among the infectious AES, this definition does not give clue to the different etiologies of AES. The viral, bacterial, parasitic, fungal, and rickettsial infections may result in AES and are presented in Table 1, and non-infectious causes are mentioned in Table 2.

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Differentiating Infectious and Non-Infectious AES

Both infectious and non-infectious encephalitis may be present in an AES patient, e.g., a patient with viral encephalitis may have associated metabolic abnormalities, e.g., hyponatremia, liver dysfunction, or kidney dysfunction. Metabolic alteration and toxic etiologies result in encephalopathy, whereas viral, bacterial, or fungal infection results in encephalitis. The clinical features are somewhat similar, and the difference between encephalopathy and encephalitis is based on CSF findings. CSF has high protein and cells in encephalitis, whereas it is normal in encephalopathy. Fever, focal seizure, and focal signs are more common in encephalitis compared to encephalopathy though there may be occasional exceptions [Table 3]. In a geographical region, the etiology of AES changes over time due to invasion of a new organism and control of existing encephalitis. Herpes simplex encephalitis is a sporadic treatable viral encephalitis; therefore, it is important to keep high index of suspicion. Certain infections are common in Indian subcontinent and present as AES such as Japanese encephalitis (JE), dengue, chikungunya (CHIK), malaria, and rickettsial diseases and are briefly presented in the following section.

The cause of AES is not always possible to establish even after detailed investigation. The most common sporadic infectious encephalitis is herpes simplex virus encephalitis (HSVE).[3,4] The California Encephalitis Project enrolled 1570 patients with suspected encephalitis over a 7-year period (1998–2005). A core battery of tests for 16 agents was performed. In addition, selective testing for other agents was performed on the basis of clinical and epidemiologic features. Only 16% of patients had a confirmed or probable etiologic agent identified, of which 69% were viral, 20% bacterial, 7% prion, 3% parasitic, and 1% fungal. An additional 13% had possible etiologies identified. In this group, there were many agents not hitherto implicated as a cause of encephalitis. Autoimmune etiology was found in 8%, which made it more common than any single infectious agent. The remaining 63% had no etiology identified.[3]

Based on various surveillance reports of AES in India, 3 phases have been reported:

1. Period before 1975 when a few cases with JE etiology were identified.
2. Between 1975 and 1999 when more JEV cases were reported with frequent outbreaks that resulted in the development of JE endemic regions near the Gangetic plains and in parts of Deccan and Tamil Nadu.
3. Between 2000 and 2010, a dramatic change was observed in the AES with a rise in non-JE outbreaks such as Chandipura virus (CHPV), Nipah virus (NiV), and other enteroviruses.[5]

In India, JE is probably the commonest and occurs in epidemics, especially in the south and east of India. In Gorakhpur, Uttar Pradesh, JEV was reported to be the main agent responsible for AES. The proportion of AES caused by JE declined in recent years, but AES itself did not decrease.[6] Over the last 5 to 7 years, dengue and scrub typhus (caused by *Orientia tsutsugamushi*) meningoencephalitis are considered as an important cause of AES in this region.[7-10] Nipah virus, a paramyxovirus that causes severe encephalitis in Malaysian pig farmers, resulted an outbreak of encephalitis in Kerela, India.[11,12] Dengue infection was known to produce neurologic manifestations including encephalopathy, and also recognized recently as a cause of viral encephalitis due to actual viral invasion of the brain.[13,14] In Muzaffarpur, Bihar, outbreaks of acute neurologic illness occurred which is regarded to be due to toxins, hypoglycemia, and methylene

Table 1: Aetiology of infective acute encephalitis syndrome

Viral
Arbovirus: Japanese encephalitis, St. Louis encephalitis, West Nile encephalitis, Murray valley encephalitis, dengue, eastern and western equine encephalitis, Venezuelan equine encephalitis
Buniya virus: Californian encephalitis
Reovirus: Colorado tick fever encephalitis.
Herpes: Herpes simplex virus I and Herpes simplex virus II, Varicella zoster, Epstein-Barr, Cytomegalo, Human herpes virus 6, B- virus.
Myxo and Paramyxo: Influenza, measles, mumps, parainfluenza, Nipah virus.
Adeno, Parvo and Rhabdovirus.
Rickettsial: Endemic and epidemic typhus, Rocky Mountain spotted fever, scrub typhus, etc.
Bacterial: Pyogenic meningitis, tuberculous meningitis, listeria, mycoplasma, leptospira, lyme, borellia, legionella, salmonella, bartonella
Fungal: Cryptococcal, candida, coccidioidomycosis etc.
Protozoal: Naegleria; Acanthamoeba, Toxoplasma.
Parasitic: Malaria, cysticercosis, toxoplasma

Table 2: Non-infectious causes of acute encephalitic syndrome

Noninfectious inflammation of brain: Acute disseminated encephalomyelitis, autoimmune encephalitis, vasculitis, Behcet's disease.
Metabolic toxic encephalopathy: Electrolyte imbalance, Reye's syndrome, hepatic coma, uremic coma, diabetic ketoacidosis, hyperosmolar coma, septic encephalopathy, toxins (lead, mercury etc.).
Mitochondrial encephalopathy
Drug induced

Table 3: Differentiating features between encephalitis and encephalopathy

Parameters	Encephalopathy	Encephalitis
Fever	Uncommon	Common
Headache	Uncommon	Common
Focal sign	Absent	May present
Seizure	Generalized	Focal/generalized
CSF pleocytosis	Uncommon	Common
EEG	Diffuse slowing	Diffuse/focal
Cranial MRI/CT	Normal	Abnormal

CSF=cerebrospinal fluid; CT + computerized CT scan; EEG=electroencephalography; MRI=magnetic resonance imaging.

cyclopropylglycine present in litchi fruit.[15] = A recent study from north India after JEV immunization, the etiology of infectious encephalitis revealed JE in 8.3%, dengue in 7.8%, enterovirus in 0.4%, HSV in 0.8%, varicella zoster in 0.4%, scrub typhus meningoencephalitis in 31.8%, *Haemophilus influenza* in 0.97%, and *Streptococcus pneumoniae* in 0.94%.[16] These studies illustrate the diversity of underlying etiology and higher frequency of infection as an etiology of AES in India. Immune-mediated autoimmune encephalitides are rare in Indian subcontinent, and it rarely presents as AES. Autoimmune encephalitis generally presents with a subacute or chronic course associated with psychiatric, seizure, movement disorders, and altered sensorium;[17] hence, it will not be discussed.

