

## Acute Febrile Encephalopathy in Adults: A Review of Three Prospective Trials

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### ABSTRACT

**Introduction:** Acute Febrile Encephalopathy (AFE) is a heterogeneous clinical syndrome that refers to fever associated or followed by mental deterioration with or without other neurologic manifestations, including seizure and sensory motor deficits. The emergency nature of AFE necessitates high levels of knowledge and skill for the physician to provide correct diagnostic plan(s) among a wide range of etiologies. Fever accompanying shortens the list of differential diagnosis to mainly infectious agents.

**Materials and Methods:** Based on a digital search in Pubmed looking for the terms mental alteration, fever, adult, elderly and topical countries, and infectious diseases, three prospective trials which met the inclusive criteria were selected and reviewed.

**Results:** A total of 430 adult and elderly patients with a mean age of 30 years old admitted to different hospitals of India and diagnosed with AFE were investigated for the most common causes of AFE and other clinical outcomes. In this review, primary CNS infections including pyogenic meningitis (PM) and viral encephalitis various in the most common viral agent in different studies were the main causes responsible for AFE in adults, followed by sepsis associated encephalopathy (SAE) and cerebral malaria (CM). Poor prognostic and protective factors were listed based on the findings and by considering other studies. Viral encephalitis is associated with the most mortality rate and physical disabling, compared to other etiologies.

**Conclusion:** Primary CNS infections including bacterial meningitis and viral meningoencephalitis account for the most causes of AFE in adult and elderly patients with the most fatality for viral agents.

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### Introduction

Encephalopathy is a non-specific syndrome that implies to etiologies or diseases involve the brain and results in structural or functional alterations in the central nervous system. They include a broad range of infectious and non-infectious diseases that are limited in differential diagnosis if patient manifests fever.

Infectious diseases are the predominant diagnosis of febrile encephalopathy. It is life-saving for the patient if diagnosis is made early and effective decisions are taken along with a timely starting of treatment.

Today as expanded life expectancy has increased elderly population, it is necessary to pay more attention to geriatric medical problems.

There are many reasons that allow infections to be more and more common in elderly subjects, including cellular and humeral immunity alterations, physiologic changes such as decrease of cough reflex and damage to circulatory system, weakening of wound healing,

growth of chronic infectious diseases, immunocompromised drugs consumption and living in crowded places (1).

On the other hand, because infections are among the most common causes of hospital admission, the best and the most cost-effective diagnostic tests should be adopted to reduce total patients costs and times.

Meanwhile, elderly subjects do not have typical manifestations of most of infectious diseases, and physiologic responses to infections are retarded and blunt in these patients. Therefore, special attention needs to be devoted to common infections, especially life-threatening CNS infections, in this age group (2).

Due to functional defects of vital organs and background diseases as well as various types of drug consumption, older people are likely to show functional defects in CNS, which could be manifested as encephalopathy and alteration in mental state.

Thus, it is a challenge to approach an older patient with brain malfunction and fever, since it is important to determine the cause of mental deterioration, either infection including CNS infection and extra-CNS infections like sepsis or other non-infective medical conditions such as poisoning with or response to different drugs, metabolic disorders, dehydration, thromboembolic phenomenon, cardiovascular or cerebrovascular accidents and so on, which all can generate encephalopathy and fever in elderly subjects. According to primary clinical estimation and finding of sign and symptoms, diagnostic and therapeutic approaches would be planned. It is of great magnitude to select the most likely diagnosis and to propose the best diagnostic and therapeutic plan(s) as quickly as possible, a process that needs to have a highly qualified and properly practiced, diagnostic and therapeutic methodology to succeed.

As mentioned above, infectious agents including viruses, bacteria and parasites are among the leading causes of AFE in hospitalized adult and elderly patients. Unfortunately, no definite incidence for AFE has been reported so far.

Furthermore, etiological agents vary across different geographical areas and even between seasons in the same area. Ancient human enemies like tuberculosis, malaria, leptospirosis and typhoid occupy considerable ranks in differential diagnosis list of AFE in tropical countries.

In fact, despite the emergency nature of AFE, especially in elderly patients, and its common hospital admission, few studies have been carried out on AFE that would explore its etiological profile and clinical outcomes and evaluate the correlation between clinical and paraclinical investigations and prognosis.

## Materials and Methods

In this brief review, the Pubmed database was explored for English articles with the keywords being acute febrile encephalopathy, adult or elderly patients, viral, bacterial and parasitic etiologies and tropical countries. The inclusion criteria were (1) age more than 14 years old, (2) hospitalized patients who had received a diagnosis of AFE based on the following three criteria: (A) body temperature more than 38.5 °C with a duration of less than 2 weeks, (B) sudden collapse of consciousness and/or cognitive level with or without other neurologic manifestations including seizure, sensory and motor deficits lasting more than 12 hours from beginning until admission in hospital, (C) total period of sickness being more than one week at the time of admission.

Non-infectious causes including trauma, thromboembolic and hemorrhagic cerebral accidents and metabolic deterioration were excluded from the study. In addition, individuals with a history of brain surgery in the month prior to the study were not enrolled.

At last, 3 prospective trials, consisting of 430 adult and elderly AFE patients, met the inclusion criteria. All admitted patients underwent routine exams, CSF analysis and brain imaging, which included computed tomographic scan and magnetic resonance image if needed. All the prospective studies had been conducted in different parts of India.

