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Clinical evaluation of the hematological profile of pediatric cases suffering from dengue fever

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Abstract

Dengue fever is an acute febrile disease characterized by sudden onset of fever of 3-5 days, intense headache, myalgia, retro-orbital pain, anorexia, gastrointestinal disturbances and rash. Early clinical features of dengue infection are variable among patients, and initial symptoms are often non-specific resembling any viral illness. Therefore, specific laboratory tests are necessary for an accurate diagnosis. Hence based on above findings the present study was planned Clinical Evaluation of the Haematological Profile of Pediatric Cases Suffered from Dengue Fever.

The study was planned in Upgraded Department of Pediatrics, Patna medical College and Hospital, Patna, Bihar. The study was conducted from the June 2017 to Jan 2018. Out of the 1058 cases admitted to the Pediatric department only 20 cases were found positive for the Dengue fever. The haematological profile of the same were evaluated in the present study.

Dengue fever does not have specific medical therapy hence clinical recovery monitoring is largely dependent on haematological parameters. This study concludes that parameter like platelet count, hematocrit, etc are studies aid greatly in clinical monitoring of patient. As dengue infection is increasing in incidence, we need to have improved diagnostic modalities. Early detection of severe cases and efficient medical management are of prime importance in all areas where it is endemic.

Keywords: haematological profile, pediatric cases, dengue fever, etc

Introduction

Dengue is a viral disease, transmitted by the infective bite of a particular mosquito known as Aedes Aegypti. Human being develops disease after 5 – 6 days of being bitten by an infective mosquito. It occurs in two forms: Classical Dengue fever also known as "break bone" fever and Dengue Haemorrhagic Fever (DHF) which is life threatening. It is very common after rainy season. It is highly contagious and spreads from one person to another through mosquito bites. It is widespread in tropical and sub-tropical regions. It is a very common disease in India since last two decades. Dengue can affect everybody, irrespective of their age and gender. However, deaths are common amongst children during DHF outbreak.

The disease is endemic in more than 100 countries in the WHO regions of Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific. The America, South-East Asia and Western Pacific regions are the most seriously affected. In the year 2015, According to National Vector Borne Disease Control Programme (NVBDCP) maximum numbers of cases were reported from Delhi followed by Punjab, Haryana, West Bengal, Gujarat, Karnataka, Maharashtra, Kerala, Tamil Nadu, Rajasthan, Andhra Pradesh, Uttar Pradesh, Orissa, Madhya Pradesh, Arunachal Pradesh, Bihar, Uttarakhand, Telangana and other states.

Dengue fever is a mosquito-borne tropical disease caused by the dengue virus. Symptoms typically begin three to fourteen days after infection. This may include a high fever, headache, vomiting, muscle and joint pains, and a characteristic skin rash. Recovery generally takes two to seven days. In a small proportion of cases, the disease develops into severe dengue, also known as dengue hemorrhagic fever, resulting in bleeding, low levels of blood platelets and blood plasma leakage, or into dengue shock syndrome, where dangerously low blood pressure occurs [1].

Dengue is spread by several species of female mosquitoes of the Aedes type, principally A. aegypti. The virus has five types; infection with one type usually gives lifelong immunity to that type, but only short-term immunity to the others. Subsequent infection with a different type increases the risk of severe complications. A number of tests are available to confirm the diagnosis including detecting antibodies to the virus or its RNA [2].

A vaccine for dengue fever has been approved and is commercially available in a number of countries. The vaccine, however, is only recommended in those who have been previously infected. Other methods of prevention include reducing mosquito habitat and limiting exposure to bites. This may be done by getting rid of or covering standing water and wearing clothing that covers much of the body. Treatment of acute dengue is supportive and includes giving fluid either by mouth or intravenously for mild or moderate disease. For more severe cases, blood transfusion may be required. About half a million people require hospital admission every year. Paracetamol (acetaminophen) is recommended instead of nonsteroidal anti-inflammatory drugs (NSAIDs) for fever reduction and pain relief in dengue due to an increased risk of bleeding from NSAID use [2].

