*International Journal of Basic and Applied Medical Sciences ISSN: 2277-2103 (Online)*
*An Open Access, Online International Journal Available at http://www.cibtech.org/jms.htm*
*2014 Vol. 4 (2) May-August, pp. 36-43/ Kanta et al.*

***Research Article***

# MAGNETIC RESONANCE IMAGING IN CHILDREN WITH DENGUE ENCEPHALOPATHY

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## ABSTRACT

This prospective study was planned to delineate the findings on magnetic resonance imaging of brain in children with dengue encephalopathy. Study was done from June 2010 to May 2011. All admitted children with a clinical picture and CSF findings suggestive of viral encephalitis were subjected to ELISA for IgM antibodies against dengue virus and Japanese Encephalitis virus in serum. Those positive for IgM antibodies were considered as a probable case of dengue encephalopathy and MRI brain was done in all cases except in those with unstable vitals. Fifty nine children with dengue encephalopathy were subjected to MRI brain. Diffuse changes were noted in the form of signal intensity alterations in various areas of brain (94.9%), bilateral thalamic changes in15 (25.4%) cerebral edema in 4 (6.8%), and it was normal in 3(5.1%). Cerebral hemorrhage was not noticed in any of the patient. One patient showed evidence of myelitis along with encephalitic changes. In conclusion wide spread involvement is common in dengue encephalopathy with bilateral thalamic changes in one fourth children of dengue encephalopathy.

***Keywords:*** *Neuroimaging, MRI, Dengue Encephalopathy*

## INTRODUCTION

Dengue virus infections are common in tropical and subtropical countries including India. Dengue virus (DV) infection is endemic in many parts of India and all 4 dengue serotypes have been detected from India. Neurological involvement due to DV has been reported, though not common and dengue encephalopathy (DE) is very well recognized. This may occur because of direct viral invasion of the brain, hemorrhage, cerebral edema, disseminated coagulation and metabolic disorders (Lum *et al.,* 1996; Thakare *et al.,* 1996; Kankirawatana, 2000). According to a recent review neurological features have been noted in 0·5-21% of admitted patients with dengue in different clinical settings. Furthermore, encephalitis-like illness has been identified in 4-47% of dengue admissions in endemic areas (Carod-Artal, 2013). Based at a teaching hospital in northern India, we observed that dengue encephalopathy (DE) is a common feature of DV infection in hospitalized children in Lucknow city and nearby areas. DE accounts for about 22% of children presenting as acute encephalitis syndrome (AES) in this region (Kumar *et al.,* 2008).

Neuroimaging has an important role in diagnosis and management of various central nervous system infections including acute viral encephalitis. Magnetic resonance imaging (MRI) is preferred over computed tomography (CT), as it provides better visualization of brain substance as well as of posterior fossa region. It helps in excluding other differential diagnoses. In acute viral encephalitis general findings include cerebral edema, white matter changes, and (later) necrosis and brain atrophy. Sometimes infarction or hemorrhage may be found. Signal enhancement with gadolinium contrast may be visualized due to breakdown of blood brain barrier. MRI brain shows characteristic changes in some types of viral encephalitis like herpes encephalitis, Japanese encephalitis (JE) but neuroimaging findings of DE are not very well described in literature except in few case reports and small case series (Cam *et al.,* 2001; Misra *et al.,* 2006; Kunishige *et al.,* 2004; Yeo *et al.,* 2005; Kamble *et al.,* 2007; Ashraf *et al.,* 2004; Wasay *et al.,* 2008; Yamamoto *et al.,* 2002, Kamble *et al.,* 2011). So, this prospective study was conducted to delineate the MRI changes in children with serologically proven DE.

## MATERIALS AND METHODS

This prospective observational study was conducted from June 2010 to May 2011 in the Department of Pediatrics of King George's Medical University Hospital, Lucknow, Uttar Pradesh, India. Ethical approval for this study was obtained from the Institutional Ethics Committee.

All admitted children aged 1- 14 years who presented with fever and altered sensorium (Glasgow Coma Scale ≤ 12, duration more than 2 hours) of 2 weeks or less in duration were enrolled after excluding pyogenic meningitis, tubercular meningitis, frank hepatic encephalopathy, and cerebral malaria. Those cases that refused to participate in the study were also excluded. Enrolled cases were subjected to ELISA for IgM antibodies against DV and JE virus in serum.

