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ROLE OF MRI IN EVALUATION OF NEUROLOGICAL DYSFUNCTIONS ASSOCIATED WITH ACUTE FEBRILE ILLNESS

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ABSTRACT

Objectives: Many cases of acute febrile illness show neurological complications of not only diseases with known nervous system affliction like cerebral malaria; but also of diseases which were previously not thought to be neurotropic like Dengue fever. Our study has described the various abnormalities in MRI Brain scans of these patients. **Methods:** A prospective study of 34 patients, who presented with acute onset of fever and some form of neurological dysfunction, underwent MRI of Brain on an elective basis. **Results:** Of the 34 patients, 25 (74%) had abnormal MRI scans and 9 (26%) had normal scans. The final diagnosis of patients were as follows- Acute pyogenic meningitis. (8 patients- 23%), Cerebral malaria (7 patients- 21%), Dengue encephalitis (7 patients- 21%), Leptospirosis (2 patients- 6%), Viral encephalitis of unknown etiology (2 patients- 6%), Japanese encephalitis (1 patient- 3%), HSV encephalitis (2 patients- 6%), Influenza associated encephalitis (1 patient- 3%), CNS Tuberculosis (2 patients- 6%). In 2 patients, a diagnosis could not be established even after extensive diagnostic work-up. **Conclusion:** In acute fever associated with neurological dysfunction, MRI brain has a good sensitivity, however, there are doubts about its specificity in conclusively diagnosing specific diseases.

KEYWORDS: Acute febrile illness, MRI, brain.

INTRODUCTION

Fever can be caused by bacteria, viruses, parasites and even fungi; and can either occur due to infection of any specific organ system or generalised bacteraemia, viremia or parasitaemia. In many infections, which are mainly endemic and epidemic in tropical and sub-tropical regions, there is an acute presentation of fever, so much so that there is a non-specific term used to encompass these diseases- Acute Febrile Illness or simply 'AFI'. There are numerous causes of AFI, a few common ones being Malaria, Dengue etc.

Now, in the sense that the brain houses the central mechanism for the regulation of body temperature, almost all illnesses that cause fever must interact with the central nervous system. There are far fewer diseases, however, in which the nervous system symptomatology is of prime diagnostic importance.[1]

Thus the spectrum of diseases presenting with neurological symptoms along with acute fever, can broadly fall into the following categories[1]:-

A. Neurologic impairment resulting from very high acute fever itself, i.e. when the temperature rises above 42 degrees Celsius, which is seldom does.
B. Fever as a manifestation of a central nervous system infection along with other neurological symptoms.
C. Systemic febrile disorders (AFI) with central nervous system signs and symptoms.
D. Fever as a manifestation of non-infectious primary neurological disorders.

As neurologic impairment resulting from very high acute fever itself is quite rare and non-infectious neurological disorders do not cause an acute onset of fever, in our study, we will be dealing only with primary CNS infections causing symptoms of fever and neurological symptoms and systemic febrile disorders (AFI) with central nervous system signs and symptoms.
Here we describe a study of 30 patients presenting with neurological dysfunction associated with acute febrile illness evaluated with MRI.

2. AIMS AND OBJECTIVES

1. To study the role of MRI in establishing the diagnosis in cases of neurological dysfunctions which are associated with acute febrile illness.
2. To evaluate MRI findings of diseases causing neurological dysfunctions that are associated with acute febrile illness.

3. MATERIALS AND METHODS

Study Design

A prospective study of 34 patients, who presented with acute onset of fever and some form of neurological dysfunction, underwent imaging i.e. MRI of Brain on an elective basis. Prior institutional ethics committee clearance was obtained for the study.

Standard tests (history taking, physical examination, relevant blood investigations) were directed to all patients. Routine/ Microscopic CSF analysis was done in all patients with additional CSF tests according to etiology suspected was done.

Informed consent was obtained from the subjects for inclusion of their images in the study. A total of 34 patients who were investigated between October 2014 and September 2015 were included. MRI Brain studies were done on a 3.0 Tesla Philips Achieva Medical System.

Examination was performed on a 3.0 Tesla Philips Achieva Medical systems. The entire examination lasted for around 45 min to 1 hr. Scans were done as per the following MRI BRAIN protocol. Examination was performed with patient in supine position. 0.1mmol/kg Gadolinium based contrast was injected at rate of 2.5 ml/sec followed by saline flush as and when required.