Dengue has become a global problem since the Second World War and is common in more than 110 countries, mainly in Asia and South America. Each year between 50 and 528 million people are infected and approximately 10,000 to 20,000 die. The earliest descriptions of an outbreak date from

1779. Its viral cause and spread were understood by the early 20th century. Apart from eliminating the mosquitos, work is ongoing for medication targeted directly at the virus. It is classified as a neglected tropical disease [3].

Typically, people infected with dengue virus are asymptomatic (80%) or have only mild symptoms such as an uncomplicated fever. Others have more severe illness (5%), and in a small proportion it is life-threatening. The incubation period (time between exposure and onset of symptoms) ranges from 3 to 14 days, but most often it is 4 to 7 days. Therefore, travelers returning from endemic areas are unlikely to have dengue if fever or other symptoms start more than 14 days after arriving home. Children often experience symptoms similar to those of the common cold and gastroenteritis (vomiting and diarrhea) and have a greater risk of severe complications, though initial symptoms are generally mild but include high fever [4].

The characteristic symptoms of dengue are sudden-onset fever, headache (typically located behind the eyes), muscle and joint pains, and a rash. The alternative name for dengue, "breakbone fever", comes from the associated muscle and joint pains. The course of infection is divided into three phases: febrile, critical, and recovery [5].

The febrile phase involves high fever, potentially over 40 °C (104 °F) and is associated with generalized pain and a headache; this usually lasts two to seven days. Nausea and vomiting may also occur. A rash occurs in 50–80% of those with symptoms in the first or second day of symptoms as flushed skin, or later in the course of illness (days 4–7), as a measles-like rash. A rash described as "islands of white in a sea of red" has also been observed. Some petechiae (small red spots that do not disappear when the skin is pressed, which are caused by broken capillaries) can appear at this point, as may some mild bleeding from the mucous membranes of the mouth and nose. The fever itself is classically biphasic or saddleback in nature, breaking and then returning for one or two days [6, 7].

In some people, the disease proceeds to a critical phase as fever resolves. During this period, there is leakage of plasma from the blood vessels, typically lasting one to two days. This may result in fluid accumulation in the chest and abdominal cavity as well as depletion of fluid from the circulation and decreased blood supply to vital organs. There may also be organ dysfunction and severe bleeding, typically from the gastrointestinal tract. Shock (dengue shock syndrome) and hemorrhage (dengue hemorrhagic fever) occur in less than 5% of all cases of dengue; however, those who have previously been infected with other serotypes of dengue virus ("secondary infection") are at an increased risk. This critical phase, while rare, occurs relatively more commonly in children and young adults [4].

The recovery phase occurs next, with resorption of the leaked fluid into the bloodstream. This usually lasts two to three days. The improvement is often striking and can be accompanied with severe itching and a slow heart rate. Another rash may occur with either a maculopapular or a vasculitic appearance, which is followed by peeling of the skin. During this stage, a fluid overload state may occur; if it affects the brain, it may cause a reduced level of consciousness or seizures. A feeling of fatigue may last for weeks in adults [4].

Dengue fever virus (DENV) is an RNA virus of the family Flaviviridae; genus Flavivirus. Other members of the same genus include yellow fever virus, West Nile virus, Zika virus, St. Louis encephalitis virus, Japanese encephalitis virus, tick-borne encephalitis virus, Kyasanur forest disease virus, and Omsk hemorrhagic fever virus. Most are transmitted by arthropods (mosquitos or ticks) and are therefore also referred to as arboviruses (arthropod-borne viruses) [7].

The dengue virus genome (genetic material) contains about 11,000 nucleotide bases, which code for the three different types of protein molecules (C, prM and E) that form the virus particle and seven other non-structural protein molecules (NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5) that are found in infected host cells only and are required for replication of the virus. There are five strains of the virus, called serotypes, of which the first four are referred to as DENV-1, DENV-2, DENV-3 and DENV-4. The fifth type was announced in 2013. The distinctions between the serotypes are based on their antigenicity [8].

