

Original Research Article

The coagulation profile of children admitted with dengue fever and correlation with clinical severity

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ABSTRACT

Background: Dengue is one of the 17 Neglected Tropical diseases (NTD) addressed in the NTD road map. Objective of present study was to find out the correlation between coagulation profile abnormalities and clinical severity of dengue fever.

Methods: All cases of dengue fever in children below 12 years of age admitted to a tertiary care medical college of South India for a period of 18 months (January 2013- June 2014) were included in the study. The liver function tests, prothrombin time, International normalised ratio and activated partial thromboplastin level were estimated and correlated with severity.

Results: Of the 306 cases of children admitted with dengue fever, 131 (42.8%) were dengue fever without warning signs, 119 (38.8%) were dengue fever with warning signs and 56 (18.4%) were severe dengue according to WHO guidelines 2012. 20.9% cases had significant PT prolongation, 50.3% had INR >1.1 and 33.3% had aPTT prolongation. Of the 56 cases of severe dengue, 83.9% had PT prolongation, 96.4% had INR >1.1 and 91.1% had significant aPTT prolongation. The mean values of PT, INR and aPTT in severe dengue was 19 ± 3.7 sec, 1.5 ± 0.3 and 46 ± 7 sec respectively. These were well above the cut off values and showed statistically significant association with severe dengue ($p < 0.001$) compared to non-severe dengue. Similarly, ALT elevation among the total cases also showed majority (67.3%) in the range of 40-400. Of the 56 cases of severe dengue, 30% had values above 1000 IU/l, 51% had AST levels 40-400, and 16% had 400-1000 and 2.5% below 40. Statistical analysis showed significant difference in AST and ALT elevation among dengue fever without warning signs, dengue fever with warning signs and severe dengue ($p < 0.001$).

Conclusions: There is statistically significant association between prolongation of coagulation markers and severity of dengue.

Keywords: Activated partial thromboplastin time, Dengue fever, International normalised ratio, Prothromine time

INTRODUCTION

Dengue is one of the 17 Neglected Tropical diseases (NTD) addressed in the NTD road map.¹

Disease incidence and deaths are highest in children aged ≤ 15 years and case fatality rates are also highest in young children.² The dengue virus belongs to the genus

Flavivirus, family Flaviviridae Aedeia (Stegomyia) aegypti is the principal vector of dengue viruses.

Dengue fever is one of the most severe arthropod borne viral diseases in terms of human mortality and morbidity. The major cause of mortality is DHF/ DSS. There are multiple reasons for abnormal haemostasis such as vascular endothelial damage. Thrombocythia and

coagulation abnormalities. Various studies have revealed significant abnormalities in the coagulation and inflammation systems in dengue fever. The imbalance between coagulation and fibrinolysis may be used a prognostic marker

As well as a target for therapeutic intervention in severe cases. The abnormality in the coagulation system may be extrinsic or intrinsic which can be demonstrated by doing PT, and aPTT. If we can predict the cases likely to go for complication and start intervening early the mortality can be reduced. These investigations are not costly and can be done in primary care level itself. Thus, a study was done on the coagulation profile of children admitted with dengue fever and correlation with severity was undertaken.

METHODS

This is a descriptive study of children admitted with diagnosis of dengue fever from January 2013-June 2014 at a tertiary care government medical college in Kerala. The study was conducted after approval of the institutional research board. Written informed consent was obtained from the parents of all study subjects. All children below 12 years age with dengue fever admitted in paediatric ward/ICU in SAT hospital based on WHO guidelines 2012. The clinical criteria for those who live in dengue endemic area with fever and 2 of the following criteria is taken as probable dengue aches and pains, nausea vomiting rash, tourniquet test positive leukopenia, any warning sign or lab confirmed dengue. Dengue with warning sign-those with abdominal pain or tenderness, persistent vomiting clinical fluid accumulation, mucosal bleed lethargy, liver enlargement more than two cm, increase in haematocrit and concurrent fall in platelet count. Following are the criteria for severe dengue-severe plasma leakage leading to shock DSS fluid accumulation with respiratory distress, severe bleeding evaluated by the clinician severe organ involvement severe AST, ALT elevation ≥ 1000 , CNS impaired consciousness, heart and other organ impairment.

