

CLINICAL AND LABORATORY PROFILE OF DENGUE FEVER IN A TERTIARY CARE CENTRE

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Abstract

To study the clinical profile and outcome of the manifestations of dengue fever in children.

Methods All children (0–12 y of age) diagnosed and confirmed as dengue fever at a tertiary care hospital at Bangalore, between the 1st of November 2018 and March 31st 2019 were

reviewed retrospectively from hospital case records as per the revised World Health Organization (WHO) guidelines. The diagnosis was confirmed by NS1 antigen based ELISA test or dengue serology for IgM and IgG antibodies.

Results Out of 60 children admitted with dengue fever. Mean age of presentation was 6.9(3.3) y. M: F

ratio was 1.2:1. The common manifestations of severe dengue infection were shock (37.4 %), bleeding (20.1 %) and multiorgan dysfunction (2.4 %). The most common atypical manifestations of dengue fever were lymphadenopathy (41.7 %), splenomegaly (21.2 %), biphasic fever (18.1 %), hepatitis

(11.4 %), febrile diarrhea (6.3 %), refractory shock (2.4 %) and impaired consciousness (1.9 %). The other atypical manifestations present were portal hypertension, acalculous cholecystitis, appendicitis, acute respiratory distress syndrome (ARDS), myocarditis, pericardial effusion, paroxysmal supraventricular tachycardia (PSVT), myositis, acute kidney injury (AKI), hemophagocytic syndrome and disseminated intravas

cular coagulopathy (DIC). Platelet count did not always correlate well with the severity of bleeding. There were six deaths (2.4 %) and out of them four presented with impaired consciousness (66.6 %). The common causes for poor outcome were multiorgan failure, encephalopathy and refractory shock. Conclusions The atypical manifestations of dengue fever are no more a rare entity. Clinicians should have a high index of suspicion and vigilance for atypical manifestations of dengue fever as lack of timely detection and management could be

fatal. Impaired consciousness was the most ominous atypical manifestation of severe dengue infection.

Keywords: Dengue fever, viral fever, child, severe dengue

INTRODUCTION

Dengue fever is the most rapidly spreading mosquito borne viral disease with an estimated 30-fold increase in incidence over last five decades [1]. With rising disease burden, atypical manifestations are also on rise. These include neurological, hepatic, renal, cardiovascular and other isolated organ involvement and termed as

Expanded dengue syndrome/unusual or atypical manifestations of dengue fever as per the revised 2011 guidelines of dengue fever and are often life threatening with very high case fatality rate [1]. Atypical manifestations could be explained as complications of severe profound shock, associated underlying host

conditions, diseases and co-infections [2, 3]. They might resemble other co-infections like enteric fever. There is limited literature describing atypical manifestations of dengue fever in children. In this communication, the authors describe the atypical manifestations in pediatric in-patients with serologically confirmed dengue virus infection.

Material and Methods

All children (0–12 y of age) diagnosed and confirmed as dengue fever at a tertiary care hospital at Bangalore, between the 1st of November 2018 and March 31st 2019 were reviewed retrospectively from hospital case records as per the revised World Health Organization (WHO) guidelines. The diagnosis was confirmed by NS1 antigen based ELISA test or dengue serology for IgM and IgG antibodies.

The SPSS 16.0 statistical software was used for data analysis. Categorical variables were expressed as frequencies and percentages, and then analyzed by the χ^2 test or fisher's exact test, where appropriate. Continuous data, expressed as mean \pm SD, or median (range), were analyzed using student's t-test, analysis of

variance (ANOVA-1 way) or Mann-Whitney U test. Odds ratio (OR) with 95 % confidence interval (CI) was calculated to measure the degree of association of warning signs with severe dengue infection. Significance was taken at P value <0.05 .

Results

Out of 60 children admitted with dengue fever, non-severe dengue and severe dengue were seen in 68.4 % and 31.6 % respectively. Severe complications with multiorgan involvement were seen in 19 cases (18.3 %). The most common affected age group was 6–12 y (53 %) and the mean age of presentation was 7(3.3) y. Male to female ratio was 1.2:1.

Table.1: clinical parameters

| | |
|--------------------|-----------|
| fever | 60(100%) |
| headache | 53(88.3%) |
| Low backache | 29(48.3%) |
| Nausea/vomiting | 39(65%) |
| rashes | 27(45%) |
| myalgia | 49(81.6%) |
| Joint pain | 36(60%) |
| Retro orbital pain | 26(43%) |
| breathlessness | 4(6.6%) |
| Bleeding diathesis | 6(10%) |
| hypotension | 9(15%) |
| Plueral effusion | 4(6.6%) |

Fever duration of <7 d was present in 48cases (80 %), > 7 d in 12 cases (20 %). The most common clinical warning signs at admission were persistent vomiting (65 %), headache (88.3%), low backache 48.3%, rashes seen in 27%, joint

pain in 60%, myalgia in 49(81.6%), retro orbital pain in 26(43%), breathlessness in 4 children, bleeding diathesis in 6, hypotension in 9 and plural effusion in 4.

Table 1. Laboratory parameters Number (%)

| Parameter | number(%) |
|--|-----------|
| Anemia (Hemoglobin <10 g/dl) | 18(30) |
| Leukopenia (TLC < 4000/mm ³) | 53(88.3%) |
| Thrombocytopenia (< 1,50,000/mm ³) | 52(31.2%) |
| PLC < 50,000/mm ³ | 28(16.8%) |
| PLC < 20,000/mm ³ | 18(10.8%) |
| Hemoconcentration (HCT > 40) | 38(22.8%) |
| Prothrombin time (PT/INR > 1.0) | 27(16.2%) |
| APTT (> 1.5 times normal) | 23(13.8%) |
| Abnormal LFT (SGOT & SGPT >150 IU) | 18(10.8%) |
| Deranged RFT (Serum creatinine >3 mg/dl) | 4(2.4%) |
| Hypoalbuminemia (serum albumin <3 g/dl) | 3(1.8%) |
| Gall bladder wall edema on USG | 29(17.4%) |
| NS1 antigen positive | 38(22.8%) |
| NS1 antigen -ve and IgM positive | 14(8.4%) |
| Dengue IgM positive | 43(71.6%) |
| Dengue IgG antibody | 17(28.3%) |

Amongst 60, 30% had anemia, leucopenia seen in 88.3%, thrombocytopenia in 31.2%, platelet count <50,000/mm³ seen in 28 children, <20,000/mm³ seen in 18 children. Raised hematocrit seen in 22.8%.

Conclusion:

The most common atypical gastrointestinal presentations of dengue fever in the index study were hepatitis, acalculous cholecystitis and febrile diarrhea.

Hepatitis was present in 11.4 % of cases and among them two children developed fulminant hepatic failure. The etiology of hepatic dysfunction in dengue fever is usually due to direct cytopathic injury, unregulated host immune response, active viral replication, and hypoxia and tissue ischemia due to prolonged shock, hemorrhage and metabolic acidosis [2, 4–6].

Acute acalculous cholecystitis is equally rare in dengue fever. The main pathophysiological changes in dengue fever could be due to increased vascular permeability causing plasma leakage and serous effusion with high protein content which causes thickening of gall bladder wall [8]. The course of the disease is usually self-limiting and gall bladder wall thickness usually returns to normal with supportive care in majority of cases, even though isolated cases of

gangrene and perforated gall bladder with peritonitis has been reported and surgical intervention is reserved only for children who have evidence of gangrene, perforation and diffuse peritonitis

[2]. Gall bladder wall edema on ultrasound was a common associated finding of severe dengue in the index study similar to the previous studies [9]. Acute acalculous cholecystitis was seen in two children who improved symptomatically and were discharged. In this study, febrile diarrhea was seen in 6.3 % cases with severe dengue which is unusual and very few cases have been reported [10]. Bilateral parotid enlargement was present in 2

children in the index study while only one case has been reported in the past [2]. Acute appendicitis was seen in two cases with severe dengue which created a dilemma for surgeons but responded to conservative management, with very few cases being reported in the past [11].

The neurological manifestations of dengue fever were first described in 1976 [12,13, 14]. Pancharoen and Thisyakorn, in their study, reported altered sensorium as the most common neurological finding followed by seizures and observed these findings in 75 % of patients with dengue shock syndrome [15]. Rigau Perez et al. and similar previous studies have reported a high proportion of impaired consciousness at presentation and dur

ing disease progression with multi-organ involvement and high mortality [16]. Dengue encephalopathy has been reported to occur in 0.5–17 % patients with dengue [17–19]. In this study, impaired consciousness and seizures at admission were seen in six patients and among them there were four deaths (66 %); all had features of refractory shock and multiorgan failure, the most ominous sign for mortality with severe dengue.

The cardiac manifestations of dengue fever in the index study were myocarditis, paroxysmal supraventricular tachycardia, sinus bradycardia, pericardial effusion and ectopic ventricular beats. Majority of the patients had a spontaneous resolution and received symptomatic supportive treatment.

The association of cardiac rhythm disturbances in dengue fever have been reportedly attributed to viral myocarditis during episodes of dengue hemorrhagic fever [20–22]. Pericardial involvement has also been attributed to dengue infection along with myocarditis [23]. Acute respiratory distress syndrome (ARDS) is one of the unusual and fatal complications of severe dengue infection. It is usually secondary to increased alveolar-capillary membrane permeability leading to interstitial and alveolar edema which leads to pulmonary dysfunction and is associated with high mortality rate [24]. Pulmonary hemorrhage with disseminated

intravascular coagulopathy (DIC) is another fatal and unusual complication in severe dengue infection [25]. In the index study four children developed acute respiratory distress syndrome and pulmonary hemorrhage and had poor outcome as described in the previous studies [26].

Acute kidney injury was present in six cases in the present study. It is an unusual manifestation of dengue fever and mainly presents as shock induced acute tubular necrosis apart from other rare causes like multi-organ dysfunction and rhabdomyolysis. The role of immune complex in development of renal failure in dengue infection is still unclear [2, 27]. Although hepatomegaly is among the WHO clinical criteria for dengue

fever, splenomegaly and lymphadenopathy are not generally held to be a feature of dengue infection [1]. In the index study there was higher percentage of splenomegaly and lymphadenopathy compared to the previous studies [28].

Splenomegaly and lymphadenopathy signified the occurrence of dengue virus antigen in the lymphoreticular cells. Hemophagocytic syndrome is an unusual manifestation of dengue fever which was present in two cases with very few cases reported in the past [29].

Although myalgia is a common manifestation of dengue fever, myositis is unusual. The probable mechanism for myositis is the release of myotoxic cytokines, particularly tumor necrosis factor (TNF- α) thereby injuring the affected muscle [30]. These patients need to be detected promptly as there is a risk of progressing to renal failure if not identified in time [31].

In children presenting with myositis, dengue fever should be considered as an important differential diagnosis.

In the present study secondary infection was less than primary infection, but it was commonly associated with severe dengue. Wichmann et al. in their study showed that secondary infection was significantly associated with severe dengue in children. During secondary infection, T-cells become activated due to interactions with infected monocytes which induce plasma leakage by release of cascade of cytokines such as interferon- γ , IL-2, and TNF- α [32]. Co-infections were seen in 17.4 % cases and it is important that they be promptly recognized. Co-infections can modify the clinical presentation of dengue and result in missed or

delayed diagnosis and treatment of dengue shock. Coexistence of malaria and dengue have been reported to be in the range of 20 % to as high as 80 % [2, 3, 33]. In the index study thrombocytopenia, bleeding and plasma

leakage did not always correlate. Since majority of the cases were dengue fever with peripheral circulatory failure without bleeding, alternate case definitions used were Dengue fever associated with shock without bleeding (DSAS) and Dengue fever with bleeding without shock (DFB) and authors' experience suggests a need for revision of the existing case definitions [1]. Another unique observation was that majority of the cases of severe dengue presented with compensated shock without bleeding and responded to fluid therapy and only

6.3 % developed complications. The most probable reasons being early detection of cases, availability of quick early diagnostic test like NS1 antigen detection, and timely hospitalization and increased awareness among the public. The bleeding manifestations also did not correlate well with platelet counts, and occurred in children with even normal platelet counts and platelet transfusion was given in children with severe dengue with severe thrombocytopenia. Coagulation profile was deranged in 13 cases (5.1 %) signifying the fact that factors other than thrombocytopenia like platelet dysfunction, consumption coagulopathy and endothelial dysfunction are responsible for bleeding in dengue fever [34].

The most common factors for atypical manifestations with complications were prolonged shock, bleeding, pain abdomen, lack of clinical improvement post defervescence, impaired consciousness, lethargy, restlessness and severe.

Conclusions

Atypical manifestations of dengue fever are more common than actually reported. However, the awareness is lacking among the health care personnels especially at primary health centers from where these cases are often referred. There is a need to update the health care personnels and community at various forums, about the various atypical manifestations of dengue for prompt recognition and management. Impaired consciousness at the time of admission should be considered as the most ominous atypical manifestation of severe dengue infection.

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