Dengue virus is primarily transmitted by Aedes mosquitos, particularly A. aegypti. These mosquitos usually live between the latitudes of 35° North and 35° South below an elevation of 1,000 metres (3,300 ft). They typically bite during the early morning and in the evening, but they may bite and thus spread infection at any time of day. Other Aedes species that transmit the disease include A. albopictus, A. polynesiensis and A. scutellaris. Humans are the primary host of the virus, but it also circulates in nonhuman primates. An infection can be acquired via a single bite. A female mosquito that takes a blood meal from a person infected with dengue fever, during the initial 2- to 10-day febrile period, becomes itself infected with the virus in the cells lining its gut. About 8–10 days later, the virus spreads to other tissues including the mosquito's salivary glands and is subsequently released into its saliva. The virus seems to have no detrimental effect on the mosquito, which remains infected for life. Aedes aegypti is particularly involved, as it prefers to lay its eggs in artificial water containers, to live in close proximity to humans, and to feed on people rather than other vertebrates [9].

Dengue can also be transmitted via infected blood products and through organ donation. In countries such as Singapore, where dengue is endemic, the risk is estimated to be between 1.6 and 6 per 10,000 transfusions. Vertical transmission (from mother to child) during pregnancy or at birth has been reported. Other person-to-person modes of transmission, including sexual transmission, have also been reported, but are very unusual. The genetic variation in dengue viruses is region specific, suggestive that establishment into new territories is relatively infrequent, despite dengue emerging in new regions in recent decades [7].

When a mosquito carrying dengue virus bites a person, the virus enters the skin together with the mosquito's saliva. It binds to and enters white blood cells and reproduces inside the cells while they move throughout the body. The white blood cells respond by producing a number of signaling proteins, such as cytokines and interferons, which are responsible for many of the symptoms, such as the fever, the flu-like symptoms, and the severe pains. In severe infection, the virus production inside the body is greatly increased, and many more organs (such as the liver and the bone marrow) can be affected. Fluid from the bloodstream leaks through the wall of small blood vessels into body cavities due to capillary permeability. As a result, less blood circulates in the blood vessels, and the blood pressure becomes so low that it cannot supply sufficient blood to vital organs. Furthermore, dysfunction of the bone marrow due to infection of the stromal cells leads to reduced numbers of platelets, which are

necessary for effective blood clotting; this increases the risk of bleeding, the other major complication of dengue fever [10]. The World Health Organization's 2009 classification divides dengue fever into two groups: uncomplicated and severe. This replaces the 1997 WHO classification, which needed to be simplified as it had been found to be too restrictive, though the older classification is still widely used including by the World Health Organization's Regional Office for South-East Asia as of 2011. Severe dengue is defined as that associated with severe bleeding, severe organ dysfunction, or severe plasma leakage while all other cases are uncomplicated. The 1997 classification divided dengue into undifferentiated fever, dengue fever, and dengue hemorrhagic fever. Dengue hemorrhagic fever was subdivided further into grades I–IV. Grade I is the presence only of easy bruising or a positive tourniquet test in someone with fever, grade II is the presence of spontaneous bleeding into the skin and elsewhere, grade III is the clinical evidence of shock, and grade IV is shock so severe that blood pressure and pulse cannot be detected. Grades III and IV are referred to as "dengue shock syndrome" [11].

There are no specific antiviral drugs for dengue; however, maintaining proper fluid balance is important. Treatment depends on the symptoms. Those who are able to drink, are passing urine, have no "warning signs" and are otherwise healthy can be managed at home with daily follow-up and oral rehydration therapy. Those who have other health problems, have "warning signs", or cannot manage regular follow-up should be cared for in hospital. In those with severe dengue care should be provided in an area where there is access to an intensive care unit [5].

Intravenous hydration, if required, is typically only needed for one or two days. In children with shock due to dengue a rapid dose of 20 mL/kg is reasonable [68]. The rate of fluid administration is then titrated to a urinary output of 0.5–1 mL/kg/h, stable vital signs and normalization of hematocrit. The smallest amount of fluid required to achieve this is recommended [5].