Sequences done included

1. Survey- Muti stack survey scan (COR/SAG)
2. FLAIR_LongTR (TRA)
3. DWI
4. T2w SE (TRA)
5. T2w FFE or GRE (T2*) (TRA)
6. FLAIR_LongTR (COR)
7. T1w SE (SAG)
8. T1w SE (TRA)
9. T1w SE GADO (Post contrast T1) (TRA)
10. T1w 3D TFE GADO (Post contrast T1) (TRA).

4. RESULTS

A total 34 number of patients who presented to the OPD or Emergency department and later admitted with presentation of acute onset of fever and some form of neurological dysfunction were included in the study. These patients were referred from medicine and pediatric departments out of which all were admitted and were indoor patients. A brief clinical history, correlating with their examination findings, was noted down from the patient. Based on clinical scenario, MRI BRAIN of all patients was performed on elective basis with their due consent and findings were correlated and compared with blood and CSF investigations.

Out of the 34 patients, 19 patients were male and the rest (15) were female.

The majority of patients (12) were in the 20-29 years age group followed by the 13-19 age group(6 patients). The least were in the 50-59 (2) and > 60 years age group (2). 20 patients were admitted to the intensive care unit while 14 were from the general ward (14). The most common neurological presentation in patients with acute febrile illness was altered sensorium (21) followed by seizures (14) while 6 patients presented with focal neurological deficit. No patient in our study presented with cranial nerve palsy.

MRI findings

9 patients (26%) had a normal MRI scan while the remainder 25 (74%) showed a positive scan. The patients with normal findings included those with acute pyogenic meningitis (3), leptospirosis (2), unknown etiology (2), cerebral malaria (1) and dengue encephalitis (1). (Table 1).

Among those with positive scans, blooming on T2* weighted images (GRE, FFE) was seen in 32% while diffusion restriction was seen in 21%. Enhancement on post-contrast scans was seen in 11% patients.

Table 1: Final diagnosis of patients.

Category	Diagnosis	No. of patients having abnormal MRI	No. of patients having normal MRI	Total
Primary CNS infections with no e/o active systemic infection at time of MRI	Acute pyogenic meningitis	5	3	8
	CNS Tuberculosis	2	0	2
	HSV Encephalitis	2	0	2
	Japanese Encephalitis	1	0	1
	Influenza encephalitis	1	0	1
	Viral encephalitis of unknown etiology	2	0	2
	Total	**13**	**3**	**16**
Systemic infection causing acute febrile illness, with secondary involvement of nervous system	Cerebral malaria	6	1	7
	Dengue Encephalitis	6	1	7
	Leptospirosis	0	2	2
	Total	**12**	**4**	**16**

Table 2: Distribution and pattern of lesions.

Basal ganglia	2
Thalami	12
Cerebellum	5
Brainstem	4
Limbic and insular cortex	5
Cerebral cortex	3
Cerebral white matter	10
Extra-axial enhancement	5
Diffuse cerebral edema	2

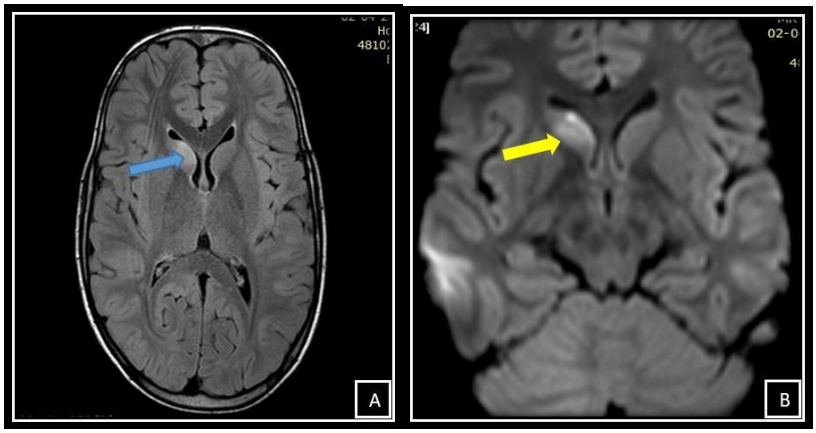

Figure 1: Cerebral Malaria: A: FLAIR, B: DWI.

A, B: FLAIR hyperintensity in the head of right caudate nucleus (blue arrow), showing restricted diffusion on DWI (yellow arrow).

