

## Development of Dengue Hemorrhagic Fever in a Patient within 2 Weeks of Contemporaneous Infection of Typhoid Fever and Primary Dengue Fever

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### ABSTRACT

Dengue virus is the most important mosquito-borne viral disease in the world. Co-circulation of the four types of dengue viruses and expansion of dengue epidemic give rise to infection enhancement and a big expansion of clinical aspects of the disease. Besides dengue, typhoid fever is an ancient disease, have emerged as major public health problem in developing countries including Bangladesh. Here we report a case of 4 years old boy, who have developed Dengue Hemorrhagic Fever within 2 weeks of contemporaneous infection of Typhoid fever and Primary dengue fever.

**Key Words:** Dengue fever, typhoid fever, dengue hemorrhagic fever, contemporaneous.

### Introduction

Dengue, a mosquito-borne viral illness, an important cause of morbidity and some mortality in many countries, mostly in Asia and Latin America, and is continuing to expand globally. Around 390 million infections occur each year with approximately 500,000 hospital admissions with potentially life-threatening forms of the disease, dengue hemorrhagic fever (DHF) and dengue shock syndrome.<sup>1</sup> Approximately 12,000 deaths, mostly among children, occur worldwide every year.<sup>1</sup> Bangladesh is facing its worst dengue outbreak since 2000, with fears of mortality running deep as the infection reaches all parts of the country, particularly affecting children, pregnant women, and older people.<sup>2</sup> In 2018, 10,148 dengue cases were reported, and as of October 31, 2019, 96,096 people have been infected, with 107 confirmed deaths.<sup>3</sup> Similarly Typhoid fever, the common bacterial cause of morbidity worldwide, with the greatest burden in low- and middle-income countries.<sup>4</sup>

*Salmonella enterica* subspecies *enterica* serovar Typhi (*Salmonella* Typhi), the causative agent of typhoid, is estimated to cause about 12 million illnesses and 128 000 deaths, and *Salmonella enterica* subspecies *enterica* serovar Paratyphi (*Salmonella* Paratyphi) A, B, and C, the causative agents of paratyphoid, are estimated to cause 4 million illnesses and 25 000 deaths annually.<sup>5,6</sup>

Concurrent infection with two agents can result in an illness having overlapping symptoms creating a diagnostic dilemma for the treating physician. Here, we report a case; initially diagnosed as a case of co-infected typhoid fever and primary dengue fever, was admitted in pediatric ward which was burdened with 30 Dengue patients in peak season of dengue in the month of July. Unfortunately this patient in his period of hospital stay again infected with dengue virus and develops secondary dengue fever in the form of Dengue hemorrhagic fever.

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### Case Report

A 4-year-old boy admitted to pediatric ward with history of fever for 3 days, loose watery stool and bodyache for same duration. Clinically the boy was ill looking, febrile, dehydrated, pulse 100 beats/minute, respiratory rate 34 breaths/minute and blood pressure 100/60 mmHg, no organomegaly and no evidence of pleural effusion or ascities. There were no signs of active bleeding and the tourniquet test was negative. Investigation reports revealed blood culture positive for *Salmonella typhi*, Platelet count was low, Dengue NS1 antigen was positive on 3<sup>rd</sup> day, and Dengue Ig M was positive and Ig G was negative on 7<sup>th</sup> day. So, he was diagnosed as a case of contemporaneous infection of Typhoid fever and Primary dengue fever and managed according to National dengue guideline along with antibiotic. He became fever free on 9<sup>th</sup> day of illness and remain afebrile for 4 days. On 13<sup>th</sup> day of his illness when he was preparing to leave hospital he again developed high grade fever along with headache, bodyache, retroorbital pain. After febrile phase of 3 days he now developed dengue hemorrhagic fever as he had narrow pulse pressure, positive tourniquet test, ascites, pleural effusion. This time again Dengue NS1 antigen was positive and both Dengue Ig M and IgG were positive. His Chest X ray and USG abdomen revealed Right sided pleural effusion and ascites. With treatment, according to National guideline, after sufferings of further 7 days he recovered completely.

**Table 1:** A summary of investigation results of the patient during the illness

Date	23/7/2019	29.7.19	6.8.19	8.8.19	10.8.19
Dengue					
NS1 Antigen	Positive	Negative	Positive	-	Negative
Dengue Ig M	Positive	-	-	-	Positive
Dengue Ig G	Negative	-	-	-	Positive
Blood culture	Positive for <i>Salmonella Typhi</i>		-	-	-
Chest X ray					Right sided Pleural effusion
USG of whole					Right sided Pleural effusion with ascites

### Discussion

Acute febrile illness (AFI) is a common clinical syndrome among patients seeking hospital care. The top two causes of acute fever during the rainy season (July- October) are Dengue fever, Typhoid fever. Typhoid and Dengue both are so different diseases but they have some similar initial routine manifestations. It is important to distinguish typhoid fever from dengue as early antibiotic therapy in typhoid fever leads to a favorable outcome, while in dengue it is urgent to diagnose as early as possible for prompt intervention, since it is difficult to predict whether, the patient will progress to the critical phase of the infection and possible circulatory collapse, shock, and death.<sup>7,8</sup> Concurrent infection with two agents can result in more serious illness.

