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Imaging in adult patients with acute febrile encephalopathy: What is better, computerized tomography (CT) or magnetic resonance imaging (MRI)?

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ABSTRACT

Objective: To compare the efficacy of cranial imaging techniques in adult patients with acute febrile encephalopathy. **Methods:** We enrolled one hundred and two patients presenting to the emergency with fever of shorter than 15-day duration and altered sensorium. All the patients were subjected to routine investigations, detailed cerebrospinal fluid analysis, computerized tomograms (Non contrast followed by contrast enhanced) and Magnetic resonance imaging of the brain. Final diagnosis was reached after considering the clinical, biochemical findings, imaging results and response to therapy. The positive yield of radiological investigations was compared against the final diagnosis. **Results:** The patients were divided into three groups. Of these patients, 48 had evidence of meningoencephalitis, 22 patients had pyogenic meningitis, and 20 were combined together in others group. In other 12 patients, a definitive diagnosis could not be made. Only 37% patients were detected to have abnormal computerized tomograms and the commonest abnormality was diffuse edema, which failed to point to an etiological diagnosis. Magnetic resonance imaging was abnormal in 62.75% cases and was able to suggest an etiological diagnosis in 100% cases of cerebral venous thrombosis, tubercular meningitis, 95% cases of meningoencephalitis and 45% with meningitis. **Conclusions:** Magnetic resonance imaging provides better information than computerized tomography in adult patients with acute febrile encephalopathy.

1. Introduction

Acute onset fever with altered mentation is a problem commonly encountered by the physician in the emergency. "Acute febrile encephalopathy" is a term commonly used to identify this condition. It is a common condition leading to hospital admissions in both adults and children in India. Central nervous system (CNS) infections are the most common cause of nontraumatic coma in children^[1]. The etiological agent may be a virus, bacterium or a parasite^[2]. The profile of acute febrile encephalopathy

varies across different geographic regions with newer agents being increasingly recognized all over the world. The physicians have to be very meticulous while approaching such a patient due to the diversity of causes and equally large number of mimicking conditions. Even after a detailed diagnostic workup, one may not be able to reach to a definitive diagnosis in many cases^[3]. Nevertheless, a detailed examination & workup is warranted, because conditions like herpes simplex encephalitis (HSE) and cerebral malaria are eminently treatable.

Many acutely ill febrile patients with encephalopathy may make complete recovery once the underlying cause is treated, but considerable skill is required for a correct diagnosis. Cerebrospinal fluid (CSF) analysis and cranial imaging modalities are extremely helpful in this regard. The most widely used imaging modality in acutely ill patients

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has been cranial computerized tomograms (CT scans). They are usually helpful in ruling out intracranial space occupying lesions, and contrast enhancement of meninges may suggest meningeal involvement. This is often the first investigation ordered in a patient with nontraumatic coma but its diagnostic yield may not justify its use as a screening tool. Magnetic resonance (MRI) of the brain is now a widely available imaging technique and it provides high resolution images without exposing the patients to the harmful effects of radiation. Characteristic MRI patterns, present in many diseases like herpes simplex virus (HSV) infection and Japanese encephalitis (JE), may provide a clue to the diagnosis. The imaging techniques are often non representative of the severity of illness. Clinically, severe cases of cerebral malaria or septic encephalopathy may have nearly normal findings on imaging. In order to facilitate the judicious use for maximum utility of imaging techniques, it is imperative to know when a CT scan or MRI should be ordered in patients with fever and encephalopathy. The aim of this study was to evaluate the utility of cranial imaging techniques like CT scan and MRI in adult patients presenting with acute febrile encephalopathy. We also studied potential clinical indicators, which could guide a clinician to use these imaging techniques judiciously.

2. Materials and methods

We enrolled all consecutive patients who presented to the medical emergency with fever of less than 15 d and altered sensorium, either at onset or following fever lasting for at least 24 h.

Patients younger than 12 years old were excluded from the study. We also excluded patients presenting with deranged metabolic indicators like hypoglycemia, hypoxia, hypercarbia, hypo or hypernatremia and azotemia at the time of presentation. Patients with cerebrovascular accidents

developing fever were also excluded from the study.

The history was recorded and the patients then underwent a detailed clinical examination. Complete hemogram, metabolic profile, chest X-ray and electrocardiogram (ECG) were done in all the patients. Malarial parasite examination and histidine-rich protein based immunochromatographic test were done in the patients to rule out malaria. Blood cultures and urine cultures were done and clinically obvious site of sepsis was investigated. Lumbar puncture was done in all the patients at admission and CSF was analyzed for cytology, protein levels, CSF glucose to blood glucose ratio, gram stain, culture, sensitivity and adenosine diaminase (ADA) levels. All patients, except two, underwent non contrast computerized tomograms (NCCT) followed by contrast enhanced computerized tomograms (CECT) of the brain. This was followed by a gadolinium enhanced magnetic resonance imaging (MRI scan) of the brain. In two patients, MRI scan was performed right at the outset.

