Febrile Encephalopathy: Challenges in Management

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Acute febrile encephalopathy is a common condition leading to hospital admission in adults and children in India. CNS infections are commonest cause of non-traumatic coma in children.1 Encephalopathy - a diffuse disease of brain that alters its structure or function may be caused by variety of infective, metabolic, toxic, ischemic/hypoxic, nutritional causes or trauma. In febrile illnesses, encephalopathy may result from pathogenic mechanisms affecting nervous system directly or systemic complications like hypoglycemia, hypovolemia, hyperpyrexia, hypoxia, anemia, hepatic/renal failure and bleeding may contribute to its pathogenesis. The physician/ intensivist is faced with the challenge of emergency management, identification of cause and its treatment not only to ensure survival but also to prevent long-term sequelae, neurological or otherwise. Few of such important clinical situations need elaborate consideration.

Encephalitis, an inflammation of the brain parenchyma, presents as diffuse and/or focal neuropsychological dysfunction. From an epidemiologic and pathophysiologic perspective, encephalitis is distinct from meningitis, though on clinical evaluation the two often coexist (meningoencephalitis) with signs and symptoms of meningeal inflammation, such as photophobia, headache, or a stiff neck. Cerebritis describes the stage preceding abscess formation and implies a highly destructive bacterial infection of brain tissue, whereas acute encephalitis tends most commonly to be a viral infection with parenchymal damage ranging from mild to profound. Post monsoon Japanese Encephalitis (JE) epidemics have been reported from Uttar Pradesh, Assam and other parts of the country. JE is the single largest cause of viral encephalitis in world today. The incidence has been reported to be high among pediatric age group with high mortality (30%).2 Persistent EEG abnormalities are common in children. Brain CT and MRI scans reveal low density areas and abnormal signal intensities in the thalamus, basal ganglia which correlate with clinical findings of tremor, rigidity and abnormal movements that are common in the acute phase of illness. Diagnosis may be established by serological tests and JE virus-specific IgM antibody or RT-PCR in the cerebrospinal fluid (CSF). Since there is no specific anti-viral therapy for JE as of today (Ribavirin is under trial), the treatment is mainly symptomatic and supportive. However, reducing the raised intracranial pressure and controlling convulsions may decrease the mortality and morbidity significantly. No satisfactory treatment exists for the relatively common acute arboviral encephalitides, which vary in epidemiology, mortality and morbidity, if not clinical presentation. Dengue virus encephalopathy is a rare but recognized cause of acute febrile encephalopathy in India and usually occurs in febrile stage. Neurological findings reported in association with dengue include mononeuropathies, polyneuropathies and Guillain Barre’s Syndrome. Around 1-4% of all dengue admissions have clouding of consciousness. Variety of pathological processes like hypotension, cerebral edema, microvascular or frank haemorrhage, hyponatremia and fulminant hepatic failure may interact to cause coma in some of these patients but in others where no such process is identified, isolation of dengue virus from CSF or brain tissue has endorsed the concept of dengue virus itself leading to encephalitis.3 Clinically distinguishing these acute arboviral encephalitis from the two potentially treatable acute viral encephalitis – a) herpes simplex encephalitis (HSE), which is a sporadic and lethal disease of neonates and the general population as well, and b) the less common varicella-zoster encephalitis, which tends to be fatal in immunocompromised patients, is important. Prompt identification and immediate treatment can be lifesaving. Most authorities advocate initiating emergency treatment with the relatively safe acyclovir (10mg/kg intravenously 8 hourly for 14 days) in any patient whose neurological manifestations have no alternative apparent explanation.

Cerebral Malaria, the potentially fatal complication of falciparum malaria is the most important cause of unarousable coma in febrile patients in endemic area. Children, pregnant women and non-immune adults are more susceptible to have cerebral malaria.4 It is seen in 20% of all severe falciparum malaria requiring ICU admissions.5 Selective cytoadherence and sequestration of parasitized RBCs in cerebral venules and ‘toxin release’ at schizont rupture are the possible pathologic mechanisms.6 However systemic complications may contribute to the development of coma. Findings on brain CT scan correlate well with level of consciousness and severity of disease but underestimate the extent of disease at pathological examination.7 Recent trial has suggested that there is absolute reduction of mortality with use of artesunate compared to quinine.

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in patients of severe falciparum malaria. Apart from prompt initiation of appropriate anti-malarial therapy, ICU care, correction of hypoglycemia, acidosis and anemia and exchange-transfusion in selected cases, none of adjuvant forms of therapy have been found to effect outcome. These include, Immunoglobulin, pentoxifylline, iron-chelators and monoclonal antibody to TNF alpha. Injectable steroids (dexamethasone) and anti-coagulation with heparin therapy are associated with adverse outcome. Overall mortality is 15-20% with neurological sequelae like cortical blindness, aphasia, ataxia, cognitive dysfunction in 10-20% of children and 1-3% adults.

Meningoencephalitis and aseptic meningitis are uncommon manifestations of leptospirosis. They can occur in anicteric patients hence high index of suspicion is required for diagnosis. Hepatic/ renal failure and intra-pulmonary hemorrhage with hypoxia may contribute to development of coma in these patients. CSF xanthrochromia, persistent polymorphonuclear leukocytosis, and increased intracranial pressure have possible negative prognostic implications.

Sepsis Associated Encephalopathy (SAE) is a poorly understood CNS condition that is associated with a wide range of manifestations from lethargy to overt delirium in sepsis patients. Numerous mechanisms have been proposed in pathogenesis including bacterial invasion of brain, endotoxin, blood-brain barrier transport, amino acids and neurotransmitter derangements and microvascular changes in sepsis patients. Whatever the pathogenesis, it is clear that SAE has serious prognostic significance. An alteration in the mental status of mechanically ventilated, critically ill patient with or without sepsis has profound implications and is independent predictor of higher six months mortality. However other measures that these patients receive, such as sedatives, resuscitation fluid, environmental stimuli may contribute to development of SAE or critical illness associated delirium.