Invasive medical procedures such as nasogastric intubation, intramuscular injections and arterial punctures are avoided, in view of the bleeding risk. Paracetamol (acetaminophen) is used for fever and discomfort while NSAIDs such as ibuprofen and aspirin are avoided as they might aggravate the risk of bleeding. Blood transfusion is initiated early in people presenting with unstable vital signs in the face of a decreasing hematocrit, rather than waiting for the hemoglobin concentration to decrease to some predetermined "transfusion trigger" level. Packed red blood cells or whole blood are recommended, while platelets and fresh frozen plasma are usually not. There is not enough evidence to determine if corticosteroids have a positive or negative effect in dengue fever [12].

During the recovery phase intravenous fluids are discontinued to prevent a state of fluid overload. If fluid overload occurs and vital signs are stable, stopping further fluid may be all that is needed. If a person is outside of the critical phase, a loop diuretic such as furosemide may be used to eliminate excess fluid from the circulation.

Dengue fever is an acute febrile disease characterized by sudden onset of fever of 3-5 days, intense headache, myalgia, retro-orbital pain, anorexia, gastrointestinal disturbances and rash. Early clinical features of dengue infection are variable among patients, and initial symptoms are often non-specific resembling any viral illness. Therefore, specific laboratory tests are necessary for an accurate diagnosis. Hence based on above findings the present study was planned Clinical Evaluation of the Haematological Profile of Pediatric Cases Suffered from Dengue Fever.

Methodology

The study was planned in Upgraded Department of Pediatrics, Patna medical College and Hospital, Patna, Bihar. The study was conducted from the June 2017 to Jan 2018. Out of the 1058 cases admitted to the Pediatric department only 20 cases were found positive for the Dengue fever. The haematological profile of the same were evaluated in the present study.

Patients with positive serology for dengue infection were studied in detail to evaluate the haematological changes. Case definition was based on W.H.O. criteria and confirmed by positive serology to dengue fever. Performa was prepared which included clinical details and information on various parameters of blood count, coagulation profile and biochemical tests. Details of chest X-ray and other imaging modalities were also recorded wherever required.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion criteria

1. Age group of 0 to12 years
2. Both genders
3. Patients with NS1 Ag positive
4. Serologically confirmed IgM positive dengue fever

Exclusion criteria

1. Age group >12 years
2. Preexisting chronic diseases

Results & Discussion

Dengue fever is the one of the most important arboviral infection. In India dengue virus was first isolated in 1946 and major outbreaks have been reported since then. Dengue hemorrhagic fever was first reported in Calcutta in 1963 [13]. The hematological effects observed are changes in blood counts, hemoconcentration due to plasma leakage, leukopenia because of decreased neutrophils near the end of the febrile phase, presence of atypical lymphocytes and relative lymphocytosis before shock, thrombocytopenia and changes in blood hemostasis with frequent presence of hemorrhagic manifestations [14]. As dengue fever can present with serious consequences and can even be fatal, this study aimed at analyzing clinical and laboratory dynamics in order to increase the sensitivity of early diagnosis.

Dengue viruses belonging to the genus Flaviviridae has antigenically four distinct serotypes DEN-1 to DEN-4. Dengue virus causes a broad spectrum of illness ranging from mild fever to classical dengue hemorrhagic fever and shock syndrome. Each serotype of virus produces lifelong immunity but provides only short-term cross immunity. It is thought that the homologous antibodies from previous infections act as nonneutralizing antibodies in any subsequent infection with a different serotype of the virus and forms new complexes with new infecting serotypes. These complexes can cause the antibody dependent enhancement of

heterotypic secondary dengue infection. The present strategy is to control infection and prevent complications. For the prevention and control of dengue infection W.H.O has proposed bioregional dengue strategy for south-east Asia and Western Pacific region. It consists of six elements, research being one of the elements.

Table 1: Demographic details

Demographic data	No. of Cases
Total Cases enrolled	1058
Positive Cases	20
Males	12
Females	8
Age (years)	
1 – 4 years	6
5 – 8 years	11
9 – 12 years	3

Table 2: Distribution of dengue cases as per revised WHO criteria

Classification	Number of cases
Dengue without warning signs	4
Dengue with warning signs	14
Severe dengue	2
Total	20

Table 3: Clinical manifestation according to type of dengue fever cases.