Search strategy

The PubMed articles in the last 10 years were searched with terms Acute encephalitis syndrome, Encephalitis, Encephalitis in India, and syndromic approach. Selected articles with clinical features and approach to diagnosis and management are included in this review.

Herpes Simplex Encephalitis

Herpes simplex encephalitis (HSE) occurs due to two closely related human viruses—HSV-1 an HSV-2, which produce infection only in humans. HSV-2 virus generally causes aseptic meningitis and rarely encephalitis. Herpes simplex virus is widely prevalent and nearly half the people have antibodies against HSV-1 by 15 years of age and 90% by adulthood. Herpes virus remains dormant in humans. Herpes simplex encephalitis is a rare complication of HSV-1 infection and is the commonest sporadic focal encephalitis in the world. During primary infection, HSV-1 is transported to sensory fibers by retrograde transport and lies dormant in sensory ganglia. HSV-1 has been isolated from explants of trigeminal ganglia on autopsy.[18] There is spontaneous reactivation of herpes labialis in 20-40% of population following stress, fever, or ultra-violet exposure.

Herpes simplex encephalitis has a distinctive clinical picture because of typical localization in orbitofrontal and medial temporal cortex. The localization of HSV-1 to limbic cortex is attributed to cytochemical characteristics of brain and spread of virus from cell to cell from base of the brain to anterior and middle cranial fossa.[19] The pathological changes in HSE are inflammation, necrosis, and inclusion bodies. Immunofluorescence and electron microscopy studies have revealed that the herpes simplex virus is localized in the olfactory nerve ipsilateral to the predominantly affected temporal lobe.[20] The infection of olfactory bulb, however, is not uniformly found in the patents dying of HSE; however, HSE in adults may as well be due to reactivation of HSV in trigeminal ganglia. The meninges of anterior and middle cranial fossa are innervated by trigeminal nerve and the mechanism of spread of HSV has been confirmed in experimental studies in which selective retrograde spread of HSV occurs along the V3 division of trigeminal nerve following inoculation of tooth by HSV resulting in ipsilateral temporal lobe infection.[21] In a PCR study, HSV DNA was detected in 14 out of 40 brains; moreover, topographic analysis revealed localization of HSV to medulla, olfactory bulb, pons, gyrus rectus, and hippocampus.[22]

Herpes simplex encephalitis has no seasonal variation or gender preference. It is primarily a disease of adults but has a bimodal distribution, about one third patients are below 20 years of age and 50% are older than 50 years. This distribution may be due to primary infection in the young age and reactivation in the elderly.

Clinical features

Herpes simplex encephalitis has an insidious to a fulminant course. About 30-60% patients have an upper respiratory or gastrointestinal disturbance prior to encephalitis. Fever is almost always present in the range of 40-41°C. Headache is a common and an early symptom. The clinical picture is determined by frontotemporal involvement leading to personality change and behavioral alterations. The typical clinical findings include fear, hallucination, and anosmia. Seizures occur in 70% of patients, which are often focal. Early seizures occur in 40% of patients.[23] Focal seizures and focal neurological symptoms occur in 75% patients, hemiparesis in one-third, and aphasia, superior quadrantaonopia, and paresthesia may also occur. Status epilepticus is more common in HSE compared to Japanese encephalitis (75% vs. 54%).[24] An opercular syndrome characterized by weakness in pharyngeal, laryngeal, tongue, and masticatory muscles may also occur. Rapidly developing coma may occur in some patients with few or no focal neurological signs. Some patients may have atypical clinical picture, which can be diagnosed by polymerase chain reaction (PCR) studies only.[25]

Diagnosis

Herpes simplex encephalitis is diagnosed by detecting HSV nucleic acid in CSF using PCR in the first week, and IgM ELISA in the second week onward if PCR is negative. Cerebrospinal fluid reveals variable pleocytosis (100-200/mm^3) which is mainly mononuclear but may be polymorphonuclear in the early stage. CSF protein is elevated (upto 528 mg/dl) and glucose may be low or normal. The sensitivity of PCR in the diagnosis of HSE is 78%–98%. In a study on 54 biopsy proven HSV, CSF PCR was positive in all 18 in whom the CSF was collected before biopsy.[10] The diagnostic yield of CSF PCR may fall to 21% after 21 days of acyclovir therapy.[26] False negative (initially negative and later positive) PCR has been reported in first 72 hours, suggesting that PCR may not be sensitive in the very early stage and should not deter the acyclovir treatment if an alternative diagnosis is not available. PCR remains positive for 2 weeks following onset of illness but its sensitivity decreases rapidly. CSF PCR may be negative if there is traumatic CSF tap, examined too late, after treatment or there is a faulty technique.

Electroencephalography (EEG) may provide supporting evidence of diagnosis by focal or generalized slowing, spike

or sharp waves in temporal lobe distribution, superimposed on slow background activity, or periodic lateralized epileptiform discharges have been noted in 90% cases. However, EEG may be normal in early stage and abnormalities persist usually for 1-2 weeks.[27]

Cranial CT or preferably MRI scan provides valuable information, suggesting the diagnosis of HSE. MRI reveals T2 hyper-intensity in basi-frontal and medial temporal regions [Figure 1a]. MRI is more sensitive and almost always abnormal in HSE. Fluid attenuated inversion recovery (FLAIR) sequence and diffusion weighted imaging are more sensitive in early stage of HSE.[28,29] In immune-compromised patients, the signal changes may extend beyond the limbic cortex. MRI also helps in excluding others etiologies, which can lead to similar clinical syndromes such as tuberculous, pyogenic, and fungal abscess.

Treatment

Herpes simplex encephalitis has a specific antiviral therapy. Acyclovir is administered in a dose of 10 mg/kg IV 8 hourly 2-3 weeks. Neonates and immunocompromised patients need 3 weeks acyclovir therapy. Treatment of seizure, status epilepticus, and raised intracranial pressure is similar in all encephalitis. Status epilepticus may be refractory in one-third patients or even be super refractory.[30] One must take care of hydration to avoid crystalluria and renal impairment in acyclovir treatment. Corticosteroids are not proven to be useful.

Japanese encephalitis

Japanese encephalitis virus (JEV) was first reported from Japan, Tokyo in 1933, and since then there has been an increase in number and area of distribution of JE. Japanese encephalitis primarily reported from the Asian countries including Japan, China, Taiwan, Korea, Burma, Bangladesh, Sri Lanka, Nepal, Thailand, Vietnam, and India. In many parts of India, low-level transmission occurs round the year, but epidemics occur mainly during post-monsoon period. In 1970s, patients with JE were reported from south India, and from 1973 onward outbreaks were reported from West Bengal,[31] Bihar,[32] Uttar Pradesh,[33] Assam, Andhra Pradesh, and Karnataka.[34] Japanese encephalitis is usually a disease of rural areas affecting population of lower socio-economic status. The ratio of clinical to subclinical infection is 1:1000. Japanese encephalitis epidemics are related to rainfall, flood, paddy cultivation, pig farming, and mosquito breeding. JE is a zoonotic disease and is transmitted by JEV-infected female *Culex* mosquito bite and human are the dead-end host. Pigs are amplifying host and JEV life cycle is maintained by pig-mosquito-pig cycle. *Culex tritaeniorhynchus* is the most efficient vector for JEV transmission. The incubation period of JEV in human is 6 to 16 days, following which either viremia subsides or there is involvement of target organs resulting in clinical symptoms. In the endemic region, children are commonly affected because adults are usually spared because of herd immunity. About 80% patients with JE in South India are below the age of 15 years, whereas in Northeast India, less than 50% patient are children.[35-37]

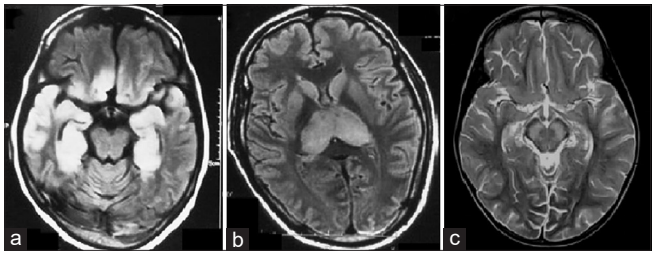

Figure 1: Cranial MRI changes in herpes simplex encephalitis and Japanese encephalitis. (a) FLAIR sequence shows bilateral temporal lobe and right basi-frontal hyper intensity in a patient with herpes simplex encephalitis. (b) FLAIR sequence in a patient with Japanese encephalitis shows bilateral thalamic and basal ganglia involvement. (c) FLAIR sequence axial section of a patient with West Nile encephalitis showing the involvement of substantia nigra

Clinical features

The clinical course of JE may be divided into three stages—prodromal, encephalitis, and convalescent phases. The prodromal stage is characterized by fever, headache, nausea, vomiting, and anorexia, which last for 3-4 days in 75%, and many may recover without progressing to encephalitic stage. Fever may reach up to 40°C and last for a week. The encephalitic stage is characterized by headache, altered sensorium, behavioral abnormality, seizures, and focal deficits, and severely affected patients may lapse into deep coma with extensor posturing. Seizures occur in less than 10% of adults and in 60-80% of children, which may be focal or secondary generalized.[38-40] In a study on 148 patients with AES, seizures were present in 42.6% and were the most common in HSE in 75% and JE in 54%. Young age, depth of coma, and cortical involvement in MRI predicted seizures.[25] Status epilepticus is common in CNS infections, and about one-third patients with viral encephalitis may be refractory to antiepileptic drugs.[30] The patients may have focal signs such as hemiplegia, quadriplegia, lower motor neuron signs (focal reflex loss and wasting), and rarely cerebellar signs. Cranial nerve palsy is rare. Tremulous eye movements have been described in JE.[41]

Japanese encephalitis is an encephalomyelitis and anterior horn cell involvement simulates polio myelitis-like illness. In the acute stage, there is focal reflex loss and later there may be focal wasting with neurogenic changes on EMG.[42] In the convalescent stage, as the patients recover from coma, a wide spectrum of movement disorders including parkinsonian features, choreoathetosis, tremor, and dystonia have been reported. In a study of 209 patients with encephalitis, 74 (35.4%) had movement disorders; 67.6% in JE, 51.2% in miscellaneous, and 11.3% in dengue. The dystonia in children with JE is more severe and protracted and has poor outcome compared to parkinsonian features only.[43,44]

Investigations

Cerebrospinal fluid reveals pleocytosis (10-200/mm^3), elevated proteins, and normal glucose. The diagnosis of JE

is confirmed by IgM ELISA or reverse transcriptase PCR in CSF. In a suspected case of JE in the first week, the sensitivity of PCR is about 25%,[3,45] whereas IgM ELISA is positive in the second week in more than 80% patients. Cranial imaging characteristically reveals thalamic, basal ganglia, and brainstem involvement. MRI is more sensitive than CT scan. In a comparative study of CT and MRI changes in JE, CT scan was abnormal in 55.3% and MRI in all the patients, and revealed thalamic involvement in 94%, basal ganglia in 35%, mid-brain in 58%, pons in 26%, and cerebellum and cerebral cortex in 19% patients each [Figure 1b].[43] Temporal lobe involvement in JE has been reported but is associated with thalamic or basal ganglia involvement.[44,45] Fluid attenuation inversion recovery sequence is more sensitive compared to T2 sequence and revealed additional abnormalities in 12.6%.[28]

West Nile Virus Encephalitis

West Nile virus (WNV) is an arthropod-born single-stranded RNA virus belonging to family *flaviviridae*. Since it was first isolated in West Nile district of Uganda in 1937, it has been named as WNV. West Nile virus is prevalent in Africa, America, Middle East, and Asia. West Nile virus spreads by the bite of *Culex* mosquitoes and is maintained between bird-mosquito- bird cycle. The activity of WNV in India was noted in 1952[46] and has been reported from almost all the parts of India.[47]