A detailed Performa directed history and clinical examination were recorded in all subjects and important attributes were entered in a computer file. Laboratory investigations carried out include hemoglobin (Hb), total leukocyte count (TLC), differential leukocyte count (DLC), platelet count (PLT count), haematocrit (HCT), liver function tests (LFT) including prothrombin time (PT), serum proteins and albumin and rapid tests for malaria. Lumber puncture and CSF examination was done in all cases. Antibody capture ELISA (Mac ELISA) test for dengue specific IgM antibodies was done using commercial IVD kits, Research Inc., USA, in the Department of Microbiology, KGMU, Lucknow. Those positive for serum IgM antibodies against DV were considered as a probable case of DE. These patients were followed up daily till discharge or any other outcome.

Conventional MRI (1.5 tesla) and diffusion weighted MRI brain was done in all cases except 6 patients (expired later on). Only clinically stable patients of DE were shifted to the MRI center of KGMU, Lko, for MRI brain. Informed consent of parents was obtained in all patients. For sedation chloral hydrate was given orally 30-45 minutes prior to procedure and children were suitably wrapped with blankets to protect against hypothermia. Following MRI sequences were obtained in all patients who underwent MRI;

Fast spin echo (FSE) T1 AXIAL (TR/TE/NEX/echo train length/ fov/frequency/phase/slice thickness/spacing =500/10.8/1/2/24x24/320/224/5/1.5/27.78)

Fast recovery fast spin echo (FRFSE) T2 AXIAL (TR/TE/NEX/ echo train length/ FOV/frequency/phase/slice/thickness/spacing/bandwidth=4000/85/2/16/24x24/384/256/5/1.5/31.25)

Fast recovery fast spin echo (FSE) T2 SAGITTAL (TR/TE/NEX/ echo train length/ FOV/frequency/phase/slice Thickness/spacing =4000/85/1/16/24x24/352/256/ 5/1.0)

Fast recovery fast spin echo (FSE) T2 CORONAL (TR/TE/NEX/ echo train length/ FOV/frequency/phase/slice thickness/spacing =4000/85/1/16/24x24/320/256/5/1.0)

FLUID ATTENUATING INVERSION RECOVERY (FLAIR) T2 AXIAL (TR/TE/TI/NEX/ FOV/frequency/phase/slice thickness/spacing =3875/85/2156/1/24x24/320/256/5/1.5)

Diffusion weighted imaging AXIAL (TR/TE/NEX/NUMBER OF SHOTS/ FOV/FREQUENCY/PHASE/ PHASE FOV/ slice thickness/spacing/ =9050/125/4/1/24X24/128/128/5/1.5) with b value = 0 AND 1000 s mm $^{-2}$

T2 GRADIENT RECALL ECHO (GRET2*) AXIAL (TR/TE/NEX/FLIP ANGLE/ FOV/FREQUENCY/PHASE/ PHASE FOV/ slice thickness/spacing/ =640/24/1/12/24X24/256/192/0.75/5/1.5).

Data was entered in to a Microsoft excel sheet. Frequencies, mean and standard deviation were calculated by using Epi info software of statistical analysis. Comparison of variables was done by using Chi square test and student t test.

## RESULTS AND DISCUSSION

Three hundred sixteen children presenting with acute encephalitis were screened for the IgM antibodies against dengue virus. Sixty five patients were found positive but MRI brain could be done in 59 children only**.** Six patients were very critical at the time of presentation and died later on, therefore MRI brain could not be done in these cases.

Average age of the enrolled patients was 5.49 ±2.8 years and male to female ratio was 1.6:1**.** Rash, bleeding manifestations, edema, hepatosplenomegaly and evidence of plasma leakage, were present in almost half of the cases. CSF pleocytosis was observed in 78% with CSF cell count of 66.9 ±83.4 / $mm^3$. Co infection with JE virus was found in five patients. Clinical and laboratory profile of enrolled cases is given in the table 1.

**Table 1: Clinical profile of enrolled cases (n= 65)**

| Clinical features | number | percentage |
|---|---|---|
| Age (mean ±SD) | 5.49 ±2.8 years | |
| M: F ratio | 1.6:1 | |
| GCS (mean ±SD) | 8.80± 3.32 | |
| Convulsions | 47 | 72.3 |
| Focal neurological deficit | 9 | 13.8 |
| Bleeding manifestations | 31 | 47.7 |
| Hypotension | 22 | 33.8 |
| Meningeal signs | 11 | 16.9 |
| Edema | 32 | 49.2 |
| Petechial rash | 35 | 53.8 |
| Hepatomegaly | 31 | 47.7 |
| Splenomegaly | 16 | 24.6 |
| Evidences of plasma leakage | 30 | 46.1 |
| Platelet count < 1 lac/mmcu | 28 | 43 |
| CSF pleocytosis | 51 | 78.4 |
| Elevated liver enzymes | 27 | 41.5 |
| Mortality | 6 | 9.2 |

**Table 2: MRI findings in children with dengue encephalopathy (n=59)**

| S. No. | Areas of brain with signal intensity changes | | Number | Percentage |
|---|---|---|---|---|
| 1 | Gray matter of cerebral hemisphere | Frontal lobe | 43 | 72.9 |
| | | Parietal lobe | 50 | 84.7 |
| | | Temporal lobe | 40 | 67.8 |
| | | Occipital lobe | 46 | 77.9 |
| | | Total | 52 | 88.1 |
| 2 | White matter | Corpus callosum | 9 | 15.2 |
| | | Periventricular | 6 | 10.1 |
| | | Deep white matter | 8 | 13.6 |
| | | Subcortical | 5 | 8.5 |
| | | Total | 15 | 25.4 |
| 3 | Deep gray matter | Thalamus | 14 | 23.7 |
| | | Basal ganglia | 17 | 28.8 |
| | | Total | 27 | 45.8 |
| 4 | Cerebellum | | 14 | 23.7 |
| 5 | Cerebral edema | | 4 | 6.8 |
| 6 | Hippocampus | | 3 | 5.1 |
| 7 | Spinal cord | | 1 | 1.7 |

MRI was positive in 55 (93.2%) cases of DE. Conventional MRI showed signal intensity alterations in 27 (46%) & diffusion weighted MRI in 55 (93.2%) children. Changes involved all parts of brain and both grey and white matter. Average number of areas of brain changes was 7.2 ± 3.5. Table 2 shows various areas of brain showing changes found on MRI brain.

Subtle signal intensity changes in cerebellum were found in 14 (23.7%), though definite changes suggestive of cerebellitis were present only in two cases. Cerebral edema was present in 4 (6.8%), hippocampal signal intensity alterations 3 and encephalomyelitis in one patient. Cerebral hemorrhage was not noticed in any of the patients. Bilateral thalamic changes were present in 14 (23.7%) children. Out of these fourteen cases 9 were JE negative and 5 had JE co infection.

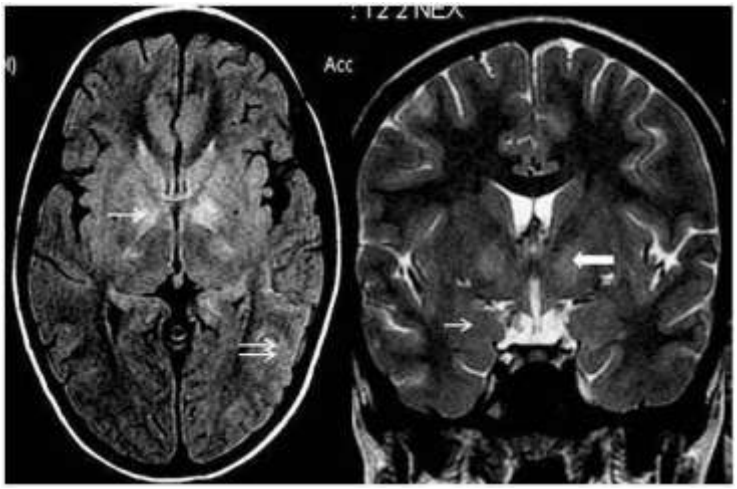


**Figure 1A: Axial T2 FLAIR MRI showing hyperintense signals in bilateral globus pallidus (single arrow) and in left parieto-occipital region (double arrows). Figure 1B: Coronal T2 weighted image demonstrating the symmetrical altered signal in bilateral globus pallidus (thick arrow) and bilateral medial temporal lobe (thin arrow)**