CSF HSV serology could be done only in a few selected patients, in which the clinical suspicion was high. Since facilities for HSV PCR and JE serology were not fully standardized in the institute at the time of the study, the CSF and paired serum samples have been preserved for these tests.

The patients were classified into broad groups of meningitis, meningoencephalitis and others after taking into consideration of the clinical findings, CSF cytology, imaging results and response to therapy. The diagnostic criteria used to classify these patients into different groups are enumerated in Table 1.

In the absence of confirmatory evidence (serological methods/PCR), we could not further classify meningoencephalitis into etiologic groups. We labeled patients as possible herpes encephalitis, when MRI suggested the involvement of medial temporal lobes or inferior surface of frontal lobes. Similarly, a diagnosis of possible Japanese encephalitis was considered when MRI

Table 1
Criteria for final diagnosis.

Disease	Criterion
Pyogenic meningitis	Fever with altered sensorium (without focal symptoms/signs) ± neck signs + CSF cytology (predominantly polymorphs) + meningeal enhancement on either CT scan or MRI.
Meningoencephalitis	Fever with altered sensorium (with focal symptoms/signs) ± neck signs + CSF cytology (predominantly lymphocytes) + EEG /MRI/CT evidence of parenchymal disease.
Acute disseminated encephalomyelitis (ADEM)	Fever with altered sensorium (with focal symptoms/signs) + Compatible CSF (Raised CSF protein + normal CSF sugar + normal CSF cytology) + Diffuse white matter changes in the MRI
Tubercular meningitis (TBM)	Fever with altered sensorium (with or without focal symptoms/signs) + CSF Compatible with chronic meningitis + CSF ADA >12
Cerebral malaria	Fever with altered sensorium (without focal symptoms/signs) with peripheral Smear/HRP antigen test positive for malaria.
Cerebral venous thrombosis (CVT)	Appropriate clinical setting + Fever with altered sensorium (with focal symptoms/signs) + Evidence of cortical venous thrombosis on MRI of brain.
Neuroleptic malignant syndrome (NMS)	Fever with altered sensorium (in the appropriate clinical setting) with normal CSF and imaging + Raised total CPK.
Septic encephalopathy	Underlying sepsis syndrome with normal CSF analysis, CT and MRI scan.

revealed lesions in thalamus and basal ganglia. The rest of the patients with meningoencephalitis were labeled as non-specific encephalitis of probable viral origin.

After classifying the patients into three major categories, we analyzed the positive yield of radiological investigations in each category and related it with the final diagnosis. Descriptive statistics like mean, standard deviation, frequency and percentages were calculated. The qualitative variables were analyzed using the "Chi-square test", and $P < 0.05$ was considered significant.

3. Results

3.1. History and diagnosis of patients

This prospective study was carried out over a period of 1 yr from July 2005 to June 2006. The patients presenting to the medical emergency in the Nehru Hospital, PGIMER, Chandigarh, were screened. A total of 122 adult patients presenting with a history of fever shorter than 2-week duration and altered sensorium either accompanying or following fever were screened. Out of the total 122 cases, 20 were excluded from the final analysis due to lack of complete data. Final analysis was done using the data available in 101 cases.

The mean age of the patients was (30.14 ± 14.79) yr. Out of 101 cases, 64 (62.75%) were males. The patients were divided into three major etiologic groups, 48 patients having evidence of meningoencephalitis, 22 patients having pyogenic meningitis, and 20 combined together in others group. The patients combined together in the others group had varied clinical conditions, six who were diagnosed as tubercular meningitis, four who had cerebral venous thrombosis, four had encephalopathy secondary to sepsis, and two each who had cerebral malaria, acute disseminated encephalomyelitis (ADEM) and neuroleptic malignant syndrome (NMS) respectively. We could not arrive at a definite diagnosis in 12 cases (11.76%) in spite of the availability of the complete clinical data. Twelve patients

(11.8%) succumbed to their illness during the study period. The mean interval between fever and the onset of altered sensorium was 6.18 d in meningitis as compared to 3.9 d in meningoencephalitis. Out of the 101 patients, 64 had seizures and 54 were generalized tonic clonic seizures (GTCS). Out of the 22 cases of meningitis, 16 (72.73%) had seizures but none had focal onset seizures in our study. Focal onset seizures, in our study, were exclusively seen in the patients with meningoencephalitis (8/48).