After an incubation period of 2-15 days, WNV infection may result in mild or self-limiting illness in more than 80% subjects. In remaining 20%, there may be fever, headache, fatigue, meningitis, myalgia, weakness, gastro-intestinal symptoms, and morbiliform non-pruritic skin rash on trunk and extremity sparing palms and soles. The neurological illness occurs in less than 1% patients and manifests with meningitis, encephalitis, and acute flaccid paralysis simulating poliomyelitis. The patients may have neck stiffness, altered sensorium, fever, myoclonus, and parkinsonian features. There may be cranial nerve palsy, myelitis, polyradiculopathy, optic neuritis, or seizures. West Nile virus infection may be more severe in elderly (>55 years) and immune-compromised patients. Rarely patients may have pancreatitis, myocarditis, or hepatic involvement.[46] The patients usually have pure motor flaccid areflexic weakness which is attributed to anterior horn cell involvement. There are reports of Guillain-Barre syndrome, axonal type of neuropathy, polyradiculopathy, and plexopathy in WNV infection. Spinal cord involvement in West Nile encephalitis may be more disabling than the encephalitis.[48]

The diagnosis of WNV encephalitis is based on detection of IgM antibody in serum or CSF using IgM antibody capture ELISA. Presence of IgM antibody in CSF suggests neuro-invasion. IgM antibody appears by the end of 1st week of infection and persists for a long time. If a patient has received JE or dengue vaccine, or had dengue, JE or St Louis encephalitis, there may be a false positive ELISA result. Nucleic acid amplification test using reverse transcriptase PCR is useful in the diagnosis of WNV infection. In an area endemic for JE, dengue and WNV infection, multiplex PCR is also helpful. CSF shows lymphocytic pleocytosis (<150 cells/mm3), elevated protein (<500 mg/dl), and normal glucose.

Imaging

Cranial MRI may be normal but may reveal FLAIR hyper-intensity in brain stem (pons, mid brain), thalamus, basal ganglia, or spinal cord. Substantia nigra involvement has been shown in Figure 1c**.**

Treatment

There is no specific antiviral treatment; patients are treated symptomatically.

Dengue

Dengue virus is a RNA virus belonged to the *Flaviviridae* family and occurs following bite of infected *Aedes aegypti* mosquito. Traditionally, dengue has 3 modes of presentation—dengue fever, dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS), which has been re-categorized in 2009 by WHO as follows[49]:

1. Dengue without warning signs.
2. Dengue with warning signs.
3. Severe dengue.

Dengue fever is a self-limiting disease of 2-7 days which manifests with fever, headache, myalgia, arthralgia, conjunctival congestion, retro-orbital pain, nausea, and vomiting. There may be skin rash on the 3rd or 4th day [Figure 2a and 2b]. Dengue hemorrhagic fever manifests with additional features of hemorrhagic complication such as gastric hemorrhage or mucosal bleeding, thrombocytopenia, and evidence of plasma leakage (interstitial edema, pulmonary oedema, ascites, pleural effusion, and pericardial effusion). Dengue shock syndrome is similar to DHF with additional features of

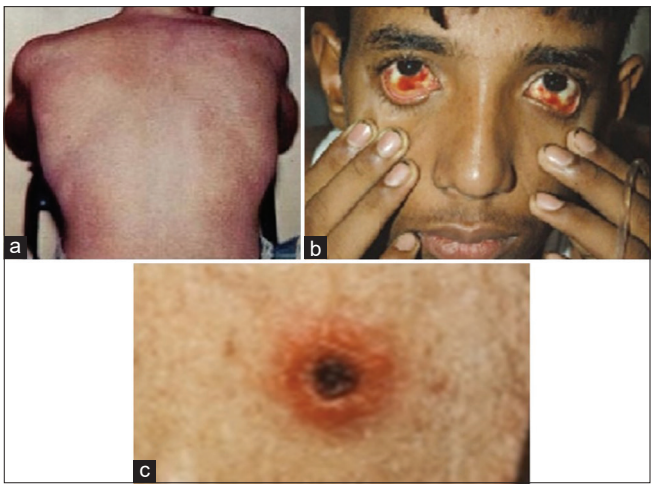

Figure 2: A&B Clinical photograph in a patient with dengue showing (a) maculopapular rash and (b) sub-conjunctival hemorrhage. (c) Clinical photograph shows eschar in a patient with scrub typhus. There is central necrotic scab with perilesional hyperaemia

circulatory failure and shock. In DSS, hypotension and plasma leakage lead to multi-organ dysfunction. The patients with DSS need monitoring in intensive care unit and correction of hypovolemia. If these patients are maintained for 48 hours, they generally have quick and full recovery. The patients with DSS need close monitoring because the interval between warning signs and development of shock may be only few hours, and for cardiac failure and cardiac arrest only a few minutes. Secondary dengue infection may be associated with DSS due to antibody-dependent immune enhancement.[48] WHO classification can identify severe dengue in 92.1% compared to 39% by traditional classification; the specificity, however, remains the same (87.5% Vs 75%).[49,50]

Pathophysiology

Thrombocytopenia, coagulopathy, and increased vascular permeability are responsible for the complications of dengue**.** Vascular leak in DHF/DSS is attributed to secondary heterotypic DENV infection. Infants born to mothers infected with DENV can also develop DHF/DSS following primary infection which is attributed to antibody-dependent enhancement.[51,52] Changes in vascular permeability in dengue are also attributed to complement activation product, which are present during acute phase of DENV infection.[52,54] DENV NS1 adheres to endothelial cells rendering these vulnerable to complement mediated injury or by direct attack by anti-NS1.[55,56] In secondary heterotypic DENV infection, T cells, monocytes, and macrophages result in the release of cytokines and chemokines, which may lead to cytokine storm.[56] DENV may also lead to direct endothelial damage (viral protein toxicosis).[57]

Neurological manifestation

Neurological signs in dengue infection were first reported in 1976 as atypical symptoms of dengue infection; their incidence rates varied from 0.5 to 20%.[57,58] Initially dengue was considered as non-neurotrophic virus. Increasing number of neurological manifestations have been reported because of direct neuro-invasion.[59,60] Miagostovich *et al*. detected the dengue virus in the central nervous system (CNS) by assessing viral proteins, ribonucleic acid (RNA), and immunoglobulins.[13,61,62] Disruption of blood brain barrier in dengue infection leading to entry of dengue virus in brain was also reported in experimental studies.[63] The neurological involvement in dengue can be discussed as dengue encephalopathy, dengue encephalitis, immune-mediated syndromes, and muscle involvement.

