

Radiological Appearance and their Significance in the Management of Dengue Hemorrhagic Fever

JAVED ASGHAR, KHALID FAROOQ

ABSTRACT

Aims & Objectives: To demonstrate various imaging features of DHF and their significance for the early recognition of moderate to severe forms of disease before they become clinically apparent.

Methodology: we have included 76 patients out of 500 admitted patients who were known cases of dengue fever and were sent for different radiological investigations including abdominal ultrasound and CT scan abdomen, x-ray chest, CT chest, MRI brain. Study was conducted October 2011 in Doctor Hospital and ghurki trust teaching hospital Lahore.

Results: out of 76 patients, 33 were female (43.4%) and 43 were male (56.6%). age range was 14 years to 80 years, mean age was 39 years). Regarding pleural effusion, we have seen that left sided pleural effusion (1.3%) while right sided pleural effusion was seen in (17.1%). Similarly bilateral pleural effusion was noted in (13.2%). Right sided pneumonia was appreciated in (1.3%) while bilateral pneumonia was noted in (3.9%). Ascites was noted in (51.3 %). Gallbladder wall thickness was seen in (36.8%). Hepatomegaly was noted in (35.5%). Splenomegaly in (28.9%). Non-specific gut wall thickening was noted in the small bowel only in one patient (1.3%). Brain hemorrhage was identified in (1.3%). Encephalitis was noted (1.3%), one patient (1.3%) showed diffuse inflammatory changes in the muscles of the neck on MRI.

Conclusion: dengue fever management is very critical especially when leaking process start in potential spaces, this stage requires early diagnosis with the help of different imaging modalities

Key words: Ultrasound, CT scan, MRI, X-ray chest, dengue fever, ascites, gall bladder wall thickness, hepatosplenomegaly, effusion, pneumonia, encephalitis .

INTRODUCTION

Dengue is a widespread mosquito-borne infection in human beings, which in recent years has become a major international public health concern. Symptomatic dengue virus infections can present with a wide range of clinical manifestations, from a mild febrile illness to a life-threatening shock syndrome. Both viral and host factors are thought to contribute to the manifestations of disease in each infected. It is important to understand its burden on health care, morbidity and mortality. Early diagnosis and suspicion of DF in primary care might reduce the complications if handled properly. We must understand the depth of the problem in terms of its transmission, clinical presentation, diagnosis, management and prevention.

The World health Organization (WHO) declares dengue and dengue hemorrhagic fever to be endemic in South Asia. WHO currently estimates there may be 50 million dengue infections worldwide every year. In 2007 alone, there were more than 890 000 reported cases of dengue in the Americas, of which 26 000 cases were Dengue Hemorrhagic

Fever (DHF)¹⁸. The disease is now endemic in more than 100 countries in Africa, Americas, the Eastern Mediterranean, South-east Asia and the Western Pacific. South-east Asia and the Western Pacific are the most seriously affected.

Pakistan is at high risk of being hit by large epidemics because of many over crowded cities, unsafe drinking water, inadequate sanitation, large number of refugees and low vaccination coverage. These conditions promote the spread of infectious diseases and consequently every year a large number of epidemics/outbreaks occur in different parts of the country, which result in increased morbidity and mortality.

MATERIALS AND METHODS

This is descriptive retrospective study of known dengue patients in ghurki trust teaching hospital & doctor's hospital Lahore. Imaging of chest abdomen and pelvis were performed through Ultrasound and CT scans, while Brain was evaluated through MRI and CT scan. X-rays of chest were taken in few patients. Generally images of 76 patients of DHF were evaluated, over a period of 1 month from 1st October to 31st October. Only those patients were included in study who showed positive findings in

Department of Radiology, Lahore Medical & Dental College/Ghurki Trust Teaching Hospital, Lahore
Correspondence to Prof. Javaid Asghar, Head of Radiology
Department Email: jasgher51@hotmail.com 0300- 8447333

different imaging modalities while those patients who did not show any positive imaging finding were excluded from study.