Exclusion criteria

Those children with bleeding diathesis. On anti-coagulants and chronic liver disease are excluded from the group or other infection producing bleeding diathesis

All children who were enrolled in the study were thoroughly evaluated with detailed history, physical examination, routine investigations, serological markers and coagulation profile. As per the institutional protocol all admitted cases of dengue routinely assess liver and renal function. The study population was classified as dengue fever without warning signs, dengue fever with warning signs and severe dengue according to WHO guidelines 2012. They were also grouped into severe and non-severe dengue to compare the baseline characteristics and coagulation abnormalities.

RESULTS

Of 306 cases of children with dengue fever 131 (42.8%) were dengue fever without warning signs, 119 (38.8%) were dengue fever with warning signs and 56 (18.4%) were severe dengue, according to WHO guidelines 2012. Majority 175 (57%) were in the age group of 6-12 years, 84 children 1-5 year group (27%) and 47 (16%) were infants. The mean age of the study population was estimated to be 7.8 ± 3.2 . Of the total 306 cases males were more in number (158) than females (148) (male: female ratio = 1.06:1). Of the 306 cases 16% required admission in Paediatric ICU. 14% had complications and the most common complication was shock (9.9%). Mortality in the present study was 21 (7%) of dengue fever, all had multi organ dysfunction (100%) in the end and the most common underlying predisposing conditions were ARDS (24%) and refractory shock (24%)

NS1Ag was done in only 168 cases due to late presentation in some cases and financial constraints in others as this was not an in-house investigation in our study IgM dengue positivity was 90.8%. IgG dengue was done in 252 cases in which IgG was done, positivity was in 131 cases.

Table 1: Summary of baseline characteristics of severe and non-severe dengue.

Characteristics	Severe (n=56)	Non severe dengue (n=250)	p value**
Lab parameters (mean\pmSd)			
Hb	13 \pm 2.5	12 \pm 1.5	0.012
PCV	44 \pm 4	35 \pm 4	0.003
Platelet count	30980 \pm 2465	61820 \pm 7620	0.003
Bilirubin	0.7 \pm 0.3	0.5 \pm 0.2	<0.001
SGOT	1835 \pm 228	182 \pm 43	<0.001
SGPT	920 \pm 115	98 \pm 27	<0.001
Total protein	5 \pm 1.5	6.3 \pm 0.8	<0.001
Serum albumin	2.8 \pm 0.6	3.5 \pm 0.4	<0.001
Blood urea	35 \pm 2	19 \pm 0.7	<0.001
Serum creatinine	0.7 \pm 0.2	0.6 \pm 0.1	<0.001
Sodium	133 \pm 5	134 \pm 3	0.190
Potassium	4 \pm 0.6	4 \pm 0.5	0.019
Calcium	7.3 \pm 1.8	8.8 \pm 0.8	<0.001
Random blood sugar	65 \pm 6	85 \pm 4	<0.001

On comparing the severe (n=56) with non-severe which comprises both dengue fever without warning sign and with warning sign. The mean age 6.9 ± 3.7 slight male preponderance 52.4 against 48.2% in severe dengue. The clinical symptoms like pain abdomen, vomiting and bleeding manifestations were more in severe dengue as compared to non-severe.

Tender hepatomegaly was seen in 75% of severe dengue as opposed to 26.4% in non-severe dengue. Positive

tourniquet test was seen in 15% of severe vs 12% in non-severe dengue. Laboratory evaluation showed significant difference between the two groups in liver enzymes and renal function with p value of <0.001. Details of lab parameters given in Table 1.

Out of the total 306 cases, 20.9% cases had significant PT prolongation, 50.3% had INR >1.1 and 33.3% had aPTT prolongation. Of the 56 cases of severe dengue, 83.9% had PT prolongation, 96.4% had INR >1.1 and 91.1% had significant aPTT prolongation (Table 2).

Coagulation abnormalities according to severity as per WHO classification is given in Table 3.

Table 2: Markers of coagulation in severe versus non-severe dengue.

Coagulation parameter	Severe dengue (n= 56)	Non severe dengue (n= 250)	P value**
Prothrombin time (sec)	19±3.7	13.4±2	<0.001
INR	1.5±0.3	0.99±0.2	<0.001
Activated partial thromboplastin time (sec)	46±7	34±6	<0.001

*Values of markers of coagulation in patients with severe and non-severe dengue are reported as mean ± standard deviation.