Earlier there have been reports of concurrent infection of dengue virus with a flavivirus, Chikungunya and with different bacteria including *Salmonella Typhi*.<sup>9</sup> A study from North Delhi, India reported co-infection of dengue fever with enteric fever in 11 cases (11/141: 7.8%).<sup>10</sup> But the route of spreading infection is totally different with each other's. The dengue virus is a RNA virus belonging to the Flaviviridae family and transmitted to humans mainly by bite of infected female *Aedes aegypti* and *Aedes albopictus*.<sup>11</sup> After an incubation period of 3-14 days, patient infected with dengue virus develop a febrile illness the manifestation of which are similar and overlapping in nature grouped into Dengue Syndromes' which encompass undifferentiated fever, dengue fever (DF), dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS) and Expanded dengue syndrome.<sup>12</sup> Causative agent of typhoid fever is *Salmonella enterica serovar Typhi*. Route of transmission is fecal-oral route by contaminated food and water. The clinical manifestation of the typhoid is high grade fever (95%) with complaints like anorexia (70%), diarrhea (36%), vomiting, headache, nausea, malaise, slight dry cough, maculopapular rash. There is emerging evidence from south Asia that the presentation of typhoid may be more dramatic in children younger than 5 years of age, with higher rates of complications and hospitalization. In the absence of localizing signs, the early stage of disease may be difficult to differentiate from other endemic diseases such as malaria and dengue fever.<sup>13</sup>

In case of Typhoid fever the onset of symptoms is insidious with an incubation of 7-14 days. The fever is unremitting; there are spikes in temperature without any return to normal (saddle back fever).<sup>13,14</sup> In a typical case of dengue fever, the patient experiences high fever (102o-104o), may be biphasic, lasting for 2 to 7days associated with flushed face. Concomitantly, a severe frontal and retro orbital headache, myalgia, especially lower back, arm, and leg pains, malaise, arthralgia and anorexia may accompany.<sup>15</sup> In typhoid fever, a dull, continuous frontal headache begins during the first two days of fever; mild arthralgia involving multiple joints and vague, poorly localized back pain may occur.<sup>14</sup> Constipation is more common than diarrhea; it occurs in about 50%, while diarrhea occurs in about 30% of typhoid patients.<sup>14</sup> In dengue fever, constipation is occasionally reported; diarrhea and respiratory symptoms are frequently reported and may be due to concurrent infections.<sup>16</sup> In approximately 25% of cases, a macular or maculopapular rash (rose spots) may be visible around the 7<sup>th</sup>-10<sup>th</sup> day of the illness, lesions may appear in crops of 10-15 on the lower chest and abdomen and last 2-3 days. In case of dengue fever diffuse flushing or fleeting eruptions may be seen on the face, neck and chest on first 2-3 days and a conspicuous maculopapular or rubelliform rash may be on 3<sup>rd</sup> and 4<sup>th</sup> day.<sup>13,15</sup>

Questions like whether or not dengue fever predisposes to typhoid fever, or do they separately infect a person, need to be answered. A possible interaction between dengue and typhoid may arise through intestinal endothelial damage or intestinal hemorrhage, or through immunosuppression superimposed by virtue of the initial virus illness.<sup>17,18</sup>

Unfortunately our patient in his period of hospital stay again infected with dengue virus and develops secondary dengue fever in the form of Dengue hemorrhagic fever. Multiple studies suggests that secondary infection typically has warning signs that suggest plasma leak and subsequent development of complicated course.<sup>19-21</sup> In addition, a large pediatric study in Thailand highlighted that primary infection predominantly presented with dengue fever, while secondary infection presented more often with Grade 3 dengue hemorrhagic fever.<sup>19</sup> The dominant

mechanism proposed for the pathogenesis of DHF is that of antibody-dependent enhancement (ADE). With ADE, preexisting neutralizing antibodies from a prior DENV infection are hypothesized to enhance a subsequent infection with a different DENV serotype, resulting in higher viral load, greater immune activation, and ultimately the profound plasma leakage characteristic of DHF.<sup>22</sup> The ability to neutralize or enhance heterologous DENV viruses has been shown to vary by antibody titer.<sup>23</sup> In vitro studies have demonstrated a titer dependence of ADE with peaks in both the percentage of infected cells and viral output per infected cell at low-to-intermediate concentrations of antibody.<sup>24</sup>

### Conclusion

Both dengue and typhoid occur seasonally especially during the monsoons where on one hand mosquito breeding and on other hand faeco-oral transmission occurs actively. This, in turn, enhances the need for continued international surveillance and improvement of public health infrastructures to meet existing and future emerging disease threats. Our Patient developed Dengue Hemorrhagic fever during his hospital stay, so people who have to stay in hospital should be aware of their personal protection to be safe from mosquito bite.

**Conflict of interest:** We have no conflict of interest.

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