The clinical diagnosis was confirmed by haemagglutination inhibition assay⁴ modified for microtitre plates, or by enzyme-linked immunosorbent assay⁵ and by virus isolation in a tube culture of C6/36 cells⁶.

This study includes 76 confirmed DHF patients (43 male and 33 females), ranging in age from 14 year to 80 years. Abdomen and pelvis scan were carried out with real-time ultrasound scanners (Toshiba Nemio XG, Nemio35) using 3.75 & 5 MHz transducers. Primarily, the emphasis was made on gallbladder wall thickness, any measurement greater than 3 mm was considered as abnormal. Liver, spleen, pancreas and any free fluid in the peritoneal or pelvic cavity were also recorded. The scan also included lower thoracic scanning done in supine posture to evaluate pleural cavity for any free pleural fluid. Both the pleural spaces were evaluated through an intercostal approach While CT scan were done on Toshiba Aquilion 64slice scanner. Only plain images were acquired through Brain, chest, abdomen & pelvis. Slice thickness was 5mm and inter-slice gap was 5mm. Matrix size was 512x512 in all cases. Similarly MRI of brain was performed on Hitachi Airis elite (0.3 tesla). Only plain images were acquired. Slice thickness was 4mm while matrix size was 250x200. Routine sequences were applied which included axial and sagittal T1,T2 andD FLAIR. For x-rays of chest we used Toshiba 500ma machine.

RESULTS

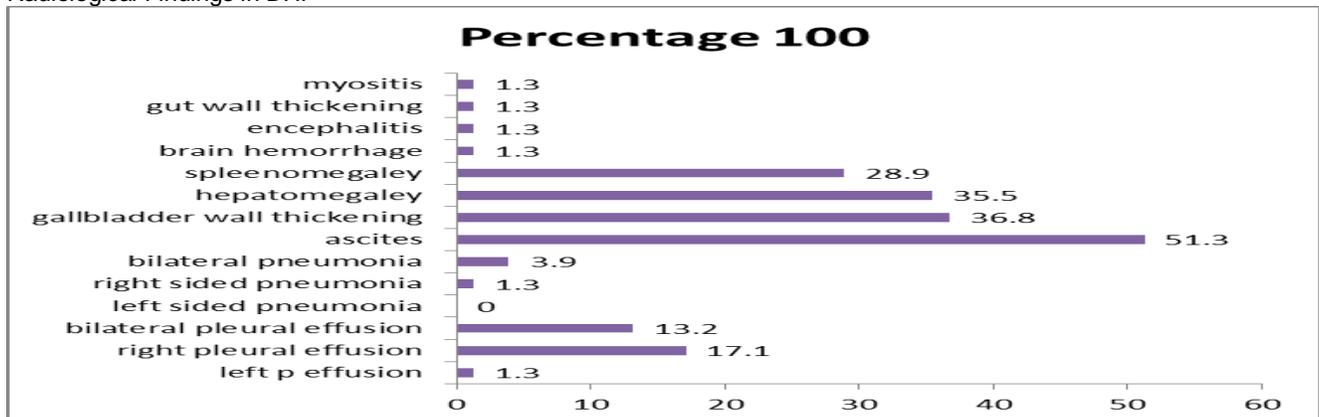
We have reviewed various radiological investigations of 500 patients who were admitted in Ghurki Trust Teaching Hospital and Doctors Hospital, Lahore. Out of these, 400 were admitted in Doctors Hospital and

a 100 Ghurki Trust Teaching Hospital. Only 76 patents were sent for imaging of different regions including brain, chest, abdomen and pelvis through x-rays, ultrasound, CT scan and MRI. Of these 76 patients, 33 were female (43.4%) and 43 were male (56.6%).