A. **Dengue encephalopathy:** Dengue encephalopathy is the commonest neurological manifestation of DENV infection, presenting with altered sensorium, behavioral abnormality, and seizures. Dengue encephalopathy can occur in DF, DHF, and DSS. Dengue encephalopathy is attributed to hypoxia, shock, cerebral edema, electrolyte imbalance, renal or hepatic failure, or because of systemic or intracerebral hemorrhage. These patients generally have normal CSF which is consistent with dengue encephalopathy. In a study from Thailand, out of 1493 children with dengue, 80 (5%) had neurological manifestations; 50% of them had dengue encephalopathy. Autopsy study in one of the four patients who died revealed histopathological evidence of encephalitis.[64,65] EEG generally reveals slowing but in the patients with seizures or status epilepticus it may reveal epileptiform discharges or periodic lateralized epileptiform discharges.[40,66]

B. **Dengue encephalitis**: The clinical manifestations of dengue encephalitis are similar to dengue encephalopathy. Seizures may occur in up to half the patients with dengue encephalitis Dengue is the cause of AES in South East Asia in 5-20%.[67,68] In a study from Vietnam, 21 patients had neurological complications and 9 of these were classified as dengue encephalitis based on CSF PCR or DENV isolation.[69] In another study on 17 dengue patients having neurological complications, 11 patients had altered sensorium and 6 had acute motor weakness. Eight out of 11 patients with altered sensorium had CSF pleocytosis suggesting dengue encephalitis. Seizures were present in three and myoclonus in one patient. Three of these patients died, 11 had poor, 2 partial, and the remaining had complete recovery.[70] Autopsy studies on fatal cases of dengue have revealed positive PCR or dengue antigen on immunostaining. There is, however, paucity of histopathological evidence of encephalitis raising doubts about direct viral CNS injury by some authors. [71-72] In recent autopsy studies on dengue patients, microscopic examination of brain revealed cerebral edema, inflammation, and hemorrhage.[73,74] The diagnosis of dengue encephalitis is based on demonstration of growth of DENV in the damaged CNS for which there is limited evidence. Direct inoculation of DENV into the brain results in minimal lesions such as scattered perivascular cuff, mononuclear infiltration, and glial nodules, but there is no evidence of neuronal dysfunction or necrosis.[75] Cranial MRI or CT scan in dengue is usually normal but may reveal nonspecific abnormality especially in the patients with hypotension, shock, or bleeding diathesis.[76,77] Co-infection with Japanese encephalitis also may result in MRI abnormality. In a study on MRI changes in 21 dengue patients, thalamic or basal ganglia lesion was seen in 3, focal cerebral lesion in 3, white matter abnormality in 2, and meningeal enhancement in 3 patients. Seven of these patients had CSF pleocytosis.[77] Dengue encephalitis patients also have systemic features making it difficult to differentiate between encephalopathy and encephalitis, especially when CSF is not possible because of coagulopathy or thrombocytopenia. However, the differentiation between encephalopathy and encephalitis is not clinically important as the management of the two conditions is similar.

C. **Dengue immune-mediated neurological syndromes:** Immune-mediated neurological syndromes are a rare complication of DENV infection. The immune-mediated syndromes manifest after 1-2 weeks of infection. The neurological manifestations are attributed to the mechanism of molecular mimicry. The immune-mediated

syndrome in dengue infection includes Guillain-Barre syndrome, acute disseminated encephalomyelitis, transverse myelitis, neuromyelitis optica and peripheral mononeuropathy, and plexopathy. There are reports of Miller-Fisher syndrome and mononeuropathy affecting 6th, 7th, and long thoracic nerves. The association of Guillain-Barre syndrome with dengue infection has been reported in epidemiological studies or in cohort of Guillain-Barre syndrome evaluated for DENV infection.[78,79] The treatment of post-infectious dengue immune-mediated syndrome is similar to that of any immune-mediated syndrome. Ischemic and hemorrhagic strokes are extremely rare in dengue. There are isolated reports of subdural hematoma or parenchymal hemorrhage. Intracerebral hemorrhage in dengue may be due to severe thrombocytopenia or coagulopathy. Isolated intracerebral hemorrhage or subarachnoid should therefore be evaluated for vascular malformation.[80]

D. **Dengue-associated transient muscle dysfunction**: Myalgia is common in dengue infection. Muscle weakness in dengue although was earlier reported as myositis,[81,82] but it is more appropriate to call it as dengue-associated transient muscle dysfunction (DATMD) because of lack of inflammatory changes and transient nature of muscle involvement. In a study from Saudi Arabia, 101 patients having DF or DHF, myalgia was present in 63%, muscle weakness in 3%, and raised serum CK in 91%.[83] Dengue-associated transient muscle dysfunction is associated with raised serum CK, myalgia, and/or muscle weakness. In a study on 31 patients from India, 16 patients had varying degrees of muscle weakness with high serum CK and 15 had only raised CK. The majority patients have mild to moderate weakness affecting proximal muscles but rarely muscle weakness may be severe and may be associated with respiratory failure. In the majority of patients, serum CK is moderately elevated but may rarely go up to 100,000 IU/L in the patients who have rhabdomyolysis.[82] Dengue may also be associated with myocarditis.[84] The EMG findings in dengue are subtle and non-specific.[85] There is no spontaneous activity and the motor unit potentials are normal to small size. These findings are in contrast to inflammatory myopathy which shows fibrillations, sharp waves, complex repetitive discharges, and short duration polyphasic motor unit potentials. Muscle biopsy in 3 patients with the DATMD revealed interstitial edema and hemorrhage, and there was paucity of inflammatory infiltrates. In patients with DSS, there were occasional myonecrosis, myophagocytosis, and inflammatory cells around necrotic fibers. The patients with DATMD improve completely by 2 weeks.[86] The patients with DATMD may have associated encephalopathy and/or encephalitis. These patients have more severe illness. The role of vascular endothelial growth factors and its receptors have also been evaluated and receptor 2 has been related to hypotension, CK, and coagulopathy.[87]

