Acute onset Fever and Altered Sensorium: Acute Febrile Encephalopathy

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Introduction

A patient presenting with fever and altered sensorium constitutes a medical emergency. Emergency clinicians need to accurately diagnose and administer timely antimicrobials and adjunctive therapies to those who need them while attempting to avoid unnecessary, time-consuming, and invasive testing and treatment of patients without these diseases. Early recognition, efficient decision making and rapid institution of therapy can be life saving. The presence of fever in itself is not sufficient to make a diagnosis of infective etiology (like meningitis or encephalitis). Moreover, encephalopathy may be precipitated by systemic infections or sepsis without cerebral inflammation (septic encephalopathy).[1] Sepsis can lead to altered sensorium secondary to systemic complications like hypoglycemia, hypovolemia, hyperpyrexia, hepatic or renal failure.[1] Even in the absence of infection, there can be uncontrolled rise in body temperature due to mechanisms like overproduction of heat, impaired dissipation of heat or due to non-infective CNS diseases or hypothalamic lesions.[2] Patients with neuroleptic malignant syndrome have fever, altered sensorium and neck stiffness along with generalized rigidity even after the offending drug has been withdrawn, and constitutes an important differential diagnosis of acute encephalitis.[3] Table 1 summarizes some common and important causes of altered sensorium with fever. In many cases, the presence of focal neurological signs and focal seizures distinguish encephalitis from encephalopathy, however, this distinction may not be possible on clinical grounds alone and other investigation like CSF analysis and imaging are usually required to rule out an infective etiology.[4,5] Figure -I outlines the systematic approach to a patient who presents with fever and altered sensorium in the emergency.

The diagnosis of acute infective meningo-encephalitis is suspected in a febrile patient who presents with altered consciousness and signs of diffuse cerebral dysfunction.[1] Worldwide, infection of the central nervous system is the commonest cause of fever with altered sensorium.[1,5,6] (Table 2). In a study from India in pediatric patients (age <18 years) commonest cause of acute febrile encephalopathy was viral encephalitis accounting for around 40 % cases and among non viral causes were the bacterial meningitis(33.8%), tubercular meningitis (7.9%) and cerebral malaria (5.2%).[7] Herpes simplex virus (HSV), varicella zoster virus (VZV), Epstein-Barr virus (EBV), mumps, measles, and enteroviruses are responsible for most cases of acute viral encephalitis among immunocompetent individuals in the United Kingdom.[1]

Three distinct clinical syndromes related to infections of CNS include acute bacterial meningitis, viral meningitis and encephalitis and brain abscess.[6] Each of these syndrome initially presents with non-specific prodrome of fever and headache, until altered sensorium, focal deficits or seizures appear. This article will focus on a systematic approach to a patient with febrile encephalopathy with emphasis on historical and physical examination findings, interpretation of CSF results, role and timing of imaging studies and other modalities of investigation (Figure-1).

Figure 1: Algorithmic approach to a patient with fever and altered sensorium

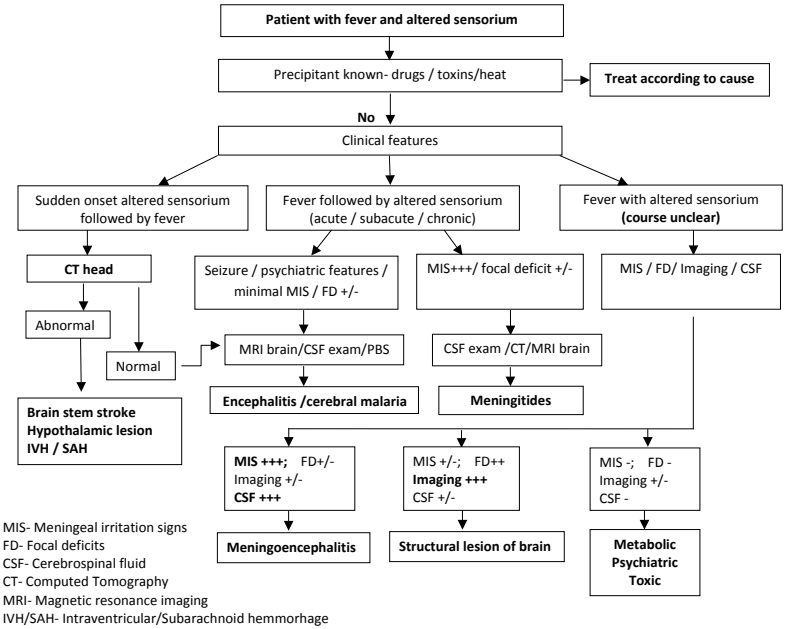

Figure 1: Algorithmic approach to a patient with fever and altered sensorium

Approach to the Patient:

