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Review article

Tropical febrile encephalopathy

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1. INTRODUCTION

Infections are the biggest cause of morbidity and mortality, within the tropics. Thickly populated and overcrowded areas, cause increased risk of respiratory and gastrointestinal infections. Malnutrition, on the other hand, can cause impaired defense against infections. Many countries in the tropics, have less developed physical infrastructure; some parasitic infestations tend to occur specifically in a tropical climate. Parasites have a life cycle, that will be interrupted, should the ambient temperature fall below a certain level [1]. Tropical medicine thus deals with health problems, mainly infection related, that occur uniquely, are more widespread and defy control in tropical and subtropical countries. Infections, that occur and thrive principally in hot humid conditions include Malaria, Dengue, Leishmaniasis (Kala azar), lymphatic Filariasis (as also Schistosomiasis, Onchocerciasis, Chagas disease and African Trypanosomiasis – to complete the list). The spectrum thus faced by clinicians includes both infectious diseases and zoonotic diseases and is diverse comprising of bacteria, viruses, parasites, fungi, rickettsia and spirochetes. The commonest seasonal, monsoon-related febrile conditions are Malaria, Dengue fever, Leptospirosis and Typhoid. Other febrile conditions include viral Hepatitis, Meningitis (*S. pneumonia*,*N. meningitidis*, *Haemophilus influenzae*, Enteroviruses, Tuberculosis), Chikungunya, Leishmaniasis-Kala azar, Filariasis, Scrub Typhus, Measles and such exanthema, Tuberculosis, HIV, Herpes zoster/simplex and Japanese Encephalitis.

Otogenic infections – atticoantral type of chronic suppurative otitis media, the commonest organisms being *Pseudomonas* spp., *H. influenzae*, *Proteus* spp. and mixed anaerobic infections, comprise a separate group with central nervous system complications like meningitis, brain abscess – temporal lobe or cerebellar abscess, subdural abscess, and sigmoid sinus thrombophlebitis among others.

Encephalopathy: It is a general term describing a disease, that affects the function or structure of the brain and has varied causes-infectious [bacteria, viruses, parasites], anoxic, alcoholic, hepatic, uremic, metabolic [hypo/hyper glycemia, hypo/hyper natremia, hyper/hypo calcemia, toxic substances [ammonia], alterations in

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intracranial pressure [bleed, tumours, abscesses, nutritional [inadequate vitamin B1], vasculitis, etc.; clinically characterized by altered mental status (manifested as reduced consciousness or altered cognition, behavior and personality] and serious ones such as seizures and coma. Encephalitis is inflammation of the brain, identified by surrogate clinical markers including inflammatory change in the cerebrospinal fluid or parenchyma and findings of inflammation on imaging. In earlier studies, the terms Encephalopathy and Encephalitis were used concurrently and simultaneously, for instance, in the context of Influenza [2]. Subsequently, only patients of Encephalopathy, with minimum two identified criteria were included as those with Encephalitis [3]. The case definition of Encephalitis includes any person of any age, admitted to the hospital, with Encephalopathy (altered consciousness that persisted for longer than 24 hours, including lethargy, irritability or a change in personality and behavior, with two and more of the following: fever or history of [fever > = 38 degrees centigrade) during the present illness, seizures and/or focal neurological findings (with evidence of brain parenchyma involvement); CSF pleocytosis (more than four WBC per micro L); EEG findings indicative of Encephalitis; abnormal results from neuroimaging (CT or MRI) suggestive of Encephalitis. The context and perspective of this review are thus the tropical fevers referred to earlier, manifesting with Encephalopathy namely- Dengue, Malaria, Leptospirosis, Typhoid, bacterial sepsis, Rickettsial infections and certain viral infections.

2. Mechanisms and pathophysiology

Encephalopathy is a diffuse disease of the brain that alters its structure or function. It may be caused by a variety of infective, metabolic, toxic, ischemic–hypoxic, nutritional causes or trauma [4]. In febrile illnesses, encephalopathy may result from pathogenic mechanisms affecting the nervous system directly or because of systemic complications like hypoglycemia, hypovolemia, hyperpyrexia, hypoxia, anaemia, hepatic insufficiency, renal injury and bleeding contributing individually and in combination, sometimes as a cascading effect.