Several important terms exist concerning CNS conditions caused by HIV. Neurological complications from HIV may arise from HIV itself, opportunistic infections (CNS tuberculosis, cryptococcal meningitis, toxoplasmosis, cytomegalovirus encephalitis, syphilis), tumors (primary CNS lymphoma) or drug-related complications.

While dealing with acute febrile encephalopathy patients in ICUs, it is important to consider hyperthermic variants of complications of neuroleptic therapy, including Neuroleptic Malignant Syndrome (NMS), poisoning/overdose in addition to infective, metabolic, hypoxic/ischemic and endocrine causes. Going by the aforesaid it is worthwhile to consider therapeutic approaches/ modalities when dealing with such a situation.

Underlying principles of management of patients with febrile encephalopathy : Most acutely ill febrile patients with encephalopathy may make complete neurological recovery once the underlying cause is treated but considerable skill is required to distinguish the group at high risk of deterioration.

The first step is to assess level of consciousness. Glasgow Coma Scale is commonly used for this but its usefulness in non-traumatic cases is not established and summation of individual score may lead to loss of information. Modified Glasgow Coma Scale, Modified James scale and Blantyre coma scale are used in children. Definite criteria are available for defining certain diseases like cerebral malaria- a) unarouseable coma (despite correction of hypoglycemia and persisting for more than six hours after a generalized seizure) with b) demonstration of asexual forms of Plasmodium falciparum in peripheral blood smear after c) exclusion of other causes of encephalopathies endemic in that area.

The next step would be to find if intracranial pressure (ICP) is raised. Intracranial hypertension is thought to cause brain damage by reducing cerebral perfusion pressure and causing cerebral ischemia or leading to brain herniation, which in turn can cause direct mechanical damage and vascular distortion. Papilloedema is very rarely seen in acute encephalopathies even if ICP is very high. Brain CT scan can detect cerebral edema or compression of lateral ventricles. Emergency management of intracranial hypertension at the time of presentation is potentially life saving in all encephalopathies. The main priority is to maintain airway, support systemic circulation and correct metabolic derangements. Mannitol (0.25-1g/kg intravenously as 20% solution, over 15-20 minutes every 4-6 hourly) is administered if not contraindicated and mechanical ventilation is offered if rapid clinical deterioration is present to reduce ICP. Seizures need to be controlled immediately as they increase ICP. Fever control reduces the threshold for seizure.

In absence of obvious cause, routine hematology, biochemistry, microbiology including thick and thin peripheral smear for malaria parasite, quantitative estimation of parasite load, rapid tests for antigen detection, and specific tests- ammonia, lactate, urine toxicology screen should be performed. With deep unconsciousness or focal signs brain CT scan/MRI scan rather than lumbar puncture is preferable. This may help detect hydrocephalus/exudates in tuberculosis, fronto-temporal pathology in herpes simplex encephalitis or thalamic involvement in Japanese B encephalitis. Lumbar puncture is crucial after initial resuscitation and control of seizure. CSF should be sent for cell count, protein, glucose, Gram stain, and Ziehl-Neelsen stain. For clear differentiation viral antibodies and PCR for specific infections may be required.

Prompt institution of empirical anti-malarial treatment (even in absence of smear-positivity) or broad-spectrum antibiotics (such as ampicillin, ceftrioxone +/- vancomycin), to treat possible meningitis is justified.
Acyclovir therapy is administered in suspected Herpes Simplex encephalitis. There is some evidence that dexamethasone given before antibiotic reduces the incidence of deafness and possible neurological sequelae, however decrease in permeability of blood-brain barrier may reduce action of some drugs.

Continuous intra-cranial pressure monitoring by intradural/epidural device connected to multi-parameter monitor is required in situations of persistently elevated ICP. In cases with bleeding diathesis extradural ICP monitoring is done provided platelet count is above 50,000/ml. Head is positioned in midline, flat or with 30-degree elevation so that venous return is not obstructed. Ventilation to normocapnia and surgical decompression of hydrocephalus may be required. Fluid management is tailored for individual cases depending on presence of SIADH, central diabetes insipidus or cerebral salt wasting. Although there may be group of patients who benefit from barbiturate therapy, risk of hypotension outweighs useful effect of reducing ICP. Reducing body temperature by 1°C can reduce cerebral metabolic rate considerably.

Most patients surviving infectious encephalopathy have good outcome. If global ischemia has occurred during the course of encephalopathy, sequelae like cortical blindness, hemiparesis, dystonia, late onset movement disorders may occur. Etiology, duration and depth of coma are associated with outcome. Neuroimaging and EEG may help determining prognosis in individual cases.

There is a large amount of experimental data available suggesting a role of substances such as free radicals, excitotoxins and calcium released during a cascade of biochemical reaction after ischemia, in causation of brain damage. In few patients with meningitis, there is evidence of inflammatory vasculopathy with spasm, stenosis and occlusion of large/small vessels. Anticoagulants cannot be recommended due to bleeding diathesis in these patients. CNS microcirculation in sepsis is current area of investigation.

To conclude, clinician needs to consider a host of conditions of diverse origin, depending on geographic area, seasonal trend and recent spurs. Index of clinical suspicion indeed needs to be high. Initial empirical treatment after collection of blood/CSF is justified. Treatment based on close continuous monitoring of clinical, hemodynamic and laboratory parameters with appropriate imaging can only help salvaging the patient and minimizing sequelae in the clinical challenge posed by acute febrile encephalopathy.

REFERENCES