E. Muscle weakness due to hypokalemia has also been reported with dengue virus infection. In a study of 12 dengue patients with hypokalemic paralysis, there was rapid and complete recovery following potassium supplementation. The severity of hypokalemia was not related to weakness.[88] In a study of 1342 patients with dengue fever from China, 28% had hypokalemia but muscle weakness was not mentioned.[89] The mechanism of hypokalemic paralysis in dengue is attributed to shift of potassium and renal tubular dysfunction leading to high urinary potassium excretion. In a study on 116 patients with dengue aged 5-70 years, 82 had DF, 18 DHF, and 16 DSS. Neurological involvement was present in 92 (79%): encephalopathy in 17 (15%), encephalitis in 22 (19%), transverse myelitis in 1 (1%) and DATMD in 52 (45%) patients. Central nervous system manifestation was commoner in DHF/DSS compared to DF (44% vs 26%). Ten patients with CNS involvement died compared to 1 with DATMD. The patients with CNS involvement had more frequent hyponatremia, renal, or respiratory failure compared to DATMD and had worse outcomes. DENV2 and DENV3 were the commonest serotype but their frequency did not differ between CNS and DATMD groups. DATMD is commoner than CNS involvement in dengue and has a better outcome.[90]

Diagnosis

The diagnosis of dengue infection is based on detection of NS1 antigen by ELISA or nucleic acid by PCR in the early stage and IgM ELISA after 5-7 days. Multiplex PCR may be able to diagnose the four dengue serotypes. Because of thrombocytopenia, there may be difficulty in lumbar puncture and the reliance is on serum sample analysis. The management of severe dengue infection requires ICU admission, fluid management especially to counter increased vascular permeability, management of anemia (including packed RBC). Platelet transfusion is generally not needed unless there is bleeding. Respiratory and renal failure may require mechanical ventilation and renal replacement therapy, respectively.

Chikungunya

Chikungunya (CHIK) is an Arboviral disease which belongs to the alpha virus of *Togaviridae* family. It spreads by *Aedes* mosquitoes. Chikungunya is also a single-stranded RNA virus, 60-70 nm in diameter with a capsule and a phospholipid envelop. There are 3 lineages of CHIK virus—West African, East-Central-South African (ECSA), and Asian. Indian Ocean lineage is a sub-lineage of ECSA.[91] The first outbreak of CHIK in India was reported in Calcutta in 1960,[92] and the virus was isolated in 2005. Chikungunya outbreaks have been reported throughout India.

The majority of patients infected with CHIK show clinical illness and only 3% patients are asymptomatic.[93] The symptoms develop after 2-4 days of mosquito bite. In the active stage, the patient has fever and ocular pain similar to dengue infection.

The clinical differentiating features between CHIK, dengue, and scrub typhus are summarized in Table 4**.** Polyarthralgia including axial pain is typical of CHIK infection. There may be mild mucosal bleeding. In chronic stage, the patients may have polyarthralgia which persist for weeks to years.[94] The neurological manifestations are rare but encephalitis with pupillary abnormality has been reported.[95] Following CHIK infection, various immune-mediated syndromes including Guillain-Barre syndrome, transverse myelitis, and stimulus sensitive myoclonus have been reported.[96,97] In a study on 30 CHIK patients with neurological manifestations, 12 had encephalitis and 12 encephalomyelitis.[98] In another study, 15 patients had encephalitis, 3 had encephalomyelitis, and 2 had optic neuritis.[99] The frequency of neurological complication in CHIK has wide variability ranging from 0.3% in Thailand[97] to 14.6% in South India,[100,101] and 61.7% in hospitalized patients from La Reunion island.[102]

CSF in CHIK infection is usually normal and MRI is ether normal or reveals nonspecific changes. Autopsy studies have shown radiculopathy, brain swelling, and subarachnoid hemorrhage. On microscopy, there was inflammatory infiltrations in periventricular and basal ganglia region, and small foci of demyelination.[103]

Diagnosis

The diagnosis of CHIK is based on detection of viral RNA by RTPCR and IgM antibodies by ELISA. RTPCR is sensitive during viremia phase (0-7 days) and IgM ELISA may persist for months. IgG antibody is detected in convalescent period and persists for a few years.

Scrub Typhus

Scrub typhus (ST) is an arthropod born rickettsial disease. About 1 billion people are at risk of developing scrub typhus in the "Tsutsugamushi triangle," which extends from Japan in the East, Pakistan in the West, and Australia in the south. Scrub typhus is a public health problem in Asia-Pacific area including Korea, Japan, China, Taiwan, India, Indonesia, Thailand, Sri Lanka, and the Philippines.[104] Scrub typhus is transmitted by the bite of trombiculid mite (Chigger). *Tsutsugamushi* is an obligate intracellular bacterium and targets endothelial cell and mononuclear cells for multiplication. Scrub typhus therefore affects highly vascularized organs such as liver, kidney, brain, and lungs manifesting with multi-organ dysfunction, meningoencephalitis, and pneumonia.[105] The neurological findings of ST and spotted fever rickettsiosis are under reported, and it accounts for 17.9% of bacterial infection of CNS and 25% of encephalitis in India.[106]

Table 4: Differentiating points among dengue, Chikungunya, and scrub typhus

Parameters	Dengue	Chikungunya	Scrub typhus
Fever	+	+	+
Rash	3-7 days	1-4 days	Eschar from beginning
Retro-orbital pain	+	-	-
Myalgia	+++	+	++
Polyarthritis	-	+++	-
Tenosynovitis	-	+	-
Hypotension	+	+	-
Thrombocytopenia	+++	+	++
Bleeding	+	-	+

+ present; - =absent

Risk of acquiring ST

Abundance of chiggers of *trombieculoid* mites determines the chance of acquiring ST which in turn determines the prevalence of ST in the region. Scrub typhus cases are especially increased in post-monsoon period and favored by high humidity (60-85%), low temperature (20-30°C), low sunshine, and dense vegetation. Humans acquire ST infection on exposure to chiggers of *trombiculidae* mites during July to November in South East Asia.[107] Risk of ST is higher in farmers, those working in vegetable fields especially harvesting in autumn months. Outdoor activities like resting on grass field, working in short sleeves with bare hands, and defecating or urinating in outdoors while squatting increase the risk of ST.[108]