The Health scenario and the clinical setting: Infections occur in diverse locational setup— remote, tribal, rural, semi urban-taluka, urban- district, regional-state capital, and metropolitan cities with reference to access to care in private practitioner, dispensary or governmental primary health centre, cottage/civil hospital, private nursing home, trust hospital, medical college setup, tertiary medical institutes, corporate speciality setup; the reason to look into this aspect is the fact that referral lines tend to be faulty and referral system may not be in place. Personal choices and preferences should not result in delay, when the clinical condition is worsening. Further the intensive care unit (ICU) [5] bed vacancy requires to be assured/made available when patient's condition is deteriorating; this is an important aspect of logistics/strategy in management as some of these conditions occur throughout the year and others are monsoon related. The clinical setting is an indoor patient admitted with undifferentiated febrile illness for observation, investigation, preliminary treatment, to which there is poor response and a general condition with altered mental status that is worsening or has shown abrupt deterioration necessitating intensive monitoring and care. The physician/intensivist is faced with the challenge of emergency management, identification of the cause and its treatment, not only to ensure survival, but also to prevent potential long term sequelae, neurologic or otherwise. A systematic approach with regards to history, thorough clinical examination and relevant investigations form an integral part of skillful management; being a heterogenous clinical syndrome it demands knowledge and skills of precision to differentiate from among a wide and diverse range of aetiologies. The common such conditions are being discussed.

1. **Dengue virus encephalopathy** is a rare but recognized cause of febrile encephalopathy in India and usually occurs in the febrile stage. Neurologic findings reported in association with dengue include mononeuropathies, polyneuropathies and Guillain Barre syndrome. Around 1-4% of all dengue admissions have clouding of consciousness [6]. Headache and retro orbital pain are the main features.

Multiple pathological processes like hypotension, cerebral oedema, microvascular or frank haemorrhage, hyponatremia and fulminant hepatic failure may interact, to cause coma. Clinically, it may be prudent to distinguish this arboviral condition from two potentially treatable central nervous systems conditions- herpes simplex encephalitis and varicella zoster encephalitis, both being amenable to intravenous Acyclovir. Rash, thrombocytopenia, multiorgan dysfunction may be additional features in Dengue.

2. **Malaria-** Cerebral Malaria, a potentially fatal complication is an important cause of arousable coma in febrile patients in endemic area. Children, pregnant women and non – immune adults are more likely to have cerebral malaria [7]. Selective cytoadherence and sequestration of parasitized RBCs in cerebral venules and "toxin release" at schizont rupture are the possible pathologic mechanisms [8]. Findings on brain CT scan correlate well with level of consciousness and severity of disease, but underestimate the extent of disease at pathological examination [9]. Prompt initiation of antimalarial – parenteral Artesunate, ICU monitoring, correction of hypoglycemia, acidosis and anaemia have been found to be effective in managing these cases. Neurological sequelae include cortical blindness, aphasia, ataxia and cognitive dysfunction, more in children than in adults. Plasmodium vivax malaria has acquired a malignant form in the last few years.

3. **Leptospirosis-** Leptospira multiply in the small blood vessel endothelium, resulting in damage and vasculitis. Meningoencephalitis and aseptic meningitis are uncommon manifestations of leptospirosis. They can occur in anicteric patients and hence a high index of suspicion becomes necessary. Hepatic and/or renal failure and intra-pulmonary haemorrhage with hypoxia may contribute to coma in these patients [10,11]. CSF xanthochromia and persistent polymorphonuclear leukocytosis, have possible negative prognostic implications. Fever, thrombocytopenia, icterus, acute respiratory distress syndrome (ARDS) and multiorgan dysfunction could be eventual additional features.

4. **Typhoid-** Infectious meningoencephalitis could occur in Salmonella typhi – typhoid fever. Fever and toxemia [12]. are important features of typhoid delirium- encephalopathy now decreasing in incidence, with early reporting and treatment.

Table 1
Incubation period of common diseases.

Short <10 days	Intermediate: 7–28 days	Long: >4weeks	Variable: Weeks to years
Dengue/Arbovirus	Malaria(falciparum/vivax)	Hepatitis B	Tuberculosis
Chikungunya	Hepatitis A,C and E	Leishmaniasis	HIV
Meningococcal disease.	Leptospirosis, Enteric fever. Typhus.	Brucellosis	Systemic fungal infections, filariasis.

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