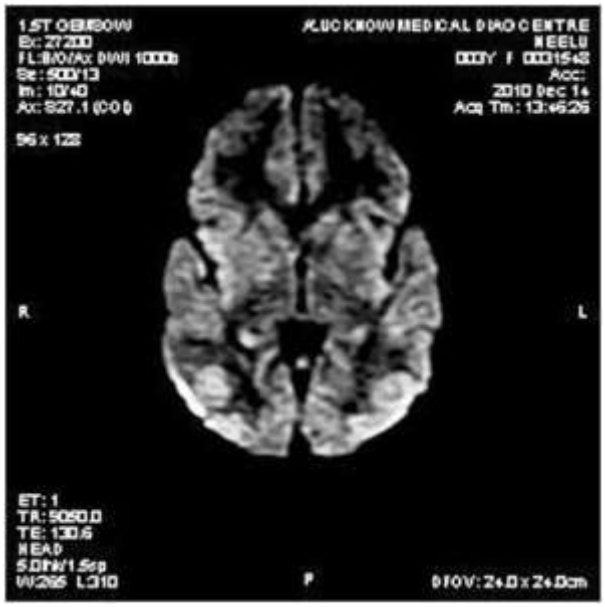


**Figure 2A: Axial Diffusion weighted images show signal abnormality in bilateral temporo-occipital region**

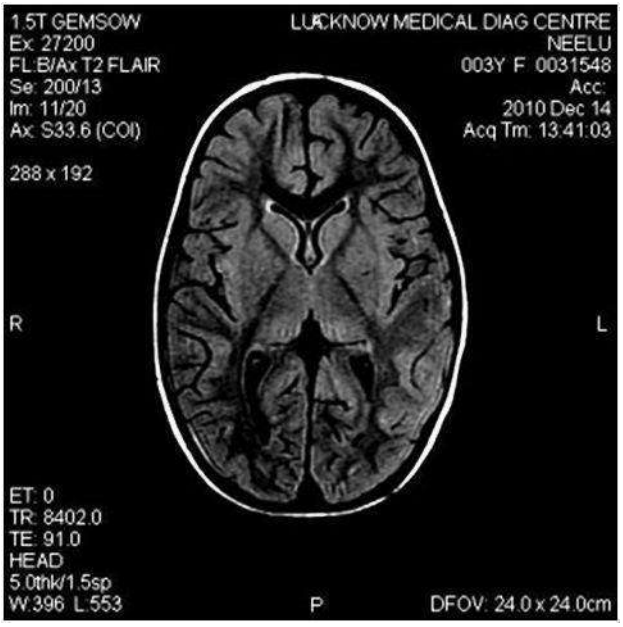


**Figure 2B: Axial T2 FLAIR image of same patient with no changes**

***Discussion***

The relationship between the dengue virus infection and neurological manifestations was first described in 1976 by Sanguansermsri *et al.,* It may occur because of virus neurotropicity, capillary haemorrhage, disseminated intravascular coagulation and metabolic disorders. Cam *et al.,* (2001) in their study found encephalopathy in .5% of admitted dengue hemorrhagic fever cases. Soloman *et al.,* (2000) from Vietnam found dengue virus infection in 4.2% patients with central nervous system infection. In endemic areas a very high incidence of DE ranging 4- 47% of admitted dengue patients has been reported (Carod-Artal, 2013). In present study 20.6% cases of acute encephalitis were positive for IgM antibodies against dengue virus. Our hospital is a tertiary care teaching hospital where most of the patients are referred cases from other hospitals, which could be the reason for high incidence of encephalopathy in our patients. Similar high incidence of DE was observed by Kumar *et al.,* (2008) in previous study done at our institute. Dengue serotypes 2 and 3 are mainly reported to cause neurological symptoms. As PCR was not done in the current study, it's not possible to comment whether this high incidence was due to any specific dengue virus serotype or not. In current study CSF pleocytosis was found in 78% of cases, which supports the hypothesis of direct viral invasion of the brain leading to dengue encephalitis.

Changes on MRI in DE have been described in few case series only. Cam *et al.,* (2001) in a cohort of 18 patients revealed cerebral edema in 14; encephalitis-like changes were present only in 4 and one patient had intracranial haemorrhage. On the other hand Misra *et al.,* (2006) performed MRI in 11 patients and found JE like changes (bilateral thalamic changes) only in 2 patients with DE. Current study is a large prospective observational study in which neuroimaging was done in 59 patients of serologically proven cases of dengue encephalopathy. We obtained T1 & T2 weighted images, FLAIR and diffusion weighted images in all patients.

