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Original research article

MRI in patients with dengue encephalitis: A prospective study

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Abstract

Introduction: Dengue counts among the most common arboviral illnesses, representing the fastest spreading tropical disease in the world. It is considered the second leading cause of acute febrile disease in travelers. Four different serotypes (DENV-1, -2, -3, and -4) cause dengue fever, with various infectious outcomes (asymptomatic to severe hemorrhagic fever). Dengue is prevalent in 128 countries, and more than 2.5 billion individuals are in danger each year of contracting dengue virus worldwide.

Material & Methods: This is prospective study conducted at Department of Radio diagnosis, Kalinga Institute of Medical Sciences from November 2016 to April 2017 among 48 serologically proven dengue patients presenting with neurological symptoms and undergoing brain MRI over a period of 6-months were included. The diagnosis of dengue encephalopathy or encephalitis was established by presence of signs/symptoms of acute encephalitic syndrome with the presence of IgM antibody against dengue antibody in the serum and/or presence of dengue antigen (NS1) in serum. Any patients found to have positive serological test for malaria, leptospirosis, scrub typhus, Chikungunya, JE virus, and Herpes simplex virus (HSV) encephalitis were excluded from the study.

Results: A total of 48 patients (29 men, 19 women; mean age of 29.84 years and age range of 2–70 years) were included in this study. Twelve patients (25%) were in the pediatric age group (<18 years of age) whereas the rest were in the adult age group. Of 48 cases, 15 cases were found to have no significant abnormality on MRI. Varying degrees of abnormality were found in rest of the 33 patients. The imaging findings are described based on a pattern recognition approach.

Conclusion: MRI is an important tool for demonstrating the degree of brain involvement in dengue infection. Although the findings are not entirely unique to dengue, it can help to narrow down the list of differential diagnosis particularly when coupled with serological tests and CSF analysis. A pattern-based approach to evaluating the brain MRI in combination with patient's clinical details in the setting of dengue can help the radiologist to identify the definitive underlying pathologic process. This is of particular significance in differentiating between dengue encephalitis and post-dengue ADEM because of their different treatment strategies.

Keywords: Dengue, encephalitis, MRI, hemorrhagic infarct, meningoencephalitis

Introduction

Dengue counts among the most common arboviral illnesses, representing the fastest spreading tropical disease in the world. It is considered the second leading cause of acute febrile disease in travellers [1]. Four different serotypes (DENV-1, -2, -3, and -4) cause dengue fever, with various infectious outcomes (asymptomatic to severe hemorrhagic fever). Dengue is prevalent in 128 countries and more than 2.5 billion individuals are in danger each year of contracting dengue virus worldwide [2]. According to some estimates, almost 400 million individuals are infected annually, with ~96 million showing clinical relevance. About 2.5% of all diseased people die. In recent years, neurological manifestations of dengue infection have been increasingly reported; however, their precise incidence rates remain undefined [3].

Neurological signs were first reported in 1976 as atypical symptoms of dengue infection; their incidence rates varied from 0.5 to 20% in recent years. Neurological manifestations have been reported in 25 countries spanning almost all continents and involve individuals aged 3 months to 60 years. High body temperature, elevated hematocrit, thrombocytopenia, rash, and liver dysfunction are independent risk factors for neurological complications [4].

Almost 20 years ago, dengue virus neurotropism in the human host was considered an opportunistic characteristic. However, more and more evidence strongly supports the notion that the virus is directly neurovirulent. Miagostovich *et al*. detected the dengue virus in the central nervous system (CNS) by assessing viral proteins, ribonucleic acid (RNA) and immunoglobulins found that the dengue virus is highly neurotropic in *Aedesaegypti*. The DENV-2 and DENV-3 serotypes are mostly related to

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neurological complications [4].

Encephalitis is considered a severe manifestation of dengue virus infection, and found in the three classical disease groups. Diagnosis of dengue encephalitis is based on criteria. [5,6] Neuroimaging of dengue encephalitis yields divergent data, with normal findings in most cases. [7] In case of abnormal neuroimaging findings, magnetic resonance imaging (MRI) has advantages over cranial computed tomography (CT) in revealing cerebral lesions in dengue encephalitis. However, changes are usually non-specific. [8] Decisive characterizations of MRI properties in dengue encephalitis remain undefined. Treatment is nonspecific, with mostly symptomatic treatment provided. Most patients have good recovery.