Regarding, chest infection and pleural effusion, we have seen that left sided pleural effusion was noted in one patient (1.3%) who was a female while right sided pleural effusion was seen in 13 patients (17.1%). Right sided effusion was more common in male patients, i.e. 7 patients while 3 female patients showed right sided effusion. Similarly bilateral pleural effusion was noted in 10 patients (13.2%), 5 female and 5 male. Isolated right sided pneumonia was appreciated in one male patient (1.3%) while bilateral pneumonia was noted in 3 patients (3.9%), all of them were male. We could not see any patient with isolated left sided pneumonia. Pulmonary and pleural changes were prominent in male patients as compared to female patients.

Considering abdominal changes in Dengue patients, we have noted ascites of mild to moderate degree in 39 patients (51.3%), out of which 16 were female and 23 were male. Gallbladder wall thickness was seen in 28 patients (36.8%), 10 were female and 18 were male. Hepatomegaly was noted in 27 patients (35.5%), out of which 16 were female and 11 were male. A similar pattern was seen in splenomegaly, where 12 patients were female and 10 patients were male with a total of 22 patients (28.9%). Non-specific gut wall thickening was noted in the small bowel only in one patient (1.3%), who was male. Brain hemorrhage was identified in only one patient (1.3%), Encephalitis was noted in one patient (1.3%), one male patient (1.3%) was seen who showed diffuse inflammatory changes in the muscles of the neck on MRI.

Radiological Findings in DHF



Graphic representation of different imaging findings seen in dengue patients in our study.

DISCUSSION

Dengue haemorrhagic fever (DHF) is characterised by high fever, haemorrhagic diathesis and a tendency to develop a shock syndrome. The disease is endemic in Indonesia with cases occurring throughout the year. DHF has become a major health problem with an incidence of 11.56/100,000 people and a mortality of 2.7% in 1991¹. Bhamarapravati et al. performed autopsies on 100 cases of DHF and reported that the most frequent pathological findings were fluid collections in the thorax, abdomen, pericardial sac and other body compartments and petechial haemorrhages². The ultrasonographic findings in DHF have been described previously³ and the purpose of this study was to demonstrate the relationship of those findings to the severity of the disease.

Epidemiology**Global Burden**

Dengue virus infection is increasingly recognized as one of the world's emerging infectious diseases. About 50-100 million cases of dengue fever and 500,000 cases of Dengue Hemorrhagic Fever (DHF), resulting in around 24,000 deaths, are reported annually¹⁸.

A pandemic of dengue began in Southeast Asia after World War II and has spread around the globe since then. In the 1980 s, DHF began a second expansion into Asia when Sri Lanka, India, and the Maldiv Islands had their first major DHF epidemics.

Local Prevalence: Pakistan first reported an epidemic of dengue fever in 1994. The epidemics in Sri Lanka and India were associated with multiple dengue virus serotypes, but DEN-3 was predominant and was genetically distinct from DEN-3 viruses previously isolated from infected persons in those countries. In Asian countries where DHF is endemic, the epidemics have become progressively larger in the last 15 years. In 2005, dengue is the most important mosquito-borne viral disease affecting humans¹⁹.

Dengue virus is now endemic in Pakistan, circulating throughout the year with a peak incidence in the post monsoon period. Recent flood in Pakistan made the situation worse.

Dengue Surveillance Cell Sind province of Pakistan reports 1,809 suspected Dengue out of which 881 confirmed till 11th October 2010 with 5 deaths while 16 confirmed cases reported in Islamabad without any mortality.

Till now 563 confirmed cases were reported at our institution since January 2010. Reported cases are usually complicated or with hemorrhagic manifestation. In primary health care the usual

presentation is mild to moderate fever treated as suspected dengue fever.

Researchers have identified that co-circulation of DEN-2 and DEN-3 was responsible for the 2006 out-break in Karachi. Primary and secondary cases were seen in both groups. Cases with DHF showed marginal association with DEN-2. Introduction of a new serotype (DEN-3) and or a genotypic shift of endemic serotype (DEN-2) are the probable factors for the recent out-break of DHF in this region²⁰.

Transmission: *Aedes Aegypti* mosquito, which generally acquires the virus while feeding on the blood of an infected person and transmit the disease to another non infected person. It is primarily a daytime feeder lives around human habitation. This mosquito rests indoors, in closets and other dark places. Outside, it rests where it is cool and shaded. The female mosquito lays her eggs in water containers in and around homes, schools and other areas in towns or villages. These eggs become adults in about 10 days. Dengue mosquitoes also breed in stored, exposed, water collection systems. The favored breeding places are: barrels, drums, jars, pots, buckets, flower vases, plant saucers, tanks, discarded bottles/tins, tires, or water coolers, and other places where rainwater collects or stored.

Dengue infection is caused by any of 4 different serotypes of the virus (DEN-1, DEN-2, DEN-3, and DEN-4). After an incubation period of 2-8 days after an infective mosquito bite, the disease usually begins with sudden onset of fever and headache.

Clinical Features: WHO Case definition

Dengue fever is a severe, flu-like illness that affects infants, young children and adults, but seldom causes death. The clinical features of dengue fever vary according to the age of the patient. Infants and young children may have a non-specific febrile illness with rash. Older children and adults may have either a mild febrile syndrome or the classical incapacitating disease with abrupt onset and high fever, severe headache, pain behind the eyes, muscle and joint pains, and rash²¹.

Common presentations in our clinical practice, high grade fever typically accompanied by any of the following: chilliness, retro-orbicular pain, photophobia, backache, severe muscle ache (one synonym of dengue is "break-bone fever"), and joint ache, nausea, vomiting, abdominal pain. High fever may be sustained over 5-6 days. Other signs and symptoms include a generalized maculopapular rash, lymph node enlargement, hepato splenomegaly, a positive tourniquet test, petechiae, and other hemorrhagic manifestations, such as epistaxis and gastrointestinal bleeding. In some cases it started as common cold and flu like symptoms. In general, convalescence occurs spontaneously and abruptly,

but it might be prolonged, sometimes taking several weeks, and may be accompanied by pronounced asthenia and depression. In DHF characteristically, the overall vascular system is damaged, vascular instability, decreased vascular integrity and platelet dysfunction resulting in bleeding from different sites²².

Clinical presentation may vary from undifferentiated fever, classic dengue fever (DF), Dengue hemorrhagic fever (DHF) to Dengue shock syndrome (DSS). The risk of severe disease is much higher in sequential rather than primary dengue infection²³.

Necessary Criteria for DHF:

- Fever, or recent history of acute fever
- Hemorrhagic manifestations
- Low platelet count (100,000/mm³ or less)
- Objective evidence of "leaky capillaries:"
- elevated hematocrit (20% or more over baseline)
- low albumin
- pleural or other effusions

Grade 1 DHF: Fever and nonspecific constitutional symptoms, Positive tourniquet test is only hemorrhagic manifestation. Thrombocytopenia and rise in haematocrit level (more than 20%).

Grade 2 DHF: Grade 1 manifestations + spontaneous bleeding, circulatory failure manifested by rapid and weak pulse, narrowing of pulse pressure (20 mmHg or less) or hypotension with the presence of cold clammy skin and restlessness, Capillary refill time more than two seconds. Thrombocytopenia and rise in haematocrit level (more than 20%)

Grade 3 DHF/DSS: Signs of circulatory failure (rapid/weak pulse, narrow pulse pressure, hypotension, cold/clammy skin)

Grade 4 DHF/DSS: Profound shock (undetectable pulse and BP), abdominal pain - intense and sustained, persistent vomiting, abrupt change from fever to hypothermia, with sweating and prostration, restlessness or somnolence.

Laboratory Tests: Usually clinical suspicion for Dengue fever is sufficient for supportive treatment. Complete blood picture may show high hematocrit, leucopenia and thrombocytopenia. Other laboratory tests include serum albumin, if required. A normal blood count does not rule out DF however platelet <50,000 and leukocyte count <3 might be a sign of bad prognosis.

Diagnosis of dengue fever or its complications is established by culture of the virus itself, by detection of viral DNA with use of PCR, or by serological methods. Although detection of specific IgM indicates fresh infection, a significant increase in IgG titer in paired serum samples is also sufficient for diagnosing dengue fever. Currently employed methods include capture ELISAs, immunofluorescence tests, and hemagglutination assays. Low white cell count, low

platelet count, abnormal liver function test, IgM ELISA test for serologic diagnosis, IgM detectable 5, 6 days after the onset of illness, IgG: day 14 of illness in primary and day 2 in secondary infections²⁴.

Pathophysiology: Studies have shown that median age of dengue patients has decreased now and younger patients may be more susceptible in the recent outbreak. Total and differential leukocyte counts and platelet count may help identify patients at risk of hemorrhage. Severity of disease depends on virus strain, pre-existing anti-dengue antibody previous infection maternal antibodies in infants, host genetics, age, secondary infections locations with two or more serotypes circulating simultaneously at high levels (hyperendemic transmission) and virus strain (genotype)[25]. Epidemic potential is dependent on viremia level, infectivity and virus serotype, DHF risk is greatest for DEN-2, followed by DEN-3, DEN-4 and DEN-1[26]. Antibody-dependent enhancement is the process in which certain strains of dengue virus, complexed with non-neutralizing antibodies, can enter a greater proportion of cells of the mononuclear lineage, thus increasing virus production. Infected monocytes release vasoactive mediators, resulting in increased vascular permeability and hemorrhagic manifestations that characterize DHF and DSS²⁷.

There are other febrile illness prevalent in Pakistan like other viral infections, Malaria, Enteric fever and Congo hemorrhagic fever which can cause leucopenia and thrombocytopenia worth considering during the investigation and relevant investigations are done according to the clinical presentation^{28,29}. Dengue IgM is a costly investigation not freely available although it confirms the diagnosis but never changes the management.

Management: There is no specific treatment available the management is entirely supportive like keeping body temperature below 39°C, give the patient paracetamol (not more than four times in 24 hours. Avoid Aspirin or Brufen/Ponston. Advice to drink large amounts of fluids (water, soups, milk and juices) along with the patient's normal diet. The patient should rest. Complete blood picture should be done if fever is continuous for three days. Oral rehydration salt (ORS) should be started even there is no significant clinical dehydration as patient can go in rapid deterioration if dehydration commences. Primary care physician can start intravenous fluid according to the patient's need as it is lifesaving if administered on proper time³⁰.

Clinical manifestation of impending hemorrhage are, abdominal pain - intense and sustained, persistent vomiting, abrupt change from fever to hypothermia, with sweating and prostration, restlessness or somnolence, Thrombocytopenia <50,000, WBC <3.0, evidence of "leaky capillaries"

high hematocrit (> 20% normal), low albumin, pleural or other effusions needs urgent referral for hospitalization.

The major pathophysiological feature of DHF is an increased vascular permeability, giving rise to loss of plasma and albumin from the vascular compartment⁸. Early diagnosis and treatment of DHF can definitely ameliorate the various complications of the disease such as haemorrhage, hypovolaemia and shock.

Considering vascular permeability we have noted effusion and ascites in our patients.

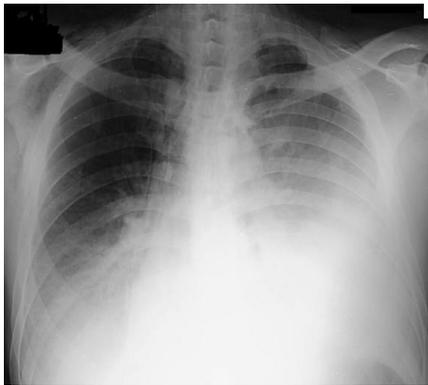


Fig 1: X-ray chest PA view showing consolidation in both lungs with left sided pleural effusion.



Fig 2: Abdominal ultrasound showing ascites.

Regarding, chest manifestation, we have seen that left sided pleural effusion in one patient (1.3%) who was female while right sided pleural effusion was seen in 13 patients (17.1%). Right sided effusion was more common in male patients, i.e. 7 patients while 3 patients were female. Similarly bilateral pleural effusion was noted in 10 patients (13.2%), 5 female and 5 male. Isolated right sided pneumonia was appreciated in one male patient (1.3%) while bilateral pneumonia was noted in 3 patients (3.9%), all of them were male. We could not see any patient with

isolated left sided pneumonia. Pulmonary and pleural changes were prominent in male patients as compared to female patients. There is a positive correlation between the amount of pleural effusion and severity of the disease³.

Considering abdominal changes in Dengue patients, we have noted ascites of mild to moderate degree in 39 patients (51.3%), out of which 16 were female and 23 were male.

Physical examination allows detection of ascites only in volumes above 1000--1500 ml, while ultrasound can demonstrate as little as 100 ml [8]. M.W. Setiawan et al analysed 84 patients with DHF, ascites was found in only 26 % of mild cases but in 94 % of severe cases⁹. In 29 severe cases, Pramuljo and Harun found ascites in 69 % and pleural effusion in all cases¹⁰.

Our findings regarding ascites are well matched with previous studies as described. Ascites seems to be the most frequent finding in dengue patients and may be considered as early phase of leakage process from capillaries. This is very critical time in management of disease and this phase of disease can be detected in its very early stage through ultrasonography.

Gallbladder wall thickness was second most frequent finding in our patients and was seen in 28 patients (36.8%), 10 were female and 18 were male. A thickened gallbladder wall is not specific for primary gallbladder disease.



Fig 3: Abdominal ultrasound showing diffuse gall bladder wall thickening

Several ultrasound studies have reported gall bladder wall thickening of more than 3 mm in children with various non-biliary conditions including ascites, hypoalbuminaemia, portal venous hypertension, acute hepatitis, chronic heart failure and renal insufficiency^{11,13}. In an autopsy study of DHF, Bhamarapravati et al. found oedema of the serous membrane of the gallbladder wall and effusion into the peritoneal cavity². In contrast to earlier reports of abnormal GBWT in only 18--28% of DHF cases^{10,14}, M.W. Setiawan et al found gall bladder wall

thickening in 33% of mild and 94% of severe cases²⁴ according to M.W. Setiawan at al gall bladder wall thickening can be relied upon as an additional criterion to support the clinical diagnosis of DHF. Gall bladder wall thickening of more than 5 mm could be adopted as a criterion for identifying DHF patients at high risk for developing hypovolemic shock (dengue shock syndrome) with a specificity of 92%¹⁵.

Hepatomegaly was noted in 27 patients (35.5%), out of which 16 were female and 11 were male. Samsi TK at al clinically found Hepatomegaly in 49% of 189 DHF patients¹⁶. Ultrasound study by M.W. Setiawan at al found hepatomegaly in 56% with no significant difference between mild and severe cases¹⁷. At autopsy, Bhamarapavati et al, found an enlarged liver in 58% of DHF cases, with fatty change, focal necrosis and haemorrhage demonstrable on histology; 27% sub capsular haemorrhages were observed². Sonographically, intraparenchymal and sub capsular haemorrhages have been observed in only 1 of 29 severe cases¹⁰. M.W. Setiawan at al found hepatic and splenic sub capsular fluid collections in 10% of cases which last for just 1--2 days suggests that they are the result of serous fluid rather than haemorrhage^{2,10}.

A similar pattern was seen in splenomegaly, where 12 patients were female and 10 patients were male with a total of 22 patients (28.9%). Mild splenomegaly in 16% of the mild and severe cases adopted as a criterion for identifying DHF patients at high risk for developing hypovolemic shock (dengue shock syndrome) with a specificity of 92%¹⁵. Mild splenomegaly in 16% of the mild and severe cases is in accordance with the autopsy study reported by Bhamarapavati et al² and also the ultrasound study in adults as reported by Wang et al¹⁴. A significant difference was found in pancreatic enlargement in 14% of mild cases and 44% of severe cases, this was due to edema of the interstitial tissue². However we could not see a single case with pancreatic involvement in our study. It could be due to early scanning of patients as they were already admitted in hospital. However we need further work up regarding this. We feel that CT scan of abdomen could be better modality for assessment of pancreatic changes.