It was found that changes on MRI were mostly evident on T2 flair images and diffusion weighted MRI images. T1 and T2 weighted, flair images showed changes in form of signal intensity alterations in 27 (46%) & diffusion weighted MRI in 55 (93.2%) children. Changes found were diffuse in distribution and involved both grey and white matter. Rao *et al.,* (2013) also reported a case of dengue encephalopathy with diffuse and extensive brain involvement. We observed that diffusion weighted MRI can pickup changes even when conventional MRI is normal. Haptipoglu *et al.,* (2008) in his study on herpes encephalitis also found that MRI with DWI is more useful than only conventional MRI. Similarly,

McCabe *et al.,* (2003) in his study found that DWI could be positive in early disease phase, even when PCR findings are negative.

In our series cerebral grey matter changes were seen in majority and were diffuse. Deep grey matter changes were present in half of children out of which one fourth had thalamic changes and one fourth had basal ganglia changes. We observed bilateral thalamic changes in nine patients of DE who were JE negative and five children who have JE co infection. As DV and JE virus both are flaviviruses changes found may be similar and has been reported previous workers also. Not only dengue, other flavi viruses like Eastern Equine Encephalitis virus may also show similar changes (Deresiewicz, 1997; Kalita & Misra, 2000). Misra *et al.,* (2006) found bilateral thalamic changes in 2 patients out of 11 patients of DE. Kamble *et al.,* (2007), Ashraf *et al.,* (2004) and Mallick *et al.,* (2012) described similar findings in their case reports of DE. In present study five patients with thalamic changes had coinfection with JE virus. Co infection of dengue virus and JE virus has been reported previously also from the places where both infections are common. Also there can be a serological cross reactivity because both viruses belong to the same family. Singh *et al.,* (2014), in an Indian study tested 76 cases of serologically proven coinfection by RTPCR and detected DV and JEV coinfection in eight cases which suggested that DV and JEV coinfection is common in our region.

White matter changes were present in one fourth. These changes were also diffuse and found in the form of abnormal signals in any site of brain. White matter changes are common in other type of encephalitis also and are not specific for DE.

Cerebral edema was found in only four patients and suggests that brain edema is not the only cause of altered sensorium in children with Misra *et al.,* (2006) also did not found cerebral edema in any patient; however Cam *et al.,* (2001) reported in 14 patients of DE out of 18 patients.

Cerebral hemorrhage in patients with DE can occur because of severe thrombocytopenia and coagulation problems but it is not common in severe dengue cases. Cam *et al.,* (2001) found hemorrhage in only one patient out of 18 patients of DE. Borawake *et al.,* (2011) also reported a case with bilateral thalami involvement and hemorrhage. We did not found cerebral hemorrhage in any patient similar to Misra *et al.,* (2006). However, MRI brain could not be done in six severe cases those died during treatment and possibility of cerebral hemorrhage in those patients could not be ruled out.

Definite changes suggestive of cerebellitis were found in two patients, though subtle signal intensity changes were present in one fourth patients. Hippocampal changes were noted in three and one patient had myelitis along with encephalitic changes. Previous case reports also documented cerebellum, hippocampal and spinal cord involvement due to DV infection. Wasay *et al.,* (2008) described a case of encephalitis associated with myelitis. Kunishige *et al.,* (2004) reported preferential grey matter involvement in a patient of dengue infection with myelitis. Withana M (2014) found a case of isolated cerebellitis associated with dengue infection in an adult patient. Yeo *et al.,* (2005) reported hippocampal involvement in a patient of dengue fever. Some authors have also reported cases of acute disseminated encephalomyelitis with dengue fever and hydrocephalus associated with a case of dengue encephalitis (Yamamoto, 2002; Gupta, 2013; Kamble, 2011). But these findings were not found in any child with DE in this study.

In conclusion, MRI changes were present in almost all children with DE in the form of signal intensity alterations in various areas of brain and diffusion weighted MRI is more likely to show changes in comparison to conventional MRI. Changes found were diffuse and nonspecific involving all parts of brain and both grey and white matter. Basal ganglia changes and bilateral thalamic changes are common in DE. Further studies with PCR positive cases of DE are required because our cases of DE were only the probable cases diagnosed by serological methods though most of them were clinically dengue and had typical rash and thrombocytopenia.

**ACKNOWLEDGEMENT**
All junior residents who helped in the study.

***Funding:*** This work was supported by intramural faculty research grant (XLVECM/ C-P2) from King George's Medical University, Lucknow, India
***Conflict of interest****: None*

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