Findings of magnetic resonance imaging (MRI) of the brain have been reported in several case reports and studies, with a variable spectrum of findings. In this study, we have evaluated MRI brain findings of serologically proven patients of dengue with clinical suspicion of encephalitis, with autopsy correlation who succumbed to their illness [9].

Material and Methods

This is prospective study conducted at Department of Radio diagnosis, Kalinga Institute of Medical Sciences from November 2016 to April 2017 among 48 serologically proven dengue patients presenting with neurological symptoms and undergoing brain MRI over a period of 6-months were included. The diagnosis of dengue encephalopathy or encephalitis was established by presence of signs/symptoms of acute encephalitic syndrome with the presence of IgM antibody against dengue antibody in the serum and/or presence of dengue antigen (NS1) in serum. Any patients found to have positive serological test for malaria, leptospirosis, scrub typhus, Chikungunya, JE virus, and Herpes simplex virus (HSV) encephalitis were excluded from the study.

Clinical Evaluation

Detailed clinical examination was done for all the patients. The presence of fever (along with pattern and periodic temperature recording), headache, nausea, vomiting, pallor, icterus, edema, bleeding diatheses, sensorium, and seizure (with number of episodes and pattern of seizure) were recorded. Vital parameters such as pulse, blood pressure, respiratory rate, temperature, and urine output were recorded. The level of consciousness was assessed using Glasgow Coma Scale (GCS). General systemic examination was done for all patients. Detailed neurological examination was done for all patients as far as feasible. Fundus examination was done for all patients to look for presence of papilledema. In cooperative patients, sensation and cerebellar signs were tested as well.

Laboratory Investigation: Haemoglobin, haematocrit level, total and differential white blood cell counts, coagulation profile (platelet count, prothrombin time, activated partial thromboplastin time), blood sugar, blood ammonia, blood urea nitrogen, serum creatinine, bilirubin, transaminases, sodium, potassium, chloride and calcium were done for all patients. Chest X-ray, electrocardiogram, and ultrasound of abdomen were done as well. Cerebrospinal fluid (CSF) analysis was done in patients with platelet count at least >40,000/mm^3 and was examined for cells, sugar, and proteins. IgM antibody against dengue virus and dengue antigen (NS1) were tested in serum in all patients. The diagnosis of JE was excluded by negative CSF IgM ELISA, and Leptospira and Chikungunya by serum IgM ELISA. Peripheral blood smear was examined for malarial parasite as well as rapid dual antigen test for malaria parasite.

MRI: The MRI included following sequences: 2D axial T2 and FLAIR sequences for brain, pre- and postcontrast 3D T1 spoiled gradient recalled sequence, postcontrast 3D FLAIR sequence, diffusion weighted images, and susceptibility weighted images. The diffusion weighted images were acquired using single-shot fast spin-echo echoplanar sequence with sensitizing gradients applied in all three orthogonal planes with *b* values of 50 and 1000 s/mm^2. The 2D sequences were acquired using a slice thickness of 4 mm, whereas the 3D sequences were acquired using a slice thickness of 0.9 mm. Intravenous gadolinium (Gd-DTPA) was injected at a dose of 0.1 mmol/kg of body weight for postcontrast sequences unless the use of gadolinium-based contrast agents was contraindicated in the patient.

Result

A total of 48 patients (29 men, 19 women; mean age of 29.85 years and age range of 2–70 years) were included in this study. Twelve patients (25%) were in the paediatric age group (<18 years of age) whereas the rest were in the adult age group.

Classification of the patients as per WHO classification

Five patients were classified as dengue without warning signs, nine were classified as dengue with warning sign, and the rest were classified as severe dengue.

