

# Dengue fever causing febrile neutropenia in children with acute lymphoblastic leukemia: An unknown entity

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Dengue fever is endemic in many parts of the world but it has not been described as a cause of febrile neutropenia. We describe here clinical features, laboratory values and outcome in 10 children with acute lymphoblastic leukemia (ALL) and with dengue fever as a cause of febrile neutropenia. These data are compared to an age-matched control population of 22 children with proven dengue infection without ALL. Except for fever in all patients and plethoric face in one patient, typical symptoms of dengue such as abdominal pain, myalgias, and headaches, were absent. Mean duration of hospital stay was  $6.3 \pm 2.0$  days in ALL patients vs.  $5.0 \pm 2.0$  in controls ( $p = 0.096$ ). Median platelet count was 13,000/cmm (range 1000–28,000) in cases vs. 31,500 (range 13,000–150,000) in controls ( $p = 0.018$ ). Mean time for recovery for platelet was  $6.0 \pm 1.3$  days in ALL patients vs.  $2.5 \pm 0.9$  days in controls ( $p < 0.001$ ). All 10 patients survived. In endemic areas, high suspicion of dengue fever should be maintained in children with ALL and febrile neutropenia although typical symptoms may be lacking. Platelet recovery may be significantly delayed.

**D**engue virus (DEN) is a small single-stranded RNA virus comprising four distinct serotypes (DEN-1 to 4). 'Asian' genotypes of DEN-2 and DEN-3 are frequently associated with severe disease accompanying secondary dengue infections.<sup>1</sup> Dengue is quite common in India in both urban and suburban areas. In 2010, a total of 27,196 cases and 104 deaths were reported in India. Delhi had the highest number: at 6240 cases and eight deaths.<sup>2</sup>

There are multiple reasons for a child to have febrile neutropenia post-chemotherapy but bacterial and fungal etiologies are usually investigated. It is important to describe dengue infection as an etiology of febrile neutropenia in children with ALL as it has not been previously reported and its clinical course is not known in this population. Management also differs with focus on fluid therapy rather than antibiotics. Here we describe clinical profiles, courses and

outcomes of dengue infection in febrile neutropenic children with ALL.

## METHOD

The medical records of all 58 cases of febrile neutropenia (Fever  $> 37.5$  °C on a single occasion or fever of 37 °C on more than two occasions, 30 mins apart with Absolute Neutrophil Count of less than 1000/ $\mu$ l) in children with ALL admitted to Sir Ganga Ram Hospital between July 2010 and December 2010 were retrospectively analyzed.

Diagnosis of dengue infection was performed at screening with a Dengue NS1 antigen (Panbio, Australia) and confirmed with an IgM and IgG capture enzyme-linked immunosorbent assay (McELISA) (Panbio, Australia). Initially all children received broad spectrum intravenous antibiotics. The antibiotics were stopped once the diagnosis of

dengue was confirmed and blood cultures were negative. All children diagnosed with dengue hemorrhagic fever received appropriate fluid therapy. A total of 10/58 (16%) consecutive children with ALL and febrile neutropenia had proven dengue infection. Data regarding symptomatology, clinical course, laboratory values and outcome were analyzed. Their laboratory values were compared with an age-matched control population of 22 children with proven dengue infection without underlying ALL. *T*-test and Mann-Whitney *U*-test were applied as these were applicable for comparison.

**RESULTS**

Ten out of 58 febrile neutropenic ALL patients had dengue infection. Their clinical profile is described (Table 1). NS1 antigen was positive in all 10 cases with a mean of 3.5 days of fever. IgM (McELISA) was positive in seven patients with a mean of 6.5 days. In two patients, NS1 antigen was negative initially and became positive after five days. Six patients had dengue fever, two had dengue hemorrhagic fever (DHF), and two had dengue shock syndrome (DSS). Except for fever, typical symptoms of dengue infection such as plethoric face, abdominal pain, myalgia, and headache were absent (only one patient had plethoric face).

Mean duration of hospital stay was 6.3 ± 2.0 days in ALL patients vs. 5.0 ± 2.0 in controls (*p* = 0.096).

Two patients required fluid replacement at a rate >10 ml/kg/hr and two at 7 ml/kg/hr. Cases had median platelet count of 13,000/cmm (range 1000–28,000) vs. 31,500 (range 13,000–150,000) in controls (*p* = 0.018). Mean recovery time for platelet was 6.0 ± 1.3 days in cases vs. 2.5 ± 0.9 days in controls (*p* < 0.001) (Table 2). One patient also had blood culture positive for *Acinetobacter baumannii*. Eight patients had deranged liver function. All 10 survived.

**DISCUSSION**

Children with ALL are immunocompromised. They face high risk of sepsis during the neutropenic phase of post-chemotherapy. Sepsis is a major barrier to improve survival of children with ALL in developing countries.<sup>3</sup> Multiple etiological factors have been mentioned for febrile neutropenia, mainly bacterial, viral and fungal infections. Dengue has rarely been mentioned in the literature as a cause for febrile neutropenia in children with ALL. Dengue and other arboviruses can be associated with bone marrow failure. It is known that dengue subtype DEN-4 can reproduce in the progenitor cells of the bone marrow. Neutropenia and thrombocytopenia are common in dengue infection due to hypocellular bone marrow and abnormal megakaryopoiesis.<sup>4</sup> It is believed that dengue-induced pancytopenia is a direct consequence of both peripheral destruction induced by immune