## Results

The mean age of all 430 patients were about 30 years of old, ranging from 14 to 70 years. Male preponderance with a proportion of 2-3 to 1 was observed in all reviewed articles. Most of admissions happened in hot and wet seasons of the year in India. The most presenting complaints on admission were fever (100%), altered mental state (100%) and headache (94%). Other manifestations including seizure, sensorimotor deficits and unstable hemodynamic situation (the latter having occurred commonly in sepsis-associated encephalopathy) varied from 25% to 50% in different trials. CNS infection was directly responsible for more than 70% of AFE cases, followed by sepsis-associated encephalopathy and other tropical infections which involve CNS like malaria, leptospirosis and tuberculosis. Primary CNS infections were identified as the most common causes of febrile encephalopathy (~70%) in admitted patients which appeared as pyogenic meningitis (~33%) and viral encephalitis or meningoencephalitis (~30%). Also, the most prevalent viral agents were enteroviruses, Japanese encephalitis virus and flaviviruses, followed by varicella zoster and HSV 1&2. In one study (4.pdf) for viral determination RT-PCR and conventional PCR of CSF fluid samples as well as ELISA. Despite extensive diagnostic tests applied to all patients demonstration of a precise cause failed to establish in about 10-15 percent of cases. In this study, viral agents resulted in the highest mortality and morbidity rate, compared to other etiologies. The level of disability was assessed using modified Rankin scale up to one month of hospital discharge. Ventilation requirement indicated a poor prognosis, while a high Glasco score and a more prolonged duration of hospitalization were associated with a better prognosis.

## Discussion & Conclusion

Acute febrile encephalopathy refer to a clinical syndrome consisting of fever with or followed by altered mental state with or without other neurologic manifestations, resulting from a diverse and broad range of etiologies. Although non-infectious disorders can cause AFE, the leading causes are infectious diseases, primarily CNS ones. According to different studies, the incidence of AFE varies between 2 to 16 per 100,000 population annually (3, 4); however, few published studies have systematically investigated different aspects of this illness (4, 5).

The aim of the current review was identifying the etiological profile and clinical outcomes of adult AFE, especially in tropical areas.

While non-traumatic coma studies on children demonstrated pyogenic meningitis, tuberculous meningitis and viral encephalitis at the top of suspected etiologies (6, 3), the current review noted that ancient infections - especially TB – have occupied lower ranks in the case of adult AFE etiologies. This is perhaps due to its subacute/chronic pathophysiological nature.

Although none of CNS infections are known to have any sex predominance, all trials in the present review showed a male preponderance. This is in line with the study by Paraqaria et al. in which males were more prominent in HSV encephalitis (7).

Predominant male social activity and, consequently, more exposure to infective agents particularly malaria, as well as greater medical attention to men in traditional societies may be the only acceptable explanation for this fact.

Mental alteration and neck stiffness are attributed to parenchymal and meningeal involvement, respectively (3, 8). This could be an appropriate explanation for mental depression in encephalitis but not in meningitis cases. It is postulated that inflammatory cells from inflamed meninges are distributed to adjacent parenchymal areas. Elevated intracranial pressure is another description for sensorinorium manifestations in meningitis.

Although viral agents account for the first and second causes of AFE in adults and elderly patients, there were diverse features in our review concerning the viral role for CNS infection. While in two studies HSV and JE were the commonest agents causing viral encephalitis (9, 6), enteroviruses, flaviviruses and HSV were the chief factors in another study investigating AFE in rural areas (10). Despite CNS fluid PCR used in one study, confirmation of viral etiology occurred only for 20% of viral suspected encephalitis cases and others remained unclear (10). This was consistent with other previous studies which had reported a typically low determination of responsible viruses (11, 12).

Enteroviruses are a wide group with about 70 members. They usually translocate rapidly from CSF into brain parenchyma (11), a possible reason for the low identification rate in CSF sample PCR (13).

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Cerebral malaria (CM) is a significant causative agent for adult and elderly AFE, especially in endemic countries (14) and in humid and hot climates that post-monsoon surges occur frequently.

Another research suggested that dengue fever serology was commonly positive (15), while our investigated articles implied that AFE cases are not categorized into a separate dengue encephalopathy.

Sepsis associated encephalopathy (SAE) has been a more likely differential diagnosis for AFE cases with a high mortality rate (16); this is probably because of multi-organ involvement.

Although brain CT scan was performed essentially as a basic imaging study for all admitted patients to resolve LP contraindications, not only was meningeal enhancement - in contrast to CT scan - not a specific sign for meningitis but CT [scan?] was normal [provided normal results?] in most cases of confirmed meningitis, suggesting that CT scan is not a reliable imaging test in AFE cases, specially for ruling in or out acute meningitis. Japanese encephalitis virus (JEV) (17) and HSV(18) have characteristic findings in brain MRI, including bilateral T2 thalamic hyperintensities in JE encephalitis and typical T2-weighted hyperintensities in the temporal lobes of HSV encephalitis, all present in the three reviewed studies.

Mortality rate of AFE varies significantly in different reports, ranging from 17 to 50% [in developing countries?] (19-21) and lower than 5% in developed countries; nevertheless, disability had an equal rate in different countries as much as 40% (22-24).

Poor prognostic factors included: low Glasgow coma score, need for mechanical ventilation (24-31), tuberculosis meningitis (32) and pneumococcal meningitis (33).

Protective factors noted in previous literature were: high Glasgow score on admission, short prodromal duration (31), seizure (25), hyponatremia(34), oculocephalic response (24), decerebrate posturing (31), CSF pleocytosis (27), high concentration of CSF protein(35) and more prolonged hospitalization.

To conclude, PM and acute meningoencephalitis followed by CM and SAE are among the most common causes of AFE in adult and elderly cases. Besides, acute viral encephalitis, especially if untreated, can be fatal or [and?] more disabling than other causes.

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