Symptoms and sign	Number of cases
Fever	18
Myalgia	18
Headache	11
Cough	3
Abdominal pain	2
Rashes	2
Epistaxis	1
Hepatosplenomegaly	2
Gum bleeding	1
Hematuria	1
Vomiting	10
Retro-orbital pain	4

Table 4: Laboratory parameters in dengue fever cases.

Criteria	No. of cases
Raised hematocrit >35%	12
Leucopenia <5000	11
Thrombocytopenia <1.5 lakh/cu mm	17
Thrombocytopenia <1 lakh/cu mm	14
Thrombocytopenia <50000/cu mm	3
Serum bilirubin>2 mg/dl	4
Serum creatinine >1.5 mg/dl	2

Sharma, *et al*. [15] in a series of five patients with hematological disease reported no difference in clinical outcome of patient compared to normal population. Ramzan, *et al*. [16] reported similar observation of lower day 1 platelet in their case series on dengue fever as a cause of febrile neutropenia in children with acute lymphoblastic leukemia [17]. Duration of illness in normal population is reported as 4-7 days [17]. Visuthranukul, *et al*. [18] in a case report of dengue in a stem cell transplant recipient, also observed prolonged duration of illness in immune compromised. Principles of treatment and prevention remain the same as in immune-competent individuals.

Leucopenia with lymphocytosis and thrombocytopenia are associated with DF. The causes include bone marrow suppression and binding of dengue antigens to platelets and antibody mediated immunological destruction of platelets. Leucopenia was observed in 50% 0f the cases in the present study. This finding is similar to the previous studies [19, 22]. Thrombocytopenia was observed in 89% of cases. There is more fall in platelet count in DHF and DSS as compared to DF. This finding is higher as compared to previous studies where thrombocytopenia was reported in 59% of cases [20, 23]. Rise in hematocrit is related to increase severity and it is caused by the increased plasma permeability which is the main pathophysiological changes in DF. A 20% rise in hematocrit was considered as cut off for diagnosis of DHF. It indicates that intensive fluid therapy is required.

Mishra *et al*. [24] also observed fever in 100% of the cases, myalgia in 76.8% and abdominal pain in 54.3% cases. The most common bleeding manifestations in both severe and non-severedengue were petechiae seen in 22.1% cases. Mishra *et al*. [24] in their study reported that 58.76% of the cases had normal leukocyte count, while leucopoenia was seen in 25.77% and leukocytosis in 15.46% of the cases. Among the liver enzymes, SGOT was elevated in a larger proportion (47.42%) of patients when compared to alanine aminotransferase (SGPT) which was 30.92%.

Srinivasa *et al*. [25] studied 200 cases andobservedthat all the cases all had fever (100%), 144 (72%) had vomiting, 92(46%) had abdominal pain, 67(33.5%) had hepatomegaly, 21 (10.5%) had rashes, 4(2%) had splenomegaly, 26(13%) had bradycardia and 47(23.5%) developed hypotension and shock. The mostcommon bleeding manifestation was petechiae (6.2%) followed by hemetemesis in 4.1% and epistaxis in 3.6% cases. According to the study by Srinivasa *et al*. [25] out of 200 cases, 194(97%) had thrombocytopenia, 189(94.5%) had hemoconcentration, 126(63%) had leucopenia< 4000/cumm and 83(41.5%) had raised liver enzymes.

Jain *et al*. [26] observed fever in all dengue patients with mean duration of 5.6 days. The common presentation by these children included headache (64%), myalgia (63%), bleeding (58%) and decreased urine output (53%). Among the clinical findings, hepatomegaly and splenomegaly were noted in 90% and 26% of the cases respectively. Clinical fluid accumulation in form of ascites and pleural effusion with reduced air entry were observed in 40% and 43% of cases.

Jain *et al*. [26] observed evidence of raised hematocrit (>35%) in 84% of cases. Thrombocytopenia (<1 lakh) was observed in 80% of cases with 10% of patients having platelet count <20,000/ mm, most of the cases had platelet count between 50,000 and 1-lakh. Leucopenia (<5000) was observed in 44% of cases. Abnormal liver enzymes were observed in 38% of patients.