History :

History may hold the most important and sometimes the only clue to the correct diagnosis. The key goal of management of patient with febrile encephalopathy includes careful and systematic assessment of patient and should be based on positive evidence and not by exclusion[4]. At the outset it is important to differentiate infective from non- infective causes of altered sensorium, because it mandates prompt empirical antimicrobial therapy. Temporal course of illness is important and it should be enquired whether fever preceded altered sensorium or altered sensorium preceded/ occurred simultaneously. The clinical hallmarks of CNS infection are fever, headache and altered mental sensorium. In one study, the historical `classic triad' of fever, stiff neck and altered mental status was found in two-thirds of 493 episodes of bacterial meningitis in adults[9]. At least one of the element of the triad was found in all patients and the non-specific finding of fever was the most common feature.[9] A pooled meta-analysis of 11 studies involving 845 patients also found that the classic triad was found in 46% of patients with meningitis, but 99% had at least one feature.[10]

These findings illustrate the difficulty faced by emergency physicians as many cases of bacterial meningitis lack the typical constellation of findings that would distinguish this

infrequent life threatening diagnosis from more common and benign condition.[4] Moreover, the sensitivity of all these symptoms go further down in children, who cannot verbalize their symptoms. Seizure is considered to be an important symptom of meningitis in children, but not as a sole manifestation and is usually associated with other findings such as persistent altered sensorium or nuchal rigidity. Hence children older than 2 months with simple febrile seizures, whose mental status clear quickly and have no other signs of CNS infection can be safely discharged home on antipyretics without lumbar puncture after age appropriate work up for the febrile illness.[11]

Once the symptoms point toward the infective cause of febrile encephalopathy, the history should also focus on the conditions that may increase a patient's risk of contracting an infection, such as asplenia, prosthetic device, HIV status and other immune deficiency status like diabetes, immunosuppressive drugs, steroids, patients on chemotherapy and/or radiotherapy etc., since immunosuppressive individuals are more prone to certain specific infections like listeriosis, cryptoccocosis, cytomegalovirus, etc.

It is essential that a history should always be sought for recent foreign travel, insect or animal bites and possible contact with individuals suffering from infectious diseases. Both the geographical distribution and seasonal occurrence may offer important clues.[1,4,5] Japanese encephalitis is endemic in Asian countries and peaks in the rainy season.[1,12] Cerebral malaria, the potentially fatal complication of Plasmodium falciparum is the most important cause of unarousable coma in febrile patients in endemic areas. The mode of onset and progression of illness also provides a valuable clue to the etiology, rapid worsening favors acute meningitis, encephalitis. Differential diagnosis in an acutely febrile and confused trauma patient should include among common causes a possibility of cerebral fat embolism.[14] History of drug intake with special reference to neuroleptics, is important. (Table 3)

Table 3: Evaluation of a Patient with Febrile Encephalopathy

History

- Fever, Headache, Vomiting, Altered Sensorium
- Geographic and Seasonal factor
- Immune status, Drug intake
- Contact with animals, Dog bite, Insect bite
- Foreign travel
- Occupation

Clinical Signs

- Fever, Neck stiffness, Altered sensorium
- Kernig's sign, Brudzinski's sign, Jolt accentuation
- Skin and mucus membrane
- Lymph node, liver, spleen
- Other sites of concomitant infection
- Neurological examination including fundus for papilloedema, Cranial nerve involvement, Focal deficits, Brain stem signs, Autonomic signs

Investigations

- Blood : including total and differential leukocyte count, coagulation profile, blood cultures, biochemistry, arterial blood gases
- Urine analysis, including myoglobinuria
- Chest x-ray
- Lumbar puncture : with detailed CSF analysis
- Neuroimaging
- EEG

In selected cases:

- Thyroid function test
- Drug levels
- Urine toxicology screen

Physical Examination

Neck stiffness, altered mental status and fever are the classical findings in a patient with suspected meningitis or meningo-encephalitis, however, the sensitivity of these signs have been found to be 70%, 67% and 85% respectively in a meta-analysis.[15]

A thorough general physical examination and neurological examination can provide important clues to the underlying cause. Identification of concomitant pneumonia, diarrhea and skin or bone lesions may offer clue to the etiology of infection. Skin rashes are common in meningococcal infection, rickettsial fever, varicella zoster, etc. Associated features may provide clues like parotitis occuring with mumps. Mucus membrane lesions are common in herpes virus infection. Upper respiration tract infection may favor influenza and mycoplasma. In addition a thorough examination should be done to look for lymphadenopathy, hepatosplenomegaly, etc.[1,4,5,6]

Detailed neurological examination will focus on signs of meningeal irritation (Table 4). Examination including pupillary size and reaction, fundus examination for papilloedema, forced eye deviation, evidence of any cranial nerve involvement, abnormal movements, decerebrate rigidity, focal neurological deficit, etc. help in diagnosis and planning investigations. In one study it was found that loss of papillary light reflex and anisocoria both were independently associated with structural cause of coma however anisocoria was found to be more specific (specificity 96%)[24]. The commonly reported focal abnormalities are hemiparesis, aphasia, ataxia, pyramidal signs, cranial nerve deficits, involuntary movements (myoclonus and tremors), partial seizures, and papilloedema etc. Presence of these signs may warrant neuroimaging before lumbar puncture in some situations. After getting clues from history and examinations, the investigations are tailored as per the diagnosis.[1,4,5,6,8,] (Table 3).

Table 4: Physical signs in suspected meningitis

Kernig's sign	Flexing the hip and extending the knee to elicit pain in the back and legs
Brudzinski's sign	Passive flexion of the neck elicits flexion of the hip
Nuchal rigidity	Severe neck stiffness
Jolt accentuation	Exacerbation of existing headache with rapid head rotation

Investigations

A. Blood Investigations:

All patients of fever with altered sensorium should undergo blood cultures. Blood cultures are positive in 30-80% of cases of bacterial meningitis.[11,16,17]

Relative lymphocytosis in the peripheral blood is common in viral encephalitis. Leucopenia and thrombocytopenia are characteristic of rickettsial infections and viral hemorrhagic fevers. Peripheral blood film is also the most sensitive and specific test for cerebral malaria.[13]

B. Chest Radiography

Chest X-ray is also advisable in all patients of febrile encephalopathy and may show changes which point towards the possibility of mycoplasma, legionella or tuberculosis.[1]

C. Lumbar Puncture

Lumbar Puncture (LP) is indicated in almost all patients who present with fever with altered sensorium, when the index of suspicion of meningitis or encephalitis is high. Certain reports have emphasized the risk of brain herniation as a complication of diagnostic lumbar puncture. Table 5 summarizes the guidelines for adult patients who should undergo CT scan before lumbar puncture[18]. Studies routinely obtained at the time of lumbar puncture

include measurement of CSF pressure, gross examination for turbidity, change in color, measurement of CSF protein and sugar concentrations, cell count, gram stain, india ink stain, fluid culture for bacteria, mycobacterium, fungus etc. Although mycobacterial and fungal infections do have subacute to chronic presentation, yet in an endemic country these tests should be performed, especially in immune-compromised patients. Depending on the clinical suspicion, CSF can also be analyzed for special investigations as discussed further for diagnosis. On an average 15-20 ml of CSF is required for routine analysis and another 5 – 10 ml may be required for special tests.[19] CSF findings in normal and abnormal conditions are summarized in Table -6 and CSF findings in various meningitides are given in Table -7. Table 8, 9 summarizes few of the tests which are helpful in predicting the underlying etiology.

The Bacterial Meningitis Score is one of the systems that has been recently validated in a multicenter retrospective cohort study of 2903 children with CSF pleocytosis. In the study, 121 (4.2%) were found to have bacterial meningitis and the absence of all five variables (one point each) included in the scoring system (i.e., positive Gram stain, CSF WBC $\geq$ 1000 cells/ml, CSF protein $\geq$ 80 mg/dL, peripheral blood absolute neutrophil count $\geq$ 10,000 cells/ml, and history of seizure before presentation) had a negative predictive value for bacterial meningitis of 99.9%. A score of 1 or more identified all children older than 2 months with this disease.[20]

Table 5: Recommended criteria for adult patients with suspected bacterial meningitis, who should undergo CT prior to lumbar puncture [21]

Immunocompromised state	HIV infection or AIDS, receiving immunosuppressive therapy, or after transplantation
History of CNS disease	Mass lesion, stroke, or focal infection
New onset seizure	Within 1 week of presentation, some authorities would not perform a lumbar puncture on patients with prolonged seizures or would delay lumbar puncture for 30 min in patients with short, convulsive seizures
Papilloedema	Presence of venous pulsations suggests absence of increased pressure
Abnormal level of consciousness	
Focal neurologic deficit	Dilated nonreactive pupil, abnormalities of ocular motility, abnormal visual fields, gaze palsy, arm or leg drift

D. Neuroimaging

Brain imaging is frequently an essential part of patient evaluation. Although an MRI (Magnetic resonance imaging) scan would be ideal, it may be simpler to obtain a cranial computed tomography (CT) scan. As already discussed, there are certain situations where an urgent CT is required to rule out a mass lesion or an abscess before doing lumbar puncture.[18] Characteristic neuroimaging changes may also offer clues as to the specific infective etiologies, for example, fronto-temporal changes in Herpes simplex encephalitis (HSE); thalamic and midbrain changes in Japanese encephalitis; disseminated lesions in brainstem and basal ganglia in Eastern equine encephalitis.[1,4,5,6,14,18]

Contrast enhancement is usually indicative of active inflammation. Basal exudates after Gd-DTPA administration are suggestive of Tubercular meningitis but very rarely may be seen in bacterial meningitis. MRI may also pick up unusual etiologies like predominant basal ganglia ring enhancing lesions may suggest toxoplasmosis is an immune-compromised individual and multiple ring enhancing lesions in a patient with chronic meningitis favors tuberculomas.[1,4,18]

E. Electroencephalogram (EEG)

EEG is important in a patient with febrile encephalopathy to rule out non-convulsive status. EEG is strongly recommended in any suspected case of acute encephalitis since it may help in distinguishing focal encephalitis from generalized encephalopathy. In the latter, EEG may show diffuse, bihemispheric slowing for example, triphasic slow waves in hepatic encephalopathy. EEG is invariably abnormal in HSE and evolve from a non-specific slowing to a more characteristic change of 2–3 Hz, periodic lateralized epileptiform discharges originating from the temporal lobes limited to about half the cases in the later stages.[1,4,6,8]

Conclusion:

The diagnostic approach to a patient presenting with fever and altered sensorium poses a real challenge, especially when the history is not available. However, in all cases of an acute febrile encephalopathy, a systematic approach with regards to history, examination and appropriate investigations form an integral part of the management strategy.

Legends to figures:

Table 1: Causes of Fever with altered sensorium

A. Infections

Encephalitis

Meningitis

Cerebral malaria

Brain abscess, subdural or epidural empyema

Sepsis associated encephalopathy (SAE)

Sepsis with DIC / TTP

B. Noninfectious causes of fever:

Over production of heat:

Neuroleptic malignant syndrome

Malignant hyperthermia

Serotonin syndrome

Cocaine, amphetamine toxicity

Ecstasy intoxication

Salicylate poisoning

Thyrotoxic encephalopathy

Convulsive status epilepticus

Catatonic schizophrenia

Impaired heat dissipation:

Anticholinergic toxicity e.g. amitryptiline

Heat stroke

Structural lesions (Impaired thermoregulatory mechanism)

Hypothalamic lesion

Brain stem lesions (stroke)

Intraventricular and subarachnoid hemorrhage

Misc. causes

Infectious or post infectious demyelination (ADEM)

Cerebral fat embolism

Altered sensorium with secondary cause of fever: e.g. Stroke with aspiration pneumonia

Table 2 : Common causes of infectious meningoencephalitis

Viral

DNA viruses: herpes simplex virus (HSV1, HSV2), other herpes viruses (HHV6, EBV, VZV, cytomegalovirus), and adenovirus (for example, serotypes 1, 6, 7, 12, 32).

RNA viruses: influenza virus (serotype A), enterovirus, arboviruses (for example, Japanese B encephalitis), and retrovirus (HIV).

Bacterial

Acute pyogenic meningitis, Listeria monocytogenes, leptospira, legionella, Salmonella typhi (typhoid fever).

Rickettsial

Rickettsia typhi (endemic typhus), Rickettsia prowazekii (epidemic typhus)

Fungal

Cryptococcosis, histoplasmosis, candidiasis.

Parasitic

Plasmodium, Toxoplasma gondii, Nagleria fowleri, Schistosomiasis.

Table -6: Cerebrospinal fluid examination (Normal and abnormal conditions)

CSF tests	Normal	Abnormal	Causes
Opening pressure	60-200 mmH $_2$O†	<60 mmH $_2$O	CSF leak
		>250 mmH $_2$O	Infection, stroke, intra-cranial tumors, IIH, CVT blood – e.g. SAH
Color	Crystal clear	Xanthochromic	Hyperbilirubinemia CSF protein > 150mg%
		Turbid	>200 WBCs
		Green	hyperbilirubinemia Purulent CSF
		Pink	Blood Breakdown products- traumatic CSF
		Orange	Carotinemia, Blood breakdown products
Total cell Count	≤ 5	>5 (depends upon condition and may range from ten to thousands)	Meningitis, Encephalitis, noninfectious inflammatory diseases, post seizure, ICH, Malignancy, Traumatic
Differential cell count	70% Lymphocytes 30% Monocytes occasionally single polymorph or eosinophil	Lymphocytes predominant	Viral, Tubercular, Fungal meningitis
		PMNs predominant	Bacterial meningitis
		Eosinophilic (>10 eosinophils/cmm field or >10% of total cells)	Parasitic uncommonly viral , fungal and rickettsial mening-oencephalitides

