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The Prognostic Role of Activated Partial Thromboplastin Time (APTT) in Children with Mild and Moderate Dengue Infection

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Abstract

Background and goals:

Dengue fever cases in children are on the rise in India. The ability of a treating paediatrician to predict the Outcome based on existing prognostic markers is critical, as it will provide early warning signs and guide management. The goal of this study was to see if activated partial thromboplastin time play a prognostic role in children with mild and moderate dengue fever.

Methods and materials:

All children admitted with dengue illness were enrolled according to WHO 2009 standards following exclusion criteria.Collected venous blood samples were sent for APTT at the time of admission.The children were divided into two groups:group A had APTT of less than 60 and group B had APTT of more than 60. The response and outcome measures compared between the two groups and the data was evaluated using suitable statistical tests.

Results: Hepatomegaly, mucosal hemorrhage, Pleural effusion, blood component transfusion, shock, and increased liver enzymes were all found to have significant differences on bivariate analysis between two groups. In children with an APTT of more than 60, the average length of stay in the hospital is longer. A p value of less than 0.05 is regarded as significant.

Conclusion: This study demonstrated that APTT is an excellent prognostic marker since it is elevated early in the course of the disease so morbidity and mortality in dengue cases can be minimized by providing effective care to these children with prolonged APTT.

Keywords: Activated partial thromboplastin time, Coagulation, Dengue, Shock, Transaminases.

Introduction

Dengue fever is a viral infection spread by the mosquito Aedes aegypti. After rainy season, epidemics are common. In India, the incidence of severe dengue has been steadily rising in all age groups over the previous two decades, although mortality among children is common during dengue epidemics. Dengue virus is divided into four serotypes. According to WHO and national Standards for the treatment of dengue fever, dengue infection can be classed as asymptomatic/Mild, moderate, and severe. Plasma leakage, fluid accumulation, severe bleeding, shock, and multiorgan dysfunction are all hallmarks of severe dengue infection [1, 2, and 3]. Virus strains enhance Antibodies and memory T cells in secondary infection with different serotypes cause a cytokine storm, which causes endothelial injury, platelet destruction, and multiorgan failure.

The World Health Organization (WHO) established warning signs for early detection of potentially severe cases and prompt management, however only 1 to

2% of children with warning signs develop severe dengue fever [1, 2].

Many studies use thrombocytopenia, leucopenia, liver enzymes, serum ferritin, PT, APTT as prognostic markers to identify those children who are more likely to have severe dengue. Many earlier studies found thrombocytopenia and leucopenia in children who did not have any bleeding or plasma leakage. So we conducted this research to see if APTT, a commonly available and low cost test, could be used as a predictive marker in children with dengue illness.

Materials And Methods:

Between July and November 2021, a prospective cohort study was undertaken on confirmed cases of dengue infection admitted to MIMS general hospital in Northern Andhra Pradesh, India. This study included 134 clinically suspected individuals with fever who met the WHO case definition criteria for DF/DHF/DSS. The study excluded children with congenital defects, cancer, autoimmune and immunodeficiency illnesses and severe dengue fever. The figure1 depicts the study subject recruitment process. The study was approved by the Institutional Ethics Committee

Collected venous blood samples were sent for APTT at the time of admission, along with other laboratory procedures. Children were split into two groups: group A had an APTT of less than 60 and group B had an APTT of more than 60. These children were monitored and response outcome measures such as abdominal pain, bleeding, hepatomegaly, pleural effusion, transfusion requirement, fluid requirement greater than or equal to 10ml/kg/hr, platelet count less than 20000, AST and ALT > 3X, hypoglycemia, severe electrolyte disturbances, length of hospital stay and mortality were compared between the two groups. The statistical analyses were performed using IBM SPSS windows Statistic 17.0's Statistical Program for Social Science program (SPSS), with the categorical data being tested using the Chi-square test. The p value is measured and considered significant when it is less than 0.05. 60 has taken as cutoff value for APTT because previous studies shown mean APTT in dengue children was 51±9. Sample size was calculated basing on anticipated incidence and type 1 and type 2 error rate that is alpha (0.05) and power (80%).