Thirty patients had a history of focal neurological deficit. Twenty of them had meningoencephalitis. The other patients with focal neurological deficit were related to cortical venous thrombosis, tubercular meningitis and ADEM (four patients) respectively. None of our patients with meningitis had demonstrable focal neurological deficit but 42% of the patients with meningoencephalitis had focal deficit. In one case with focal deficit, final etiological diagnosis could not be achieved. Hemi paresis was the most common focal deficit occurring in 53% patients.

3.2. Diagnosis by CT scan

CT scan of the brain was done in 99 out of 101 cases. MRI was performed directly in two cases as there was a very strong suspicion of encephalitis. Abnormalities in CT scan were present in 38 out of 99 cases. About 50% of the patients with meningoencephalitis were detected to have abnormal CT scan. Only four out of 22 scans done in meningitis were abnormal. Focal abnormality on CT scan was found in eight cases. In four cases, it was suggestive of cerebral venous thrombosis but was confirmed on MRI. The most commonly reported abnormality was edema seen in 23.5% cases and it suggested parenchymal involvement. Other abnormalities included meningeal enhancement and focal hypo density (seen in eight patients each), hydrocephalous and intra cranial bleed (seen in four cases each). The detailed results of CT scan are shown in Table 2.

3.3. Diagnosis by MRI scan

Table 2

Details of the findings on computerized tomography (CT scan) ($n=99$).

CT scan	Pyogenic meningitis	Meningo encephalitis	Tubercular meningitis (TBM)	Cerebral venous thrombosis (CVT)	Others	Total
Normal CT	18	24	2	0	16	60
Abnormal CT	4	24	4	4	3	39
Edema	2	18	0	0	3	23
Meningeal enhancement	4	2	0	0	0	6
Hypodensity	0	4	0	4	0	8
Bleed	0	0	0	4	0	4
Hydrocephalus	0	0	4	0	0	4
Total	22	48	6	4	19	99

MRI was done directly in two patients with focal onset seizures.

MRI scan was reported as abnormal in 64 (62.75%) out of 101 cases. MRI was abnormal in 95.83% cases of meningoencephalitis and as many as 87.5% had grey matter changes. Only 2/48 (4.2%) patients with meningoencephalitis had white matter changes. Grey matter changes in meningoencephalitis were focal in 26 cases and diffuse in 16 cases. One patient of meningoencephalitis had white matter changes along with grey matter changes and another case with ADEM had similar changes. About 50% of our patients with meningoencephalitis had changes on MRI suggestive of either HSE or JE. The rest 50% patients with meningoencephalitis were without any specific pattern of changes on MRI and were labeled as nonspecific encephalitis, of probable viral origin. The detailed results of MRI scan are shown in Table 3.

Meningeal enhancement on MRI was seen in 8/22 patients with clinical evidence of pyogenic meningitis. Basal exudates were demonstrable on all six patients with tubercular meningitis on MRI. The presence of meningeal enhancement was also demonstrated in 4/48 patients with meningoencephalitis. As many as 22 patients with meningitis (16 pyogenic and six tubercular) and 44 patients with meningoencephalitis did not show meningeal enhancement on MRI.

As many as 95% case of meningoencephalitis had parenchymal abnormalities on the MRI thereby meaning that MRI was more useful in picking up parenchymal abnormalities in patients suspected of having encephalitis.

3.4. Comparison between CT scan and MRI scan

In febrile patients having seizures, 40% had abnormal CT scans, whereas 37% of patients who did not have seizures had abnormal CT scan findings. Even though six out of eight patients with focal seizures had abnormal CT scans, these abnormalities (edema and bleed) were very suggestive of a

localized parenchymal lesion but it failed to provide specific etiological diagnosis. In addition, 53.84% (14/26) patients with focal neurological deficit (FCD) had an abnormal CT scan as compared to 33% (24/72) who did not have focal deficit.

Abnormal MRI findings were seen in 62.5% of patients who had seizures, but it was not very significant because 63.16% of patients without seizures also had abnormal MRI findings. A very significant correlation was observed between MRI abnormalities and focal seizures, with all the cases with focal seizure showing abnormalities on MRI. All patients with focal neurological deficit had an abnormal MRI scan but only 50% of patients without focal neurological deficit (FND) had abnormalities in their MRI. This finding also suggests a significant correlation between focal neurological deficit and an abnormal MRI.