Protein	15-50 mg%	<15 mg% >50mg%	Children <2 years age, CSF leak, acute water intoxication, IIH(few cases) CNS infections, Tumors, ICH, demyelination, some endocrine disorders (Myxoedema) AIDP, CIDP, few Metabolic disorders
Glucose	45-80 mg% or 2/3rd of plasma glucose (CSF to plasma glucose ratio-0.6 to 0.7)	<35mg% or <2/3rd of plasma glucose in normoglycemic conditions#	Infectious Meningitis, Encephalitis, chemical meningitis, SAH
Microscopy			
Gram stain	-	+ve	90% untreated Bacterial meningitis (depends on causative organism also) 40-60% partially treated bacterial meningitis
AFB stain	-	+ve	Tubercular Meningitis (37%)
India ink	-	+ve	Cryptococcal Meningitis(50% cases)
Geimsa	-	+ve	Special stain used to detect toxoplasma

+ opening pressure is low (10-100mm H2O) in young children <8 years of age, obese persons may have normal opening pressure upto 250mm H_2O

normal CSF glucose does not rule out infection as it is normal in most of the viral meningitis and may be normal in 50% cases of bacterial meningitis

Table -7: CSF picture in various Meningitides

Tests	Viral	Bacterial	Tubercular	Fungal
Opening pressure	Usually normal	Elevated	Elevated / variable	Elevated / Variable
Color	Normal	Turbid	Xantho-chromic variable	Clear/ variable
Total cells	<100/cmm	≥1000/cmm	Variable (100-500/cmm)	variable
Differential#	Lymphocytic	polymorpho-nuclear	Lymphocytic	Lymphocytic
Protein	normal to elevated	marked elevation	elevated	elevated
Glucose	Usually normal	Decreased	Decreased	Decreased
# Early stages of viral, tubercular and fungal meningitis may show polymorphonuclear leucocytosis and early stages of bacterial meningitis may show lymphocytic predominance				

Table 8: Rapid CSF tests for determination of Bacterial Etiology

Gram stain	Sensitivity of this test varies from 50% to 90%, but decrease to 7% to 41% among patients taking oral antibiotics.[9,11] Concentration of ≤10^3 colony forming units (CFU)/ml are associated with a positive gram stain result 25% of the time;10^3 to 10^5 CFU/ml yield a positive gram stain result in 60% and >10^5 CFU/ml lead to positive results in 97% of cases.[24]
Latex agglutination	The sensitivity of this test varies from 78% to 100% for H. influenzae, 67-100% for S. pneumonia, 69-100% for streptrococcus and 50-93% of N. meningitides. Latex agglutination may be most useful for the patient, who has been pretreated with antimicrobial therapy and whose gram stain and CSF culture results are negative.[8,26]
Limulus lysate assay	It detects ~10^3 gram negative bacteria/ml of CSF and as little as 0.1 ng/ml of endotoxin. [8,26]
PCR	Sensitivity of 100%, specificity of 98.2%, a positive predictive value of 98.2% and negative predictive value of 100%.[8,27]

Table 9: Lab tests helpful in distinguishing bacterial from Viral Meningitis

CSF Lactate level	CSF lactate concentration of >4.2 mmol/L were considered to be a positive discriminative factor for bacterial meningitis, with sensitivity of 96% and specificity of 100%. It is valuable in the subgroup of postoperative neurosurgical patients, in which empirical antimicrobial therapy should be considered if CSF lactate concentrations are ≥4.0 mmol/L, pending results of additional studies. [8,28,29]
CRP concentration	Serum CRP concentration was capable of distinguishing gram stain negative bacterial meningitis with a sensitivity of 96%, a specificity of 93% and a negative predictive value of 99%. A normal CRP has a high negative predictive value in the diagnosis of bacterial meningitis. [8,30,31]
Procalcitonin concentration	In children, the sensitivity of procalcitonin levels (>5 mg/L) for diagnosis of bacterial meningitis was 94% and specificity was 100%, while in adults, serum concentration > 0.2 ng/ml had a sensitivity and specificity of upto 100% for diagnosis of bacterial meningitis. [8,32,33,34]
PCR	Viral testing using PCR is another modality to identify patients with aseptic meningitis, especially enterovirus. [8,35]

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