**Denotes the resulted p value after comparison of severe and non-severe dengue using the student t test.

Table 3: Coagulation abnormalities in dengue fever according to severity (WHO 2012).

Parameters	Reference value	Dengue without warning sign (DNW)	Dengue with warning sign (DWS)	Severe dengue (SD)
PT	>16	3 (2.30%)	14 (11.80%)	47 (83.90%)
INR	>1.1	29 (22%)	71 (59.7%)	54 (96.40%)
APTT	>38	10 (7.60%)	41 (34.50%)	51 (91.10%)

Table 4: Liver enzyme changes in various sub group of dengue fever.

	AST				ALT				P value
	<400		>400		<400		>400		
	N	%	N	%	N	%	N	%	
Dengue without warning sign	125	95.4	6	4.60	129	98.5	2	1.5	P value <0.001
Dengue with warning sign	109	91.0	10	8.4	115	96.5	4	3.4	
Severe dengue	23	41.1	33	58.9	30	53.6	26	46.4	
total	257	83.98	49	16.0	274	89.54	32	10.45	

Of 306 cases, 80.7% had AST elevation in the range of 40-400. 9.2% had AST levels above 1000. But in 56 cases of severe dengue, 50% had AST levels above 1000, 38% had 40-400, 9% had 400-1000 and 3% below 40. Similarly, ALT elevation among the total cases also showed majority (67.3%) in the range of 40-100. Of the 56 cases of severe dengue, 51% had ALT levels 40-400, 30% had above 1000, 16% had 400-1000 and 2.5% below 40. AST was more sensitive than ALT. However statistical analysis showed significant difference in both AST and ALT elevation among dengue fever (Table 3) without warning signs, dengue fever with warning signs and severe dengue.

DISCUSSION

Dengue is one of the 17 Neglected Tropical diseases (NTD) addressed in the NTD road map.¹ Estimates of the global incidence of dengue infections per year have ranged between 50 million and 200 million; however, recent estimates using cartographic approaches suggest it is closer to almost 400 million. The goals of the Global

strategy initiative by WHO to reduce dengue mortality by at least 50% by 2020. Disease incidence and deaths are highest in children aged ≤15 years and case fatality rates are also highest in young children.² Kerala can be considered hyper endemic for dengue and the circulation of all four DENV serotypes in Kerala may lead to an increase in the prevalence of more severe complications of this emerging disease, such as dengue haemorrhagic fever and dengue shock syndrome.

Recently it has shown that non-structural protein 1 (NS1) of dengue virus can bind both to thrombin and pro thrombin. Binding to thrombin will not make any changes whereas pro thrombin activation is inhibited. This can explain changes in aPTT occur early before antibodies are formed.^{3,4} NS1 also contribute plasma leakage by producing endothelial changes independent of immunological mechanism.^{5,6} During acute phase of dengue lot of inflammatory mediators and cytokines are released. Complements like C3a C5a IL6, IL10, TNF α and histamine leading to plasma leakage, thrombocytopenia, and decrease in fibrinogen coagulation factors. In addition, the inflammation of

hepatocytes leading to increase in AST, ALT. Damage to liver cells further decreases the coagulation factor synthesis this can alter the PT APTT, systems. Various studies have shown the participation of DV in the down regulation of the thrombomodulin-thrombin-protein C complex formation at the endothelial surface, with a reduction in activated protein C (APC). APC is the most important vasoprotective protein because it down regulates thrombin generation (by the inactivation of procoagulant factors Va and VIIIa) and has anti-inflammatory, ant apoptotic, and barrier protection properties. These biological functions of APC are associated with the endothelial protein C receptor (EPCR) and protease-activated receptor 1 (PAR-1) signalling pathways, which link the coagulation-inflammation responses. Alterations in the antithrombotic and cyto protective protein C pathways during DV infection of human endothelial vascular cells have been observed, which may explain the vasculopathy observed during DHF/DSS.⁶

The analysis of coagulation markers in our study revealed that of the total 306 cases, 20.9% cases had significant PT prolongation, 50.3% had INR >1.1 and 33.3% had aPTT prolongation. Of the 56 cases of severe dengue, 83.9% had PT prolongation, