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DENGUE INFECTION IN CHILDREN WITH THALASSEMIA- IS IT DIFFERENT?

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ABSTRACT

BACKGROUND: Children with thalassemia are at equal risk of getting dengue. Atypical manifestations of dengue in children with thalassemia are highlighted in studies from South Asia. Burden of suboptimal transfusion and chelation in children with thalassemia prompted us to undertake this study

OBJECTIVES: To study the clinical course and short term outcome of children with thalassemia affected by dengue, and compare them to dengue infection in children without chronic illness.

METHODS: Retrospective case note review of children with thalassemia, admitted with dengue from April 2013 to April 2018. Comparison group included children without chronic disease admitted with dengue from November 2012 to April 2014. Severity, complications, hematological/ biochemical parameters, treatment given were analysed. Management was according to 'WHO 2009 Guideline on Dengue'

RESULTS: 15 children with Thalassemia (n=207) had confirmed dengue (NSI positive/ Dengue IgM positive), M: F=1:1.1, median age 6 years (interquartile range IQR 3-11). Median duration of hospital stay 6 (IQR 4-6) days. WHO Group A, B and C had 5, 6 and 4 patients respectively. Clinical features included fever in 15 (100%), persistent vomiting in 9 (60%), abdominal pain in 4 (26.7%) and excessive fluid accumulation in 2 (13.3%). 12 (80%) had anemia at presentation, median Hb 83 (IQR 70-101) g/l, while 2 (13.3%) had hematocrit >36%. 14 (93%) patients had platelets </= 150,000/ cu.mm, 9 (60%) with severe thrombocytopenia (</= 50,000/cu.mm). TC </= 4000/cu.mm present in 7 (46.7%) patients. AST/ ALT elevated in 14 (93.3%) patients. 4 (26.7%) patients required intensive care. 10 (66.7%) children required red cell transfusion. There were no deaths.Comparing with other group, there was significant difference in number of patients with anemia (p=0.0001, 95% CI 5.6 to 3.8) and hemo-concentration (P=0.0001, (95% CI -15.3 to -9.7).

CONCLUSION: Children with thalassemia and dengue infection present with anemia requiring red cell transfusion, hence HCT may not be a useful monitoring tool. In comparison to national statistics (INCLEN Study Group data 2014), the proportion of patients in Group B (40 vs 9.5%) and group C (26 vs 5.9%) appears to be higher in children with thalassemia. Such patients require in-patient care as they may be at greater risk of developing severe disease

KEYWORDS : Dengue, Thalassemia, child

INTRODUCTION

Dengue is the most extensively spread mosquito-borne disease, transmitted by infected mosquitoes of Aedes species. Dengue infection in humans results from four dengue virus serotypes (DEN-1, DEN-2, DEN-3, and DEN-4). It is a single stranded enveloped RNA virus belongs to the family Flaviviridae, genus Flavivrus. It had a predominant urban distribution a few decades earlier, but is now also reported from peri-urban as well as rural areas. In India, there is an increase in the incidence of dengue outbreaks during the monsoon and post-monsoon seasons with each year. Children and young adults are the populations that are most affected. Dengue can present with non specific symptoms, especially in younger children.(1) Therefore early identification of severe disease can be challenging, causing delays in the institution of life-saving interventions. To assist clinicians in making triage decisions, the World Health Organisation (WHO) published a dengue infection triage and treatment guideline in 1997 and further revised it in 2009. The new classification, retained the three-level severity grading and divided the infection into Group A (dengue without warning signs), Group B (dengue with warning signs) and Group C (severe dengue with severe plasma leakage, hemorrhage and organ impairment). The warning signs include abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy, restlessness, liver enlargement, and laboratory parameters such as increase in hematocrit with concurrent decrease in platelet count. (2)

The thalassemias are a group of inherited hematologic disorders caused by defects in the synthesis of one or more of the globin chains of hemoglobin. Alpha thalassemia is caused by reduced or absent synthesis of alpha globin chains, and beta thalassemia is caused by reduced or absent synthesis of beta globin chains. Imbalances of globin chains cause hemolysis and impair erythropoiesis. Silent carriers of alpha thalassemia and persons with alpha or beta thalassemia trait are asymptomatic with no excessive haemolysis or features of ineffective erythropoiesis . There are two main clinical phenotypes, non transfusion dependent thalassemia (NTDT also called Thalassemia intermedia) and transfusion dependent thalassemia (TDT also called thalassemia major). Patient with both forms of the disease show varying degree of clinical features such as poor growth, extra medullary hematopoiesis and iron overload causing hepatic and cardiac impairment and endocrine problems.

Dengue fever is one of the leading causes of pediatric hospitalization in India and South Asia. Children with thalassemia are at equal risk of getting dengue infection. Atypical manifestations of dengue in a paediatric population with thalassemia have been highlighted in few studies from South East Asia.(3)(4) In a resource limited environment, suboptimal transfusion and chelation may complicate dengue illness. The presence of high burden of endemic dengue and thalssemia in our population prompted us to undertake this study.

Objectives

1. To study the clinical course and short term outcome of children with thalassemia affected by dengue.
2. To compare the clinical and laboratory profile of dengue infection in children with thalassemia to that in children without chronic illness.

METHODS

Case notes of all children with thalassemia aged 1 month to 18 years of age hospitalised at St. John's Medical College Hospital in the Department of Pediatrics with a diagnosis of probable/confirmed dengue from April 2013 to July 2018 were reviewed. The comparative

cohort included all children aged 1 month- 18 years of age admitted with a diagnosis of probable/ confirmed dengue, excluding any children with chronic disorders, from November 2012 to April 2014. The severity and complications of disease, haematological and biochemical parameters, and treatment given were analysed. Management was according to The 2009 World Health Organisation (WHO) guideline on Dengue .

The following laboratory results that were performed as per clinical management protocol, were recorded in this study:

- Complete blood count, including serial monitoring of hematocrit.
- Platelet count
- Liver function tests
- Fibrinogen degradation products, D-dimer, prothrombin time and activated thromboplastin time(as clinically indicated)
- Tests for diagnosis of dengue fever (Ig M by ELISA and NS1 by rapid antigen detection test)

Institutional Ethics Committee approval obtained. Statistical calculaions were done using the software Stata 13.0

RESULTS

Table 1 Results: Clinical and laboratory features

Parameter	Children with thalassemia & Dengue (n=15)	Children with no chronic illness & Dengue (n=149)
Fever	15 (100%)	149 (100%)
Persistent vomiting	9 (60%)	146 (98%)
Abdominal pain	4 (26.7%)	121 (81.2%)
Fluid accumulation	2 (13.3%)	109 (73.15%)
Anemia	**12 (80%)**	**9 (6%)**
Hemo-concentration	**2 (13.3%)**	**120 (80.5%)**
Leucopenia	7 (46.7%)	54 (36.49)
Thrombocytopenia	14 (93.3%)	148 (99.3%)
Raised AST/ ALT	14 (93.3%)	146 (98%)

Of 207 children with thalassemia registered at our centre, 15 had probable or confirmed dengue (Dengue IgM positive and/or non structural antigen NSI positive respectively), M: F = 1:1.1, median age 6 years (interquartile range 3-11).

Group A (dengue without warning signs), B (dengue with warning signs) and C (severe dengue) had 5(33%), 6(40%) and 4 (26%) patients respectively. The median duration of hospital stay was 6 days (interquartile range 4-6). Fever was present in all patients, persistent vomiting in 9 (60%), abdominal pain in 4 (26.7%) and excessive fluid accumulation in 2 (13.3%). 12 patients (80%) had anemia at presentation with median Hb 83g/l (interquartile range 7-10.1), and only 2 (13.3%) had haemoconcentration (Haematocrit >36%). 14 (93%) patients had thrombocytopenia (platelets </= 150,000/ cu.mm), and 9 (60%) with severe thrombocytopenia (</= 50,000/cu.mm). Leucopenia (TC </= 4000/cu.mm) was present in 7 (46.7%) patients. Aspartate transaminase (AST) / Alanine Transaminase (ALT) were elevated in 14 (93.3%) patients.

Four patients (26.7%) required intensive care treatment. 2 (13.3 %) had severe bleeding and coagulopathy and received plasma and platelet transfusion. 10 (66.7%) children required red cell transfusion. There were no deaths.

In the comparative group, 330 children were admitted with suspect dengue, of which 149 were included for analysis by virtue of being positive for NS1 antigen/ Dengue IgM or both. M:F =1.6:1, mean age 9.3 years (SD +/- 4.12). There were 3 (2%) patients in group A, 116 (77.9%) in group B, and 30 (20%) in group C. The mean duration of hospital stay was 5.7 days (SD +/-7.58), with median of 4 (interquartile range 3-6) days.

Fever was present in all patients, persistent vomiting in 146 (98%), abdominal pain in 121 (81.2%) and excessive fluid accumulation in 109 (73.15%) patients.

120 (80.5%) patients had hemoconcentration, with mean hematocrit of 40.65% (SD+/-4.95). and only 9 (6%) had anemia.

148 (99.3%) patients had thrombocytopenia (platelets </= 150,000/ cu.mm), and 75 (50.3%) with severe thrombocytopenia (</= 50,000/cu.mm). Leucopenia (TC </= 4000/cu.mm) was present in 54 (36.49%) patients. Aspartate transaminase (AST)/ Alanine Transaminase (ALT) were elevated in 146 (98%) patients.

22 (14.8%) patients required intensive care treatment. 6 (4.03%) required red cell transfusion. 5 (3.4%) patients died.

Comparing the two groups of patients, there was no significant difference in the gender distribution or symptoms of dengue illness, duration of hospital and intensive care stay, or laboratory features such as leucopenia, thrombocytopenia and elevation of liver enzymes. There was a significant difference in the number of patients presenting with anemia (p=0.0001, 95% CI 5.6 to 3.8) and hemo-concentration (P=0.0001, (95% CI -15.3 to -9.7) between the two groups.

DISCUSSION AND CONCLUSION

Dengue inflicts a significant health, economic and social burden on the populations of endemic areas. Children, especially infants and teenagers are at risk of severe dengue. Most patients tend to recover from the illness. Pediatric patients with thalassemia infected by dengue virus frequently present with anemia instead of hemoconcentration. Many require red cell transfusion to maintain adequate intravascular volume. This is congruous with studies on similar populations in Thailand and South East Asia. Our study is limited by part of it being conducted in a retrospective manner, and selection bias of patients with more severe disease being admitted to hospital, particularly in the comparative group. However in comparison to national statistics (INCLEN Study Group data 2014)(1), the proportion of patients in Group B (40 vs 9.5%) and group C (26 vs 5.9%) appears to be higher in children with thalassemia.

It is prudent to admit all children with thalassemia with suspected dengue infection to hospital for close monitoring and prompt intervention to yield a favorable outcome. Elevated hematocrit is less useful as a tool for guiding treatment in these patients, as they usually present with anemia and require red cell transfusion.

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