**Table 1.** Clinical profile of patients of acute lymphoblastic leukemia with dengue.

| No. | Phase of Protocol                 | Diagnosis | Symptoms on admission     | Hb g/dl (Max) | Lowest platelet/mm <sup>3</sup> | Platelet support | NS1 Ag positive   | Fluid req. ml/kg/hr | Complications                   | SGOT/SGPT | Outcome  |
|-----|-----------------------------------|-----------|---------------------------|---------------|---------------------------------|------------------|-------------------|---------------------|---------------------------------|-----------|----------|
| 1   | Maintenance                       | DSS       | Fever                     | 9.9           | 13,000                          | yes              | Day 3             | 10                  | Pl. effusion, ascites           | 306/159   | Survived |
| 2   | Maintenance                       | DHF       | Fever                     | 9.7           | 1000                            | yes              | Day 3             | 7                   | none                            | 130/116   | Survived |
| 3   | Day+10 post reinduction           | DSS       | Fever with plethoric face | 13.7          | 9000                            | yes              | Ng day 2 Ps day 5 | 10                  | Pl. effusion, ascites           | 235/116   | Survived |
| 4   | Maintenance                       | DF        | Fever                     | 10.8          | 14,000                          | yes              | Day 2             | 3                   | None                            | 190/154   | Survived |
| 5   | Maintenance                       | DF        | Fever                     | 11.2          | 13,000                          | yes              | Day 2             | 3                   | None                            | 118/102   | Survived |
| 6   | Just off treatment                | DF        | Fever                     | 17.1          | 28,000                          | no               | Day 3             | 3                   | None                            | 46/26     | Survived |
| 7   | Day+11 post reinduction           | DF        | Fever                     | 8.3           | 8000                            | yes              | Day 3             | 3                   | None                            | 120/80    | Survived |
| 8   | Day+8 post second intensification | DHF       | Fever                     | 9.9           | 9000                            | yes              |                   | 7                   | Pl. effusion, ascites, bleeding | 324/180   | Survived |
| 9   | Maintenance                       | DF        | Fever                     | 10            | 20,000                          | No               | Day 3             | 3                   | None                            | 124/116   | Survived |
| 10  | Maintenance                       | DF        | Fever                     | 11.5          | 15,000                          | No               | Day 3             | 3                   | None                            | Not done  | Survived |

Hb – Hemoglobin, Plt – Platelets, Req – Requirement, Ng – negative, Ps – Positive.

complexes and direct viral injury to the bone marrow.<sup>5</sup>

In our patients there was a significant difference in platelet recovery time and lowest TLC between children with ALL and controls ( $p < .001$ ). The possible explanation could be prior immunocompromised status in ALL patients and neutropenia due to chemotherapy with superimposed marrow invasion by dengue virus which leads to marked neutropenia and thrombocytopenia and/or peripheral immune destruction of platelets after dengue virus infection. Reticulocytopenia, lymphocytopenia, thrombocytopenia and granulocytopenia appear in this order.<sup>6</sup> Our six patients were in the maintenance phase of chemotherapy (daily oral 6-Mercaptopurine and weekly oral Methotrexate) and one had recently completed treatment. They had significant neutropenia and thrombocytopenia which were less likely to be due to oral maintenance chemotherapy. One patient developed DHF post intensification chemotherapy and another developed DSS post re-induction chemotherapy. Both developed severe neutropenia and thrombocytopenia along with other complications like bleeding, pleural effusion and ascites. Systemic symptoms such as increases in hematocrit, thrombocytopenia, and hemorrhagic manifestations due to abnormalities of capillary permeability which characterize DHF, usually appear during the second episode of dengue infection in 95% of cases.<sup>5</sup> However, the four patients who developed DHF and DSS had no past history of dengue infection. A recent report of dengue infection in six cancer patients which included one case of ALL highlighted a mean delay in diagnosis of 10 days.<sup>7</sup> Due to early suspicion and timely diagnosis of dengue infection, all patients in our series received prompt adequate fluid therapy according to their clinical condition. All 10 patients survived. Prevention of the mosquito bite is the best strategy to reduce dengue induced febrile neutropenia. We routinely educate parents and patients on how to avoid mosquito bites.

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**Table 2.** Comparison of platelet recovery time, hospital stay, Hb, TLC and lowest platelets between cases and controls.

|                          | Case               | Control             | P value             |
|--------------------------|--------------------|---------------------|---------------------|
| Mean+/-S.D               |                    |                     |                     |
| Hospital stay (days)     | 6.3+/-2.0          | 5.0+/-2.0           | <0.096 <sup>a</sup> |
| Platelet recovery (days) | 6.0+/-1.3          | 2.5+/-              | <0.001 <sup>a</sup> |
| Median and range         |                    |                     |                     |
| Hb                       | 10.4 (8.3–12.1)    | 12.7 (11.2–15.4)    | 0.031               |
| TLC                      | 1500 (650–2400)    | 4600 (2900–8100)    | <0.001              |
| Lowest platelet count    | 13000 (1000–16000) | 31500 (21000–70000) | 0.018               |

<sup>a</sup>T test, TLC (Total Leucocytes Count), Hb (Hemoglobin).

Government also supports this effort through newspapers, television and radio advertisements on the prevention of mosquito bites. Prevention can be achieved by use of mosquito nets, application of mosquito repellent, regular insecticidal spray and avoidance of water collection in and around homes to avoid mosquito breeding.

We recommend high suspicion of dengue fever as a cause of febrile neutropenia in children with ALL in endemic areas even in the absence of typical symptoms of dengue fever. Platelet recovery may be significantly delayed.

## CONFLICT OF INTEREST

Authors have nothing to disclose.

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