In addition, when we compared CT and MRI in our study population, we found that MRI was better than CT scan in all our patients with meningitis and meningoencephalitis (Table 4).

4. Discussion

Fever with diminished sensorium is a common symptom complex leading to hospital admissions in both adults and children in India. Various studies have shown that CNS infections are the commonest cause of acute febrile encephalopathy[1], which is also supported by our findings in adults. Alteration in sensorium in a patient with CNS infection indicates parenchymal involvement; therefore encephalopathy is expected in patients having encephalitis or meningoencephalitis. The reason for altered sensorium in meningitis is postulated to be the adjacent brain parenchyma inflammation resulting in border zone encephalitis and results in encephalopathy[4].

Table 3

Description of MRI changes (n=101^a).

MRI scan	Meningitis	Meningo encephalitis	Tubercular meningitis (TBM)	Cerebral venous thrombosis (CVT)	Others	Total
MRI Changes	8	46	6	4	10	64
Meningeal enhancement	8	4	6 ^b	0	0	10
White	0	2	0	0	2	4
Grey	0	42	0	0	6	48
Focal	0	26	0	4	2	28
Diffuse	0	16	0	0	4	20
Total	22	48	6	4	20	101

^aAbout 2/3 patients with TBM had hydrocephalous sign as detected by MRI. ^bExudates were observed.

Table 4

Comparison between CT and MRI in picking up abnormalities.

Scanning results	Meningitis	Meningo encephalitis	Tubercular meningitis (TBM)	Cerebral venous thrombosis (CVT)	Others
MRI abnormal	8 (36.36%)	46 (85.7%)	6	4	8 (25%)
CT abnormal	4 (18.18%)	24 (50%)	4	4	8 (25%)
Total	22	48	6	4	32

We observed that 81.8% (81/101) of all our patients had an infective etiology. Tubercular meningitis, pyogenic meningitis and encephalitis constituted 75.9% of our patients with “acute febrile encephalopathy”, with meningoencephalitis being the commonest etiology. This finding is little different from an Indian study in children. In this study, tubercular meningitis, pyogenic meningitis and encephalitis together constitute more than 90% of such cases, with tubercular meningitis being the commonest cause^[1]. Our results are similar, to some extent, to a study evaluating acute encephalopathy in children at UK. In this study, 77% children were detected to have evidence of viral encephalitis^[5]. The reason for the lower incidence of tubercular meningitis encountered as a cause of acute fever and encephalopathy in adults is not very clear. It could be due to the fact that tubercular meningitis, in adults, is usually a subacute to chronic illness. Hence, a number of cases of tubercular meningitis would not have satisfied our inclusion criterion for acute febrile encephalopathy. The other etiologies that were identified included acute disseminated encephalomyelitis, cortical venous thrombosis, neuroleptic malignant syndrome, cerebral malaria and septic encephalopathy.

Failure to identify a definitive cause for encephalopathy is not unusual. In 11.76% cases, even after all the investigations (CSF, CT and MRI), we could not arrive at a definite diagnosis. Our findings are very similar to a study evaluating encephalopathy in children, 20% cases were labeled as nonspecific encephalopathy, when a diagnosis could not be established even after all possible investigation^[6].

It is difficult to correctly establish etiological diagnosis in patients with viral encephalitis even when all possible investigations are available. In our study, we could not determine the definite etiologic agents in patients with meningoencephalitis, due to the non availability of tests for neurotropic viruses. In various studies, specific etiological agent could not be confirmed in patients with viral encephalitis, in 50%–60% patients^[5,7].

Radiological investigations are important tools in evaluation of encephalitis. Both MRI and CT are known to provide useful information in the evaluation of febrile unconscious patients^[8]. In our study population, we observed that CT scan (NCCT/CECT) did not add much to the information available on the basis of clinical evaluation and baseline biochemical investigations. Only one of our patients was detected to have space occupying lesion (brain abscess) on NCCT. Out of 28 patients with meningitis, only 4 (14%) patients showed meningeal enhancement. Although 42.4% cases of meningitis or meningoencephalitis had abnormal CT scans, meningeal enhancement was suggestive of etiology only in four patients. CT scan did pick up hydrocephalus in six patients, suggesting a possible diagnosis of TBM and

hemorrhagic infarcts suggesting a possibility of CVT, but no definite conclusions could be drawn regarding etiology from these abnormal imaging findings in isolation.

It is known that CT scan is likely to be normal in as many as 40% cases with viral encephalitis, especially early stages and is more likely to pick up abnormality in the later stages when the pathology is well established^[9,10-12]. It is also known that non-enhanced CT scans and MRIs of patients with uncomplicated acute bacterial meningitis may be unremarkable^[13]. Therefore, the utility of early CT scan in the emergency for picking up etiological diagnosis in acute febrile encephalopathy is questionable.