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Indication for MRI

Twenty cases underwent MRI for acute onset of altered sensorium, whereas Nine patients underwent MRI for altered sensorium with associated seizure. Rest of the patients underwent MRI for acute onset severe headache and/or concomitant suspicion for intracranial hemorrhage. The clinical and demographic profiles of the patients undergoing brain MRI are summarized in Table 1.

Table 1: Demographic profile of the patients

Factors	Total
Demographic parameters age (in years)	Mean‑ 29.85±17.86 (range 2-70 years)
Gender (male/female)	M=29, F=19
Duration of illness (in days)	7.86±2.36
Altered sensorium	29
GCS	10.24±3.82
Seizures	9
Pattern of seizure	GTCS in all 9 patients

Table 2: Clinical profile of the patients

Platelet count <20,000/mm^3	18 (37.5%)
20,000‑ 50,000/mm^3	12 (25%)
50,000‑ 100,000/mm^3	11 (22.9%)
>100,000/mm^3	7 (14.6%)
Interval between onset of fever and MR acquisition <1 day	4 (8.4%)
1-3 day	11 (23%)
3-7 days	20 (41.7%)
>7 days	13 (26.9%)
Interval between onset of neurological symptoms and MR acquisition <1 day	15 (31.3%)
1-3 day	16 (33.4%)
3-7 days	9 (18.8%)
>7 days	8 (16.5%)

Findings of 48 cases, 15 cases were found to have no significant abnormality on MRI. Varying degrees of abnormality were found in rest of the 33 patients. The imaging findings are described based on a pattern recognition approach.

Encephalitis pattern of 33 cases having positive MRI finding, 16 were found to have MRI abnormality consistent with an encephalitic pattern. The diagnosis was considered when there was involvement of basal ganglia, thalami, cerebellar structures, brainstem and cortical gray or subcortical white matter in isolation or combination. In five patients, involvement of basal ganglia, thalami, cerebellar structures, and brainstem was seen. Involvement of cortex and subcortical white matter in addition to involvement of basal ganglia, thalami, brainstem, and cerebellum was seen in three patients. Involvement of cerebellum and brainstem without ganglio-thalamic involvement was seen in three patients. Isolated cerebellar involvement was noted in one patient. Altered signal intensity (SI) was noted in the form of T2/FLAIR hyperintensity and T1 hypointensity in the structures involved in all the patients. True diffusion restriction with hypointensity on corresponding apparent diffusion coefficient (ADC) maps was noted in the areas of altered SI in all the cases. Interspersed hemorrhage was seen in the area of altered S.I in 11 of the 16 patients. Mild patchy postcontrast enhancement was seen in four of the cases in the areas of altered SI. Nine of the 16 patients in this group had platelet count less than 20,000/mm^3, whereas rest 7 had platelet count below 50,000/mm^3.

Encephalopathy pattern including posterior reversible encephalopathy syndrome: Two patterns of MRI brain change consistent with encephalopathy were encountered– seizure-related/metabolic encephalopathy and posterior reversible encephalopathy syndrome (PRES). Two patients were found to have diffuse cerebral edema with altered S.I in bilateral hippocampi, whereas in one patient, white matter structures (periventricular and frontoparietal deep and subcortical white matter and corpus callosum) were involved without features of cerebral edema. These features are consistent with seizure-related encephalopathic changes. The posterior parieto-occipital subcortical white matter predominant pattern of involvement suggesting PRES was found in one patient.

Acute disseminated encephalomyelitis: Three patients showed presence of multifocal, asymmetrical, non-enhancing, fluffy T2/FLAIR hyperintensities involving the bilateral periventricular and frontoparietal white matter which is suggestive of an imaging diagnosis of ADEM. Brainstem, cerebellar, and involvement of gangliothalamic complexes are not seen in any of the cases. In two of these cases, diffusion restriction was present within the lesions, whereas in one patient, true diffusion restriction was absent; and the lesions showed increased mean diffusivity and appeared bright on both diffusion

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weighted imaging (b = 1000) and ADC map. The imaging for this group of patients was done at 8th, 10th, and 13th day after onset of fever.