Non-specific gut wall thickening was noted in the small bowel only in one patient (1.3%), who was male. One male patient (1.3%) showed diffuse inflammatory changes in the muscles of the neck on MRI. There is no supporting imaging data in literature regarding above mentioned changes. We need to work more on this and need more patients to study any of such findings. Brain hemorrhage was identified in only one patient (1.3%), who was a male.

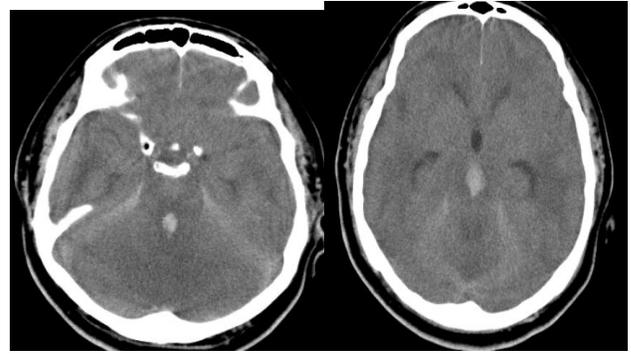


Fig 4: Plain CT examination showing hemorrhage in the brain stem and fourth ventricle with diffuse edema in both supra as well as infra tentorial compartment.

Encephalitis was noted in one patient as well (1.3%), who was a female and showed symmetrical increased signal in hippocampal areas associated with history of amnesia. This is a rare finding and has been noted previously in literature by P S D Yeo et al [39]. P S D Yeo et al reported a 25-year-old man with dengue fever complicated by selective hippocampal involvement, manifesting as amnesia. Magnetic resonance imaging of the brain showed bilateral hippocampal involvement³⁹.

Encephalopathy is a rare complication of dengue virus infection and may occur as a consequence of intracranial hemorrhage, cerebral edema, hyponatremia, and cerebral anoxia, fulminant hepatic failure with Porto systemic encephalopathy, micro capillary hemorrhage or release of toxic products.

From January to May 2002, Rio de Janeiro state was affected by an epidemic of dengue fever that resulted in 255,483 notified cases and 91 deaths. The predominant strain was viral type 3 (DENV-3)³². Approximately one year later, the epidemic that was principally affecting the city of Rio de Janeiro spread to other areas, and DENV-3 was detected in the northern region of the state. During this period, 1,585 cases of the disease were confirmed by the Dengue Fever Reference Center (CRD) in Campos dos Goytacazes (RJ) city and one case of dengue shock syndrome (DSS) involving hemorrhagic encephalopathy was registered³⁴.

Various atypical manifestations of dengue virus infection, including involvement of the central nervous system, cardiac disturbances and elevated levels of aminotransferases, with reactive hepatitis, have been reported during recent years^{31,34,36}.

The relationship between hemorrhagic dengue fever (HDF) and neurological disturbances was first described in 1976, and since then several publications have added to the information available on this disease^{31,37}. Encephalopathy in HDF is an atypical manifestation and may appear in various

forms, including depressed sensitivity, convulsion, behavioral disorders, meningeal involvement and focal signs of the virus in the central nervous system^{34,35,38}.

Physiopathology of neurological involvement may include the following factors: direct tissue lesion caused by the virus, capillary hemorrhage, disseminated intravascular coagulation, metabolic disorder (hyponatremia and metabolic acidosis), fulminant hepatic failure and cerebral edema caused by the increase in vascular permeability^{34,35,36}.

Encephalopathy is a rare manifestation of HDF. It should, however, be investigated in endemic areas and during epidemics of dengue, since early diagnosis is essential for its management. Hemorrhagic complications and circulatory collapse are determinant factors in the prognosis and are the principal causes of death in these patients.

CONCLUSION

We believe that imaging can be very useful for the early recognition of moderate to severe forms of DHF before they become clinically apparent.

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