Focal seizures and presence of focal neurological deficits indicate a localized lesion and are expected to be picked up by CT scan. In our study, although more than half of patients who had focal neurological deficit had abnormal CT scans, the utility of the CT scans was limited by its apparent inability to point towards a particular definitive diagnosis and resultant management. This was due to the fact that the abnormality was in the form of diffuse edema in most of the cases. Similar concerns have been raised in a study, where emergency cranial computed tomography in children with febrile encephalopathy had little influence on management^[14].

Although CT scan is known to be useful in picking up focal lesions in the brain parenchyma like abscess/infarcts, demonstrating meningeal enhancement and detecting hydrocephalous^[14], MRI was much more informative in the setting of acute febrile encephalopathy in our study.

The presence of diffuse edema on CT scan may suggest an underlying parenchymal involvement and focal hypodensities in temporal lobe and basal ganglia may point towards a possible diagnosis of viral encephalitis (HSV or JE). MRI is known to be superior in picking up subtle changes and is likely to be more helpful in establishing a diagnosis by picking up characteristic pattern of grey matter involvement^[9,10,15]. The sensitivity of MRI in picking up abnormal parenchymal changes in viral encephalitis varies from 44% to 100%^[7,9]. More than 90% of our patients with an encephalitic form of illness had abnormal MRI findings, suggesting parenchymal involvement, whereas only around 30% of patients with pyogenic meningitis had an abnormal MRI.

About 87.5% patients having brain parenchymal involvement showed grey matter lesions and these changes were focal in 62% cases. In one study on viral encephalitis, grey matter changes were seen in as many as 93% cases and the rest had white matter changes^[9]. Although MRI is supposed to be better in picking up meningeal enhancement, in our study, it was able to pick up meningeal enhancement in only 10 patients with documented meningeal involvement^[13]. This indicates that MRI is a better modality in detecting parenchymal involvement in patients presenting

with acute febrile encephalopathy but may not pick up meningeal involvement.

No correlation was found between generalized seizures and abnormal MRI in our patients, but abnormalities in MRI were observed to be correlated with focal onset of seizures in all patients. The results indicate that occurrence of focal seizures correlates well with parenchymal involvement observed on MRI. It is well known that febrile convulsions may be the only presenting manifestation of encephalitis and focal seizures are known to occur with increased frequency in encephalitis^[5,16]. In addition, we also noted that all patients with focal onset seizures and focal neurologic deficit had abnormal MRI scans. Thus we can conclude that MRI of brain in patients of acute febrile encephalopathy presenting with focal seizures or focal neurological deficit is more likely to pick up encephalitic process early. In patients presenting with focal seizures and focal neurological signs, MRI may be preferred radiological investigation over CT scan.

The fallibility of laboratory tests in the diagnosis of encephalitis is well known, as these tests are able to pick up etiological diagnosis in only about 40% patients^[5,7]. In our study population, MRI showed abnormal findings in almost all cases of meningoencephalitis but was able to suggest a possible etiological diagnosis in only 50% cases. About 16/48 patients had characteristic MRI findings of temporal lobe lesions suggestive of HSE while only 8/48 had thalamic involvement suggestive of JE^[9,11,12,15]. In the absence of a supportive serology or definitive polymerase chain reaction, these patients can at best be labeled as possible herpes/Japanese encephalitis on radiology. This is important as serological tests or PCR may take a longer time and definitive therapy can be instituted early based on MRI findings.

In our study, MRI was found better than CT scan in all our patients with meningitis and meningoencephalitis, a fact well documented in the literature for individual disorders resulting in acute febrile encephalopathy in adults^[10,13–16]. We recommend that MRI should be the preferred radiological investigation than computerized tomography, where ever it is available. However, the institution of treatment should not be delayed in case radiological imaging is not available.

Our study had a few limitations. Small number of patients and inability to identify definitive etiological agent in patients with meningoencephalitis were the major ones. A larger multicentric study with emphasis on isolation of neurotropic viruses would be needed to answer these questions.

We can conclude that, “acute febrile encephalopathy” in adults is a heterogeneous syndrome. A variety of conditions can lead to acute fever and encephalopathy. CT scan of the brain is of limited value in patient with acute febrile encephalopathy, since it does not definitely indicate either

meningeal or parenchymal involvement. MRI is more likely to pick up early lesions in patients with acute febrile encephalopathy and should be the radiological investigation of choice in such patients.

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