Kumar *et al*. [27] observed fever in all of their patients, with the duration of hospital stay <5 days in 205 (72%) and 5–10 days in 75 patients (25%). The most common symptoms were vomiting in 168 (54.90%), abdominal pain in 111 (36.3%), bleeding manifestation in 43(14.05%), headache in 41(13.40%), myalgia in 32 (10.5%), and lethargy (9.8%). The other symptoms observed in their study were arthralgia (9.5%), altered sensorium (7.8%), rash (7.2%), diarrhea (6.5%), oliguria (6.5%), cough/rhinitis (5.2%), anorexia (3.9%), and retro-orbital pain (1.3%). Kumar *et al*. [27] observed 14.1% of their patients had a platelet count <20,000 and low platelet count had significantly correlated with the severity of dengue. The mean platelet recovery time was 2–5

days.

Alam *et al*. [28] observed fever >5 days duration in 63% children with continued type of fever beingpredominant (75.9%). About 60% of patients had abdominal pain, 57% vomiting, 46.3% myalgia, 31.5% had headache, 18.5% arthralgia, 14.8% retro-orbital pain, 9.3% loose stool and 3.7% had runny nose/cough. In the study by Alam *et al*. [28] about one-third (32%) of the patients had positive tourniquet test. Five (9.3%) had low WBC count. Onethird (33%) of patients had platelet count, 51000 to 1 lakh, 25.9% had between 21000 to 50000 and 9.3% had <20000 platelet count and 31.5% patients had platelet count > 1 lakh. All children exhibiting a packed cell volume (PCV) of less than 45% and over 40% had raised serum alanine aminotransferase (ALT).

Conclusion

Dengue fever does not have specific medical therapy hence clinical recovery monitoring is largely dependent on haematological parameters. This study concludes that parameter like platelet count, hematocrit, etc are studies aid greatly in clinical monitoring of patient. As dengue infection is increasing in incidence we need to have improved diagnostic modalities. Early detection of severe cases and efficient medical management are of prime importance in all areas where it is endemic.

References

1. "Dengue and severe dengue Fact sheet N°117". WHO? May 2015. Archived from the original on 2 September 2016. Retrieved 3 February, 2016.
2. Kularatne SA. "Dengue fever". BMJ, 2015; 351:h4661. doi:10.1136/bmj.h4661. PMID 26374064.
3. "Neglected Tropical Diseases". cdc.gov. 6 June 2011. Archived from the original on 4 December 2014. Retrieved 28 November, 2014.
4. Simmons CP, Farrar JJ, Nguyen VV, Wills B. "Dengue" (PDF). The New England Journal of Medicine. 2012; 366(15):1423-32. doi:10.1056/NEJMra1110265. hdl:11343/191104. PMID 22494122.
5. WHO (2009), pp. 25–27. https://en.wikipedia.org/wiki/Dengue_fever#refWHO2009
6. Knoop KJ, Stack LB, Storrow A, Thurman RJ, eds. "Tropical medicine". Atlas of emergency medicine (3rd ed.). New York: McGraw-Hill Professional, 2010, pp. 658-9. ISBN 978-0-07-149618-6.
7. Gould EA, Solomon T. "Pathogenic flaviviruses". Lancet. 2008; 371(9611):500-9. doi:10.1016/S0140-6736(08)60238-X. PMID 18262042.
8. Solomonides Tony. Healthgrid applications and core technologies: proceedings of HealthGrid 2010 ([Online-Ausg.]. ed.). Amsterdam: IOS Press, 2010, p. 235. ISBN 978-1-60750-582-2. Archived from the original on 1 May 2016.
9. Gubler DJ. "Dengue viruses". In Mahy BWJ; Van Regenmortel MHV (eds.). Desk Encyclopedia of Human and Medical Virology. Boston: Academic Press, 2010, pp. 372-82. ISBN 978-0-12-375147-8. Archived from the original on 9 June 2016.
10. Martina BE, Koraka P, Osterhaus AD. "Dengue virus pathogenesis: an integrated view". Clinical Microbiology Reviews. 2009; 22(4):564-81. doi:10.1128/CMR.00035-09. PMC 2772360. PMID 19822889.
11. WHO. "Chapter 2: clinical diagnosis" (PDF). Dengue haemorrhagic fever: diagnosis, treatment, prevention and control (2nd ed.). Geneva: World Health Organization, 1997, pp. 12-23. ISBN 978-92-4-154500-6. Archived (PDF) from the original on 22 October 2008.
12. Zhang F, Kramer CV (July 2014). "Corticosteroids for dengue infection". The Cochrane Database of Systematic Reviews. 7 (7): CD003488. doi: 10.1002/14651858.CD003488.pub3. PMC 6555473. PMID 24984082.
13. Arindam Sarkar, Debjani Taraphdar, Shyamalendu Chatterjee. Molecular typing of dengue virus circulating in Kolkata. India Jour of tropical medicine, 2012; 1-5.
14. Dengue. Guidelines for diagnosis, treatment, prevention and control, 2nd Edition, World Health Organization, Geneva, 2009, 1-144.
15. Sharma SK, Seth T, Mishra P, Gupta N, Agrawal N, Broor S, *et al*. Clinical profile of dengue infection in patients with haematological diseases. Mediterr J Hematol Infect Dis. 2011; 3:e2011039.
16. Ramzan M, Yadav SP, Dinand V, Sachdeva A. Dengue fever causing febrile neutropenia in children with acute lymphoblastic leukemia: an unknown entity. Hematol Oncol Stem Cell Ther. 2013; 6:65-7.
17. Rigau-Pérez JG, Clark GG, Gubler DJ, Reiter P, Sanders EJ, Vorndam AV. Dengue and dengue haemorrhagic fever. Lancet. 1998; 352:971-7.
18. Visuthranukul J, Bunworasate U, Lawasut P, Suankratay C. Dengue haemorrhagic fever in a peripheral blood stem cell transplant recipient: the first case report. Infect Dis Rep, 2009, 1:e3.
19. Meltzer E, Heyman Z, Bin H, Schwartz E. Capillary leakage in travelers with dengue infection: implications for pathogenesis. American Journal of Tropical Medicine and Hygiene. 2012; 86:536-39.
20. Priyanka M Patel, Shilpa K Patel, Monica Arvindbhai Sabalpara, Cherry K Shah, Nailesh R Shah. Hematological and biochemical changes in dengue fever. International Journal of Medical Science and Public Health. 2016; 5:1934-36.
21. Achalkar GV. Dengue: a clinic-pathological study of 50 cases. J Evol Med Den Sci. 2013; 2:9380–5.
22. Ratageri VH1, Shepur TA, Wari PK, Chavan SC, Mujahid IB, Yergolkar PN. Clinical profile and outcome of dengue fever cases. Ind J of Pediatr. 2005;7 2:705-6.
23. Avarebeel S, Prahlad KA, Tabassum L. Study of clinical and demographic profile of dengue fever. J Evidence Based Med Healthcare. 2014; 1:211-30.
24. Mishra S, Ramanathan R, Agarwalla SK. Clinical Profile of Dengue Fever in Children: A Study from Southern Odisha, India. Scientifica 2016, Article ID 6391594, 6 pages.
25. Srinivasa S, Nawab T, Nair CC. Clinical profile and ultrasonographic findings in children with dengue fever. Curr Pediatr Res. 2014; 18(2):87-90.
26. Jain H. Clinical profile and outcome of dengue fever in hospitalized children of South Rajasthan, India. Int J Contemp Pediatr. 2016; 3(2):546-549.
27. Kumar BV, Simna L, Kalpana D, Kailas L. Clinical profile and outcome of children admitted with dengue fever in a tertiary care hospital in South India. Indian J Child Health. 2018; 5(1);32.
28. Alam AS, Sadat SA, Swapan Z, Ahmed AU, Karim MdK, Paul HK, *et al*. Clinical profile of dengue fever in

children. Bangladesh J Child Health. 2009; 33(2):55-58.