Clinical findings

The clinical picture of ST ranges from asymptomatic cases to severe illness with a mortality as high as 50% in untreated patients.[5,109] The patients present with fever, headache, cough, abdominal pain, and myalgia. Eschar is typical of ST and is reported in 7-97% patients. Eschar is painless and has a crust of black scab with erythematous hallow and minimal edema, more easily seen in fair than in dark persons [Figure 2c]. Eschar is commonly found in covered areas of the body such as groin, axilla, chest, low back, and buttocks. Detailed examination for eschar increases the diagnostic yield of ST from less than 10% to 55%.[110] Eschar appears few days after the bite before the symptoms appear. There may be seizures, diarrhea, coma, and multi-organ dysfunction: lymphadenopathy, hepatosplenomegaly, tachycardia, and swollen raw muscles. The neurological manifestations include meningitis, encephalitis, myositis, intra-cerebral or subarachnoid hemorrhage, and post-infective demyelination syndromes such as cranial nerve palsy, ataxia, and transverse myelitis.[110,111]

Diagnosis

The diagnosis of ST is favored by eschar (2 points), age above 65 years (2 points), recent history of farm work (1 point), and onset of disease in ST outbreak (2 points). More than 3 points support the diagnosis of ST and less than 3 are unlikely to be due to ST.[107] The features compatible and incompatible with ST are presented in Table 5.

Scrub typhus without eschar in a febrile patient without any localization is termed as acute undifferentiated fever. This illness is indistinguishable from malaria, dengue, other rickettiosis, leptospirosis, and enteric fever.

Table 5: Features compatible for scrub typhus

Compatible	Incompatible
Eschar	Bone pain (dengue)
Regional lymphadenopathy	Bleeding (dengue)
Fever >8 days	Loose stool (enteric fever)
CRP >22 mg/L	WBC <5000/mm^3 (dengue)
ALP/AST >1	Platelet <50000/mm^3 (dengue)
Defervesence in 48-72 hours of treatment	Serum bilirubin >2 mg/dL
	AST >500 U/L (dengue)
	ALT <100 U/L (malaria)
	ALT >500 U/L (hepatitis A)

Laboratory diagnosis

Demonstration of IgM antibodies against ST is the mainstay of ST diagnosis. A fourfold rise in paired sera provides definite evidence. Since paired sera are often not available, a cut off of immunofluorescence assay (IFA), ELISA, and rapid test can be used. Immunofluorescence assay is semi-quantitative, requires fluorescent microscopy, which is labor-intensive and has intra-assay and inter-assay variability, and its popularity for diagnosis of ST is being questioned.[112] ELISA on the other hand can be automated to screen a large number of samples, is objective (optical density value), technically simple, cost-effective and is an alternative to IFA.[113] Rapid diagnostic test are becoming important. Weil-Felix agglutination test is a cheaper option in the diagnosis of rickettsial infection including ST in resource poor setting, although it has poor sensitivity but has good specificity.[109,114] Polymerase chain reaction may be useful when facilities are available.

Co-infection

Co-infections are common. In a study of 82 serologically confirmed cases, PCR was positive for leptospirosis in 43 (52%), ST in 3 (11%), and both in 5 (6%), whereas 25 (36%) were negative for both leptospira and ST.[13] The difference in serologic and molecular tests may be due to low sensitivity of molecular assay and failure of blood samples to be obtained during bacteraemia in leptospirosis. Serological cross-reactivity and infection caused by one pathogen in the background of recent but inactive infection by another pathogen.[115] Multiple infections include malaria, dengue, and scrub typhus in five cases, 21 were dengue cross-reactive, malarial parasite was positive in 14, and nine had IgM antibodies to scrub typhus and dengue.[116] In the presence of eschar, tests of leptospira may not be necessary as both ST and leptospira respond to doxycycline and erythromycin.

Cerebral malaria

Cerebral malaria (CM) is a common cause of AES in India. In 2016, about 216 million cases of malaria have been reported form 99 countries with an increase of 5 million cases compared to the previous year. Eighty percent of global malaria burden is in Africa and India. Malaria is a protozoal disease with four hemophagocytic species: *Plasmodium falciparum*, *P. vivax, P. ovale, and P. malariae. Plasmodium falciparum is the* most virulent and is responsible for cerebral malaria, which is associated with high mortality. *Plasmodium knowlesi* is a zoonotic disease, but has been reported to affect humans in South East Asia.[117] About 99% of cerebral malaria occurs in *South East Asia*. *Plasmodium falciparum* is also prevalent in Sub Saharan Africa and *P. vivax* is common outside Africa including Americas and Eastern Mediterranean region.[118] Malaria is transmitted by infected female anopheles mosquitoes and human infection occurs during blood meal. Incubation period of malaria is 7-30 days, after which the patient may develop fever or severe infection leading to cerebral malaria (CM).

Cerebral malaria or severe malaria manifests with anemia and respiratory distress. There may be metabolic acidosis, hypoglycemia, acute renal failure, and hypomagnesaemia.[119] Cerebral malaria occurs in 1% of children infested by *P. falciparum*[120] and is more common in children above 3 years of age. The patients with cerebral malaria present with 2-3 days history of fever followed by convulsion and coma. Headache, fever, muscle pain, and neck stiffness are common. Child may have hepatosplenomegaly, jaundice, pallor, pulmonary edema, bleeding, and hypotension. Retinopathy in malaria occurs in young and adults and is associated with whitening of retina, retinal hemorrhage, or papilledema. In 30% children with malaria, retinopathy in Africa had some neurological abnormality, e.g., cognitive, behavioral, motor dysfunction, or seizure.[121] Sequelae in treated patients with malaria is although uncommon, but has been reported in up to 30% of adults with cerebral malaria including hemiplegia, blindness, deafness, cerebellar, ataxia, or cognitive impairment.

Plasmodium falciparum is a disease of vascular endothelium. There is parasitic sequestration, clogging the cerebral capillaries and blood vessels by infested RBCs, thereby releasing inflammatory cytokines which lead to vascular leakage and hypoxia. The diagnosis of CM is confirmed by asexual forms of *P. falciparum i*n peripheral thin and thick blood smear.[122] In endemic areas, there is a high rate of incidental asymptomatic parasitemia; therefore, a systematic approach is needed. CT scan or MRI is generally normal but may reveal focal abnormality.