Results:

Between July 2021 and November 2021, a total of 134 children with dengue infection were admitted to MIMS general hospital in Vizianagaram, with 98 meeting the inclusion criteria. NS1 antigen, IgM/IgG antibody, or IgM MAC-ELISA was used to confirm dengue infection in all cases. Out of 134 children, 98 had non-severe dengue, which is defined as a moderate or undifferentiated dengue infection or dengue with warning signs as defined by WHO criteria; 28 children with severe dengue were eliminated from the study. Male children out number female children (2.2:1) in this study, and the average age of dengue-infected children admitted to the hospital was 9.2 years.

APTT was less than 60 in 70 (69%) children of group A and higher than 60 in 28 (31%) children group B. In this study, APTT more than 1.5INR and up to 100 seconds was observed, among them 91 percent of children developed severe dengue fever. The parameters of Group A and Group B children were matched as stated in Table 1. In our study, the majority of the hospitalized children in both groups experienced vomiting, loss of appetite, abdominal pain/tenderness, and hepatomegaly. Petechiae and ecchymosis are the most prevalent bleeding manifestations in both groups, however gastrointestinal bleeding in the form of malena is reported in 50% of Group B children ($p<0.001$).Severe thrombocytopenia, defined as a platelet count of less than 20,000, is seen in 32% of group B children and 17% of group A children, but the difference is not significant.

APTT was less than 60 in 69 %(70) of total children and higher than 60 in 31 %(28) of total children .Our institute is a tertiary care centre, and the number of severe dengue cases is higher than in prior research. When it comes to managing dengue fever cases, our institute adheres to strict guidelines. The majority of the children in this study tested positive for NS1, which was followed by IgM. Almost majority of the children tested negative for the tourniquet test. Children with warning signs and stable vitals were encouraged to drink oral fluids first, but if they were not tolerated, intravenous fluids were administered strictly according to WHO/CDC guidelines. Platelet transfusions were only given to children with counts below 10,000 or in cases of severe bleeding and

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shock. For 11 patients, single donor aphaeresis or random door blood group compatible platelets were transfused based on affordability and availability and FFP to five children and whole blood to two more. Four children in group B received inotropic assistance in the form of adrenaline, dobutamime, or dopamine, while none in group A received any. Three children in group B received albumin - colloid, but none in group A.

Discussion:

Vomiting, abdominal pain, and loss of appetite were common in both groups in our study, although hepatomegaly, the most common physical sign, was somewhat more common in children with an APTT more than 60 and statistically significant in both groups. R. Joshi and V. Baid's findings, as well as those of S. Ahmed, F. Arif, Y. Yahya et al, are similar[4,5] . Hepatitis is frequent in 80 percent of children with dengue fever, but increased liver enzymes SGOT and SGPT usually appear late in the course of the disease. Despite these precautions, one child with raised liver enzymes of more than 1500 IU/ml died. Similar findings were found in the research of Laoprasopwattana K et al. and Malavige GN et al [6, 7]. SGOT and SGPT values that are extremely high suggest the severity of the disease [8].Total blood counts should be serially examined to determine the disease progression because leucopenia and thrombocytopenia are prevalent in dengue children. Leucopenia and thrombocytopenia were not found to be significantly associated with severe dengue cases, contrary to some previous findings [9].Although the initial leukocyte and platelet count cannot predict the outcome; it can help direct early referral in resource constrained settings such as PHCs. Many studies have found that severe thrombocytopenia with a count of less than 20000 can be considered as a prognostic indicator when compared to simple thrombocytopenia. In their meta-analysis, Sorawat Sangkaew et al stated that they were unable to provide solid clinical evidence of a platelet count cutoff to assess the risk of severe dengue [10].