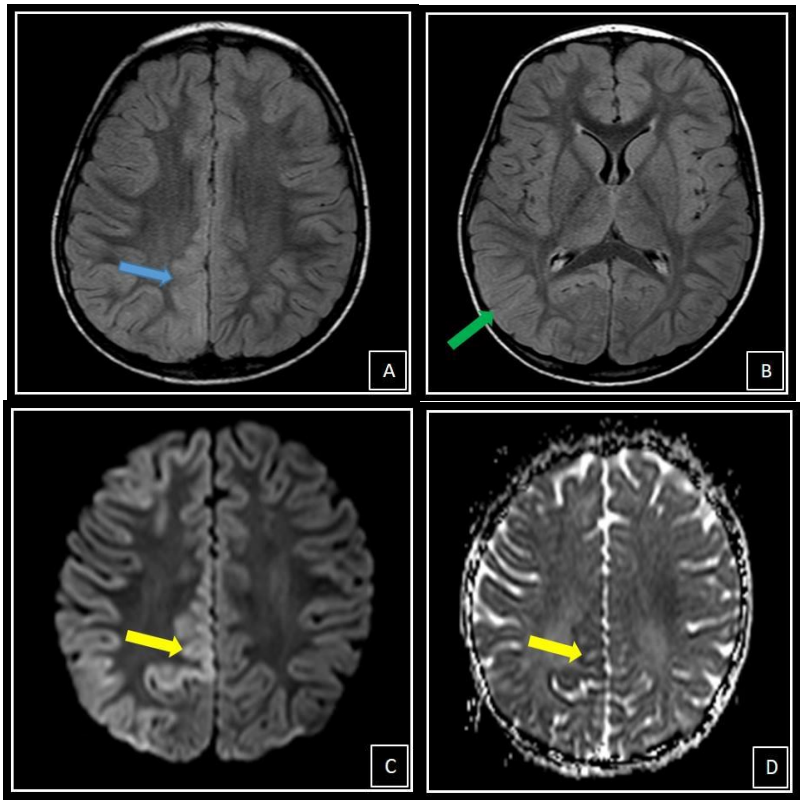

Figure 2: Cerebral Malaria A, B: FLAIR C: DWI D: ADC

A, B: FLAIR hyperintensity involving the cortex associated with gyral swelling in the right para-falcine parietal region (blue arrow) and right posterior parietal region (green arrow).

C, D: Restricted diffusion with corresponding low ADC values in the right para-falcine parietal region suggestive of cortical Infarct (yellow arrows).

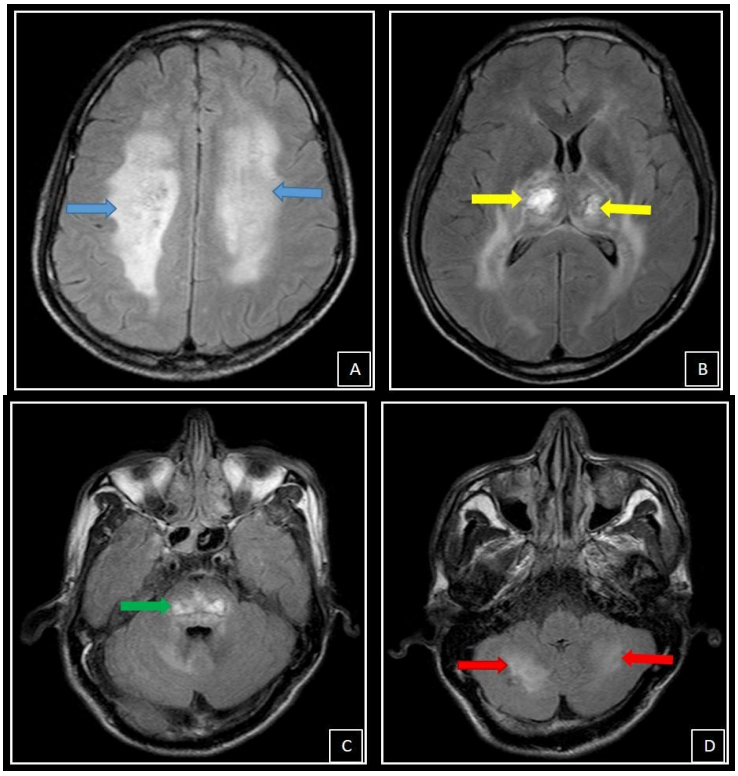

Figure 3: Dengue Encephalitis A, B, C, D: FLAIR.

A, B, C, D: Confluent FLAIR hyperintensity in the corona radiata bilaterally (blue arrows). FLAIR hyperintensities in both thalami (yellow arrows) and pons (green arrow), showing peripheral hypointense rims. Patchy FLAIR hyperintensities in the cerebellar white matter bilaterally (red arrows).

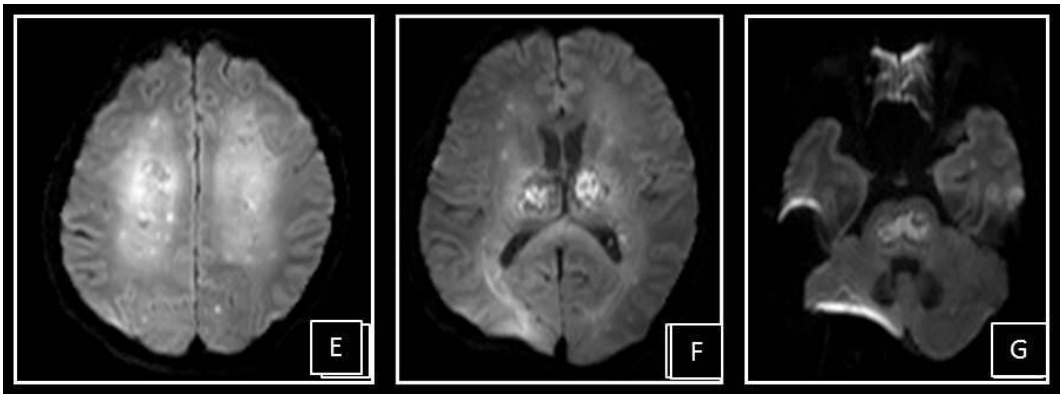

Figure 3: Dengue Encephalitis E, F, G: DWI E, F, G: Restricted diffusion on DWI in the hyperintensities shown in A, B, C, D (FLAIR images) of figure 3.

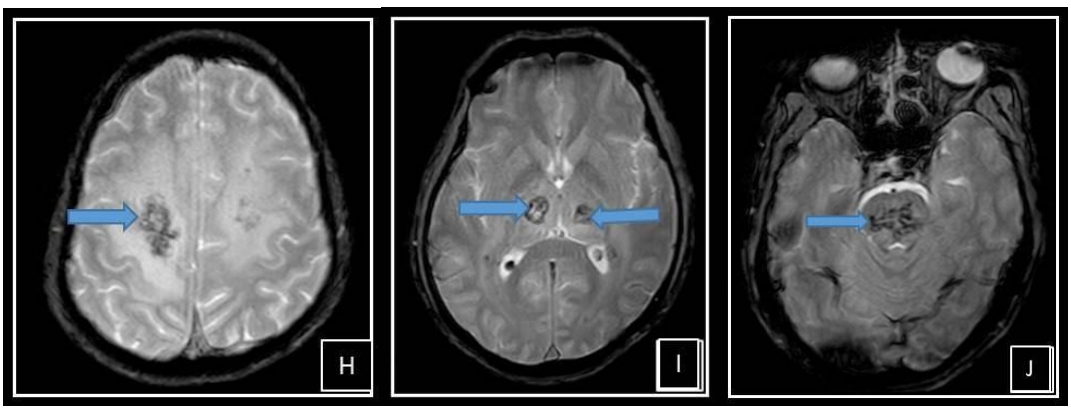

Figure 3: Dengue Encephalitis H, I, J: FFE (GRE) H, I, J: Blooming (blue arrows) in the hyperintensities shown in A, B, C, D (FLAIR images) of figure 3, suggestive of haemorrhage.

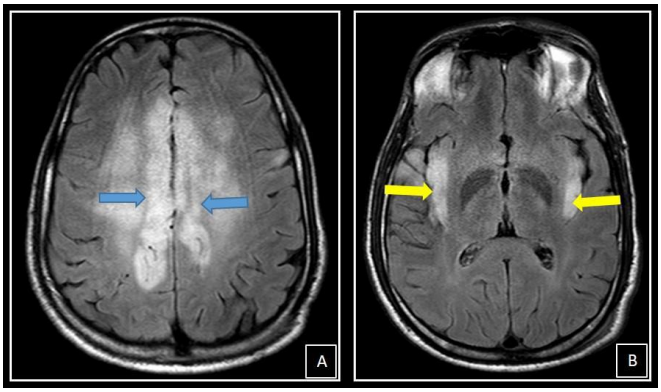

Figure 4: HSV encephalitis A, B: FLAIR axial C: FLAIR coronal D: DWI A, B, C: FLAIR hyperintensity noted in both the cingulate gyri (blue arrows) and the insular cortices (yellow arrows).

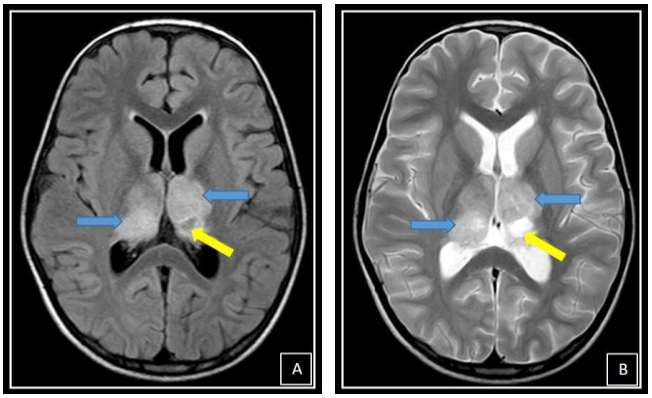

Figure 5: Influenza Encephalitis A: FLAIR axial B: T2 axial.

A, B: T2 and FLAIR hyperintensities noted in both thalami (blue arrows). A liquefied area noted within the left thalamus, which is partially suppressed in FLAIR (yellow arrows).

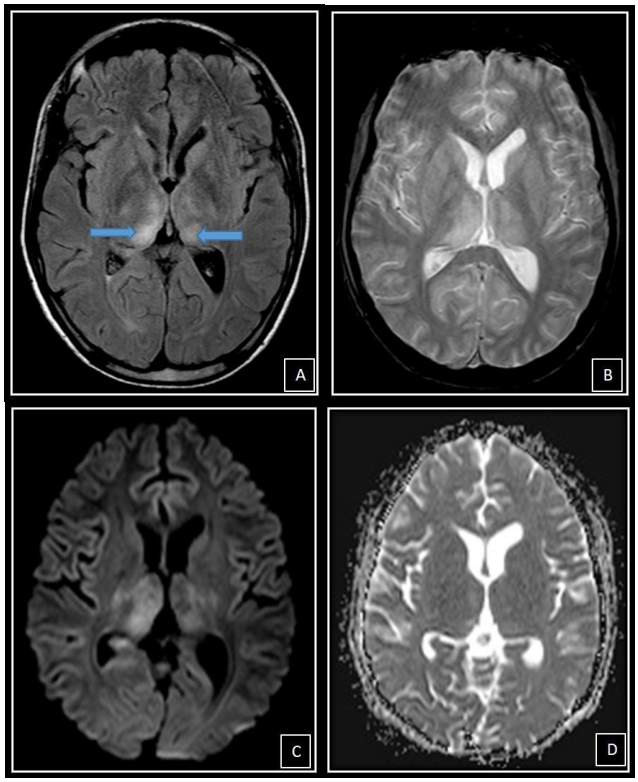

Figure 6: Japanese Encephalitis A: FLAIR axial B: FFE (GRE) axial C: DWI D: ADC A, B, C, D: FLAIR hyperintensities in both thalami (blue arrows), not showing blooming on FFE (GRE) or restricted diffusion.

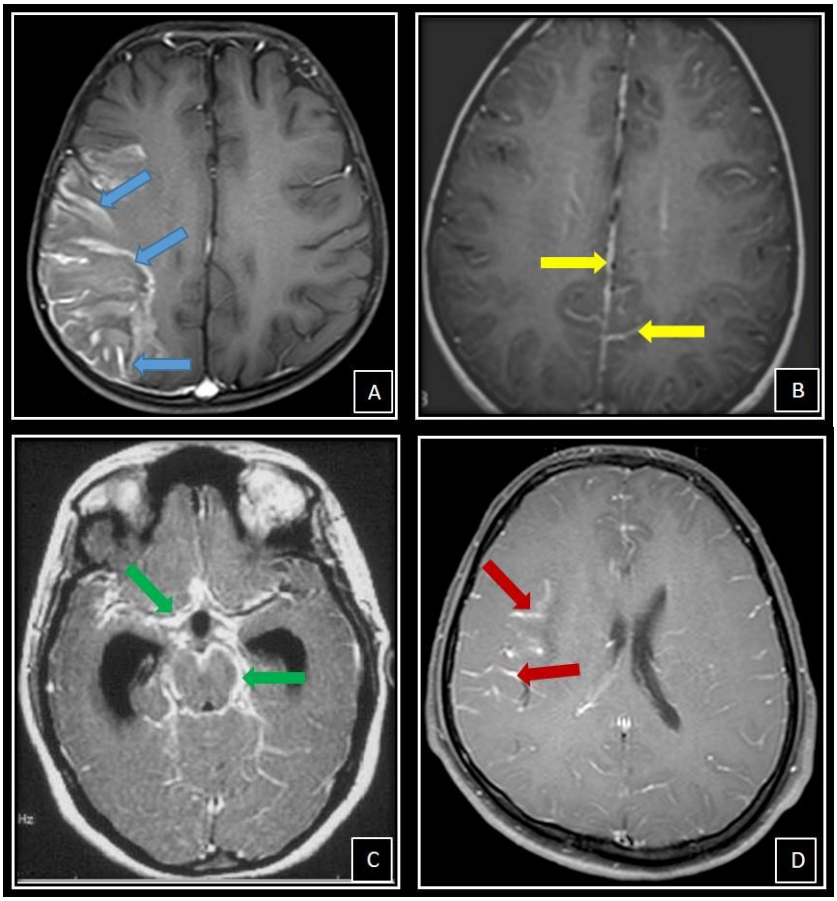

Figure 7: Acute Pyogenic meningitis A, B, C, D: Post-contrast T1.

A: Leptomeningeal enhancement along cortical sulci s/o exudates (blue arrows) B: Leptomeningeal enhancement along para-falcine cortical sulci and falx cerebri s/o exudates (yellow arrows) C: Extra-axial enhancement in ambient cisterns and right sylvian fissure s/o exudates (green arrows) D: Leptomeningeal enhancement along cortical sulci s/o exudates (red arrows)

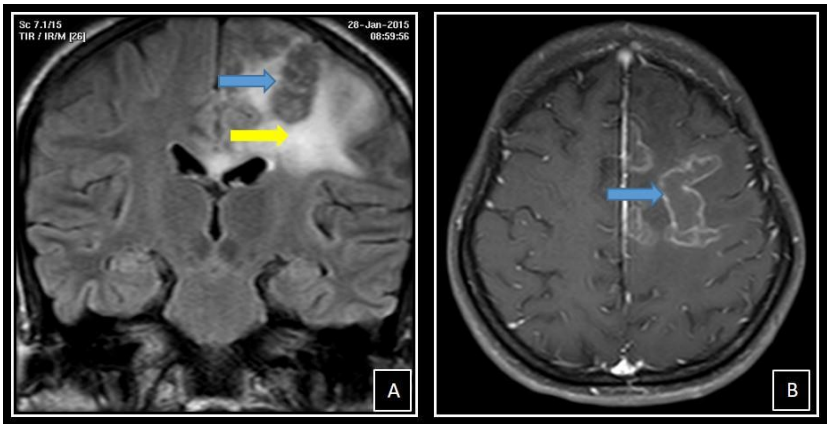

Figure 8: CNS Tuberculosis A: FLAIR coronal B: Post-contrast T1.

A, B: Ring enhancing conglomerate T2/ FLAIR hypointense lesions noted in the left frontal cortex and white matter (blue arrow) with surrounding white matter hyperintensity suggestive of vasogenic edema (yellow arrow).

DISCUSSION AND CONCLUSION

In our study, we found abnormal MRI scans in 25 out of 34 patients, i.e. in 74% cases. Thus in acute fever associated with neurological dysfunction, MRI brain has a good sensitivity, however, there are doubts about its specificity in conclusively diagnosing specific diseases.

Imaging characteristics

Among the 25 patients with an abnormal MRI brain scan, 16 patients had only intra-parenchymal lesions, 5 patients had only extra-axial enhancement, 3 patients had intra-parenchymal lesions as well as extra-axial enhancement and 1 patient had only diffuse cerebral edema. (Table 2).

a. Cerebral Malaria

Out of 7 cases whose final diagnosis turned out to be cerebral malaria, 6 showed abnormal MRI brain findings. There have been numerous case reports published describing a wide range of abnormalities detected in MRI scans of patients of cerebral malaria.[2,3,4]

In our study, 2 patients had cortical infarcts, detected on DWI as lesions showing restricted diffusion, however, with no blooming on GRE. One patient had a well-defined focal lesion appearing T2/FLAIR hyperintense and showing restricted diffusion on DWI but no blooming on GRE in the head of the right caudate nucleus. One patient showed multiple small well defined discrete and confluent T2/FLAIR hyperintense lesions showing restricted diffusion distributed in the cerebral white matter, with similar lesions in left thalamus. One patient showed a T2/FLAIR hyperintense well-defined lesion in the splenium of corpus callosum showing restricted diffusion on DWI which and multiple tiny foci of blooming within on GRE s/o micro-haemorrhages within. One patient did not show any focal lesion, however showed diffuse cerebral edema. None of the above patients showed enhancement on post-contrast T1 scans. (Figures 1,2).

b. Dengue Encephalitis

In our study, we found 7 cases (21 % of total cases) of Dengue Encephalitis of which 5 patients were female and 2 were female. Of these, 6 cases showed abnormal MRI brain findings and 1 patient had a normal MRI. In all 6 of our patients with abnormal MRI scans, symmetrical involvement of B/L thalami was noted.[4,5]

One patient only showed lesions in both thalami. 4 out of 6 patients showed diffuse ill-defined lesions in the deep cerebral white matter. Involvement of the Pons and the cerebellum was seen in 3 patients each. Only one 87 patient showed involvement of the midbrain and only one patient showed involvement of the cortex.

The lesions in all 6 patients were T2 and FLAIR hyperintense and T1 hypointense. On DWI, all 6 patients either showed restricted diffusion in the lesions or few foci of restricted diffusion within the lesions. All 6 cases did not show any enhancement within the lesions on post-contrast T1 scans. On GRE, 4 patients showed areas of blooming within the lesion s/o haemorrhagic lesions. (Figure 3).

Varatharaj et al had concluded in their study that much of the data is disparate and a conclusive characterization of the MRI features of dengue encephalitis is not yet possible, although the focal nature of imaging abnormalities adds weight to the theory of viral neurotropism.[7]

c. Acute pyogenic meningitis

Of the total 8 cases, 5 cases showed abnormal MRI features of exudates which were best seen on post-contrast T1 sequence as extra-axial enhancement along cortical sulci and CSF cisterns with no intra-axial lesions.

To diagnose bacterial meningitis, CSF examination is mandatory, imaging having a supportive role. MRI is the most sensitive imaging modality, because the presence and extent of inflammatory changes in the meninges, as well as complications, can be detected.[8] (Figure 7).

d. HSV encephalitis

We found 2 cases of HSV encephalitis, both of whose diagnosis were confirmed by discovery of HSV DNA by PCR test in the CSF. Both patient had similar findings which were T1 hypointensity, T2, FLAIR hyperintensity in the bilateral insular cortex, cingulate gyri, deep white matter in frontal, parietal and anteromedial temporal lobes. Both our patients also had extra-axial enhancement along the cortical sulci of temporal lobes and B/L sylvian fissures. Thus our final diagnoses of both patients was Herpes Meningo-encephalitis. (Figure.4).

These features are consistent with all available literature available which concurs that HSE has a striking affinity for the limbic system.[9]

e. Japanese Encephalitis

In our study, there was only one confirmed case of Japanese encephalitis, confirmed by JE virus IgM detected in the CSF.

The MRI was abnormal and revealed B/L symmetrical T1 hypointense and T2/FLAIR hyperintense lesions in both the thalami showing no restriction of diffusion or blooming on GRE or post-contrast enhancement. (Figure 6).

In Japanese encephalitis, MRI reveals pathological changes in 90.6–95.5% patients. Thalamic abnormalities on T2w images can be found in upto 87.5% patients, both in children and adults.[10]

f. Influenza Encephalitis

In our study, there was only one confirmed case of Influenza encephalitis, confirmed by Influenza virus DNA in the CSF detected by PCR test.

The MRI was abnormal and revealed B/L nearly symmetrical T1 hypointense and T2/FLAIR hyperintense lesions in both the thalami not showing restriction of diffusion or blooming on GRE or post-contrast enhancement. The lesion in the right thalamus, showed a non-enhancing well-defined CSF intensity area within. These findings were consistent with Influenza encephalitis.[11] (Figure 5).

g. CNS Tuberculosis

Tuberculosis usually does not have an acute onset, but rather a subacute to chronic onset. However in our study,

which included patients with only an acute onset of fever, we found 2 cases of CNS tuberculosis. This can be due to an abnormally large prevalence of tuberculosis in India as compared to other nations.[12]

The MRI of one patient in our study showed multiple conglomerate ring enhancing lesions or tuberculomas in the left frontal region, body of corpus callosum and in the cingulate gyrus. Additionally meningeal enhancement was also noted along cortical sulci of left frontal region on post-contrast T1w sequence. In the second patient, the MRI revealed multiple small ring enhancing lesions or tuberculomas in the corpus callosum, left putamen and left basifrontal region, however no meningeal enhancement was noted. These findings and typical CSF findings led to the diagnosis of CNS tuberculosis. (Figure 8).

h. Others

We found 2 cases which were diagnosed as viral encephalitis, on the basis of their CSF findings.