Changing spectrum of AES and diagnostic challenge

In India, the AES in 1990 was dominated by malaria and JE, which were especially noted in the post-monsoon period. The patients with JE were suspected clinically especially during the post-monsoon outbreaks by a variety of movement disorders, anterior horn cell involvement, and thalamic lesions on CT scan or MRI.[33-35,123] In the late 1990s and early 2000s, the encephalitis patients were associated with systemic manifestations such as thrombocytopenia, liver, and kidney dysfunction, and these patients turned out to be due to dengue.[70] The neurological manifestations of dengue fever included encephalitis, encephalopathy, and immune-mediated syndrome and dengue-associated transient muscle dysfunction.[86,87] Fluid

management and supportive treatment result in recovery in the majority. In the subsequent years, lack of improvement in some of these patients resulted in further investigation and scrub typhus was found to be responsible.[42] Scrub typhus although simulated dengue infection by systemic manifestations such as thrombocytopenia, liver and kidney dysfunction, elevated serum CK, encephalitis, encephalopathy, but the muscle involvement in scrub typhus is due to vasculitis as opposed to myoedema in dengue-associated transient muscle dysfunction.[110,111] However, a group of investigators considered enterovirus infection being another etiological agent.[124] These findings resulted in recommendation for doxycycline or erythromycin by Indian Council of Medical Research for any patient with AES in India. Co-infection of *flavivirus* infection, malaria, and ST is possible and has been reported. In the initial stage, the laboratory confirmatory tests are not easily available or may take long time to be of clinical significance.

Syndromic approach

The patients with AES are subjected to detailed investigations including blood counts, serum chemistry, electroencephalography, CT/MRI brain, and a number of viral serological, bacteria, fungal, parasitic and immunological tests to exclude rare types of encephalitis. Many patients receive a cocktail of therapy including antiviral, antibiotics, anti-fungal, antimalarial, and even immunotherapy to cover possible treatable cause of AES.

A syndromic approach in the AES patients is quite helpful. Acute encephalitis syndrome patients can be categorized into:

A) AES patients with primarily CNS involvement (JE, HSE, West Nile).
B) AES patients with systemic features such as rash, myalgia, thrombocytopenia, hypotension, and liver or kidney dysfunction. The systemic AES may be due to cerebral malaria, scrub typhus, dengue, chikungunya, and leptospirosis.

In neurological AES, cranial CT/MRI is helpful. Cranial MRI has typical features in JE and HSE,[11,13,63,76] whereas MRI is normal or reveals nonspecific changes in dengue, ST, CHIK and cerebral malaria. In a study on 210 patients with AES, pure neurologic AES was present in 45 and systemic AES in 165 patients. Specific ethology could be established in 130 (62%). After excluding 36 patients with multiple infections, 94 patients were evaluated for sensitivity and specificity. In the 20 patients with neurologic AES, HSE was present in 12 and JE in 8, whereas in 74 patients with systemic AES, ST was diagnosed in 42, dengue in 20, and cerebral malaria and leptospirosis in 6 patients each. Absence of myalgia and rash categorized neurological AES with 100% specificity. In neurological AES, thalamic involvement in MRI predicted JE with 100% specificity.[125,126] The patients with neurological AES therefore should undergo MRI evaluation; if there is fronto-temporal involvement, acyclovir should be prescribed. If there is thalamic, basal ganglia, or brainstem involvement on MRI, acyclovir may be withheld because HSE is very unlikely without frontotemporal and basofrontal involvement.[4,70] In the patients with systemic AES, malarial parasite in smear or malarial antigen should be done, and positive patients should be treated with artesunate. If malaria negative in systemic AES, doxycycline and ceftriaxone may be started pending confirmation of ST, leptospirosis, and CHIK. In dengue endemic region, ELISA for both dengue antigen and IgM antibody should be done. In systemic AES, cranial MRI and CSF PCR and IgM antibodies for JE and HSE may not be informative and acyclovir is not indicted [Figure 3]. Using this syndromic approach, the

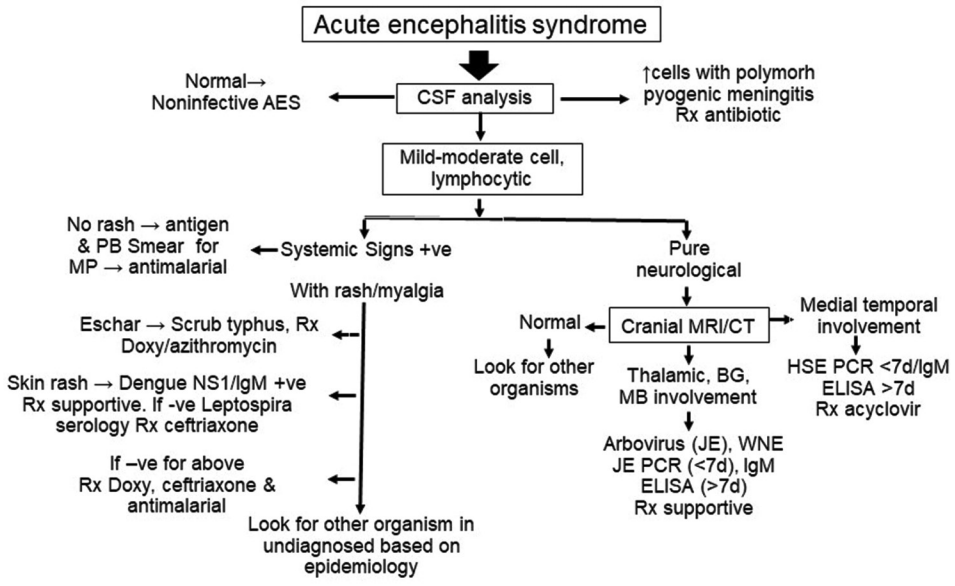

Figure 3: A flow chart showing approach to an infective acute encephalitis syndrome. Doxy = doxycycline, HSE = herpes simplex encephalitis, JE = Japanese encephalitis, MP = malarial parasite, PB = peripheral blood, WNE = West Nile encephalitis

direct cost of diagnosis and treatment may be substantially reduced.[126]

Sometimes, the patients with neurologic AES may have systemic features because of associated infection, sepsis, and drug toxicity leading to diagnostic dilemma; therefore, overall clinical picture should be considered and treatment decision may be individualized. The syndromic approach should lead to development of protocols suitable to different geographical regions considering the prevalent etiologies of AES for cost effective management of patients without compromising the quality and outcome of patients.

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Conflicts of interest

There are no conflicts of interest.

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