Dengue virus non-structural protein 1 (NS1) can bind to both thrombin and prothrombin. Binding to thrombin has no effect, but inhibiting prothrombin activation does. This may explain why APTT alterations occur before antibodies are produced [11]. Certain investigations have indicated that IL-6 inhibits the production of factor XII, the first factor to activate the intrinsic pathway of coagulation, which causes APTT to be increased than PT. In a meta-analysis research, Adane T et al found that APTT is prolonged in 43% of dengue patients, but In Indonesia and India, the minimum and maximum magnitudes of extended APTT were 12.6% and 91.10% respectively [11, 12, 13].Because IL 6 causes APTT to rise early in the course of the disease, our study found that children with a prolonged APTT > 60 upon admission have a higher risk of developing severe dengue with shock and bleeding.

Conclusion:

The majority of dengue children experience leucopenia and thrombocytopenia. Many children with severe thrombocytopenia recovered well in our trial without experiencing significant bleeding or shock. Serial monitoring of clinical symptoms, signs, vitals, and labs such as cell counts aids in the identification of severe dengue fever and prompt treatment. Liver enzymes and serum ferritn are elevated late in the course of disease so not good early prognostic markers. Our study showed that Children with prolonged APTT at the time of admission operate as a useful prognostic marker and help to identify children who are more likely to develop severe dengue infection. Early identification of these children, serial monitoring of vital signs, and cell counts lead to early recognition of warning signs and shock, as well as adequate management following WHO guidelines, which helps to reduce morbidity/mortality.

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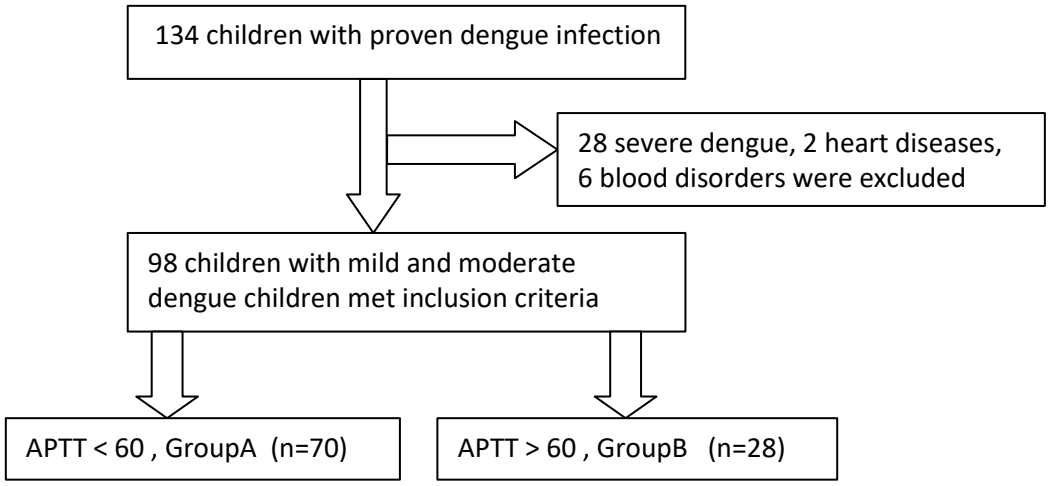

"Figure 1: depicts the subject recruitment process"

Table 1: showing response outcome measures between two groups

Parameter	***Group A (APTT < 60) n=70 (71%)***	***Group B (APTT > 60) n=28(29%)***	***p value***
Abdominal pain and vomiting	55(78)	26(93)	NS
Hepatomegaly	38(54)	28(100)	<0.001
Petechiae / ecchymosis	12(17)	18(64)	NS
Gastrointestinal bleeding	3(4)	14(50)	<0.001
Pleural effusion	42(60)	26(93)	0.003
Severe Dengue (DHF/DSS)	3(4)	24(86)	<0.001
Platelet count < 20,000	12(17)	9(32)	NS
Transfusion required	2(3)	18(64)	<0.001
Fluid rate required >= 10ml/kg/hr	2(3)	24(86)	<0.001
Colloids	0(0)	3(11)	0.03
AST and or ALT > 3X	1(1.5)	5(18)	0.009
Hypoglycemia	0(0)	2(7)	0.04
Inotropic support	0(0)	4(14)	0.03
Length of hospital stay	5.4	10.2	<0.001

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