Hemorrhagic diathesis: Ten of the 33 patients with positive MRI findings showed presence of either intracranial macro- or micro-hemorrhage or both. The cases of hemorrhagic encephalitis are not considered under this group. Only cases with isolated intracranial hemorrhage are considered under this subgroup. All the nine patients were found to have thrombocytopenia (<20,000/mm^3 in eight of the cases and <30,000/mm^3 in two of them). In four patients, multiple punctate foci of micro-hemorrhages, which appeared as foci of blooming on susceptibility weighted imaging (SWI) sequence, were seen scattered in bilateral cerebral and cerebellar hemispheres and brainstem. Two patient had right frontal intra-parenchymal hematoma with multifocal micro-hemorrhages in basal ganglia, thalami in addition to bilateral cerebral and cerebellar hemispheres. In rest of the patients, isolated intra-parenchymal hemorrhage was seen at right parietal region.

Outcome of the cases: Of the 48 cases included in the study, 13 had a good outcome and were discharged from the hospital in after acute episode in a fairly satisfactory status. In 20 patients, 8 hospital deaths were encountered. Four patients were discharged with decreased sensorium (GCS >12), whereas eight patients were discharged in a conscious, oriented state with residual deficit (four with hemiparesis, two with swallowing difficulty requiring nasogastric feeding, and two with truncal ataxia). Of the 15 patients having normal MRI, 14 had good outcome, whereas1had poor outcome.

Imaging follow-up

Follow-up MRI was available in five cases at a mean interval of 3.6 months. Two patients were form the encephalitis group which showed volume loss with gliosis in the areas involved in the index scan. Follow-up imaging of one case of each of ADEM and seizure-related encephalopathy was available and showed no residual abnormality. One case of macro-hemorrhage also had a follow-up scan which showed evolution of the hematoma to a chronic stage with surrounding gliosis.

Discussion

Dengue virus has four serotypes (DENV-1 to DENV-4). Dengue usually presents with fever, headache, rashes and hemorrhagic manifestations. Dengue is classically thought to be a non-neurotropic virus [9]. The serotypes, most frequently implicated in causing neurological manifestations are DEN2 and DEN3 [10]. Cases of dengue encephalitis has been reported by Solomon *et al.* and recently by Borawake *et al.* from India [10]. However, there is hardly any recent data documenting dengue encephalitis in adult patients from India.

The main symptoms of dengue encephalitis are headache, seizures and altered consciousness [11]. Typical symptoms of dengue fever like myalgias, rash and bleeding are seen in less than 50% of encephalitis cases [12]. So Solomon *et al.* have suggested that dengue should be considered in all encephalitic patients in endemic areas, regardless of the presence or absence of classical features. Our patient did not have classical features of dengue like rashes or hypotension [13].

The criteria for dengue encephalitis are:

1. Fever.
2. Acute signs of cerebral involvement.
3. Presence of anti-dengue IgM antibodies or dengue genomic material in the serum and/or cerebrospinal fluid.
4. Exclusion of other causes of viral encephalitis and encephalopathy [14].

Varathraj also has defined criteria for dengue encephalitis [15]. Our patient had fever with seizures and altered sensorium and we could demonstrate dengue-IgM in his blood. We also ruled out other causes for encephalitis in our patient by appropriate investigations. So, our patient satisfied the criteria for dengue encephalitis.

MRI findings in dengue encephalitis are mostly nonspecific, and these findings can be seen in Japanese and herpes encephalitis. In difficult cases, serological examination is helpful in differentiating it from other viral encephalitis. Chikungunya encephalitis also presents with clinical presentations similar to dengue encephalitis [16-19]. However, Chikungunya encephalitis shows T2-weighted hyperintense white matter lesions with restricted diffusion.

Conclusion

MRI is an important tool for demonstrating the degree of brain involvement in dengue infection. Although the findings are not entirely unique to dengue, it can help to narrow down the list of differential diagnosis particularly when coupled with serological tests and CSF analysis. A pattern-based approach to evaluating the brain MRI in combination with patient's clinical details in the setting of dengue can help the radiologist to identify the definitive underlying pathologic process. This is of particular significance

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in differentiating between dengue encephalitis and post-dengue ADEM because of their different treatment strategies.

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