Both their MRI features were abnormal. One patient had cerebellitis with diffuse T1 hypointensity and T2/ FLAIR hyperintensity in the B/L cerebellar hemispheres which. There were few foci of nodular extra-axial enhancement along cerebellar foliae. The other case showed patchy T2/FLAIR hyperintense lesions noted in the B/L thalami and in the right half of midbrain, predominantly in the substantia nigra region. Both scans did not show restriction on DWI or blooming on GRE.

However despite extensive laboratory and imaging work-up, the exact causative agent could not be detected in our study.

It is worthwhile to remember that enterovirus encephalitis is a common cause of viral encephalitis, other than HSV and Japanese encephalitis. Enterovirus encephalitis is usually associated with EV 71 serotype. The most consistent finding is that of brain stem encephalitis.[13]

i. Normal Studies

There were 9 normal studies out of total 34 patients (26%). Out of these 1 patient was diagnosed as cerebral malaria and 1 as dengue encephalitis despite no abnormality on MRI.

3 patients were diagnosed as acute pyogenic meningitis, on the basis of their clinical features and typical CSF findings of increased poly-nuclear leukocytes, increased proteins and decreased sugars. Thus it should be noted that not all patients of uncomplicated pyogenic meningitis show meningeal enhancement on post-contrast T1w sequence and that absence of meningeal enhancement does not necessarily rule out meningitis, but when such enhancement is found, there is very high probability that it is due to meningitis.

2 cases with normal MRI were diagnosed as leptospirosis with positive anti-leptospira antibody IgM in the blood samples of both these patients, with one patient testing positive for Anti-leptospira antibody IgM by macroscopic agglutination test (MAT) in the CSF. However the normal MRI can be explained by the fact that in neuroleptospirosis aseptic meningitis is the commonest manifestation, which can be missed on MRI.[14]

One disease that was conspicuous with its absence was Chikungunya Fever which a fairly common cause of AFI in India. This can be attributed to the fact that neurological complications are infrequent in Chikungunya, being present only in about 16% patients.[15] Another common cause of AFI that was not detected in our study was scrub typhus fever, caused by rickettsial infection. This can be due to the fact that though most studies in India report scrub typhus as a common cause of AFI, it remains rampant only in northern, eastern, and southern India.[16] Besides, it is difficult to differentiate scrub typhus from other dengue fever like illnesses, especially after rains. Our study was being conducted in a tertiary hospital in western India, where apart from low incidence, there is also decreased clinical awareness. Also neurological complications of scrub typhus are not very common, occurring in a varying number of patients. When scrub typhus does present with neurological symptoms, it usually causes encephalitis, meningitis, myelitis or plexus neuropathy and no specific MRI features are recognizable.

2 patients having normal MRI scans in our study could not be allotted a diagnosis even after extensive laboratory and imaging work-up.

LIMITATIONS OF THE STUDY

- Relatively small sample size: Our sample size was 34
- No definitive standard investigation.
- Absence of some diseases like Chikungunya encephalitis etc.
- Study being carried out at a tertiary care hospital.

CONCLUSION

Ours is the first study wherein MRI Brain findings of patients of acute fever associated with neurological dysfunction were evaluated. Previous similar studies only focussed on clinical and laboratory findings, or were isolated case reports/case series of specific diseases. Ours is the first study in such patients which was evaluating and putting emphasis on MRI findings.

Owing to a high incidence of certain systemic infectious diseases, we are finding an increasing number of cases showing neurological complications, of not only diseases with known nervous system affliction like cerebral malaria; but also of diseases which were previously not thought to be neurotropic like Dengue fever. Our study

has described the various abnormalities that can be found in MRI Brain scans of these patients and has highlighted the importance of MRI in aiding the diagnosis of such cases. Apart from this MRI remains an invaluable tool in the diagnosis of primary CNS infections, as is evident in our study.

We conclude that MRI Brain is an excellent and crucial investigation which helps in the diagnosis of patients having acute fever along with any neurological dysfunction. However, the final diagnoses should be based on a combination of clinical features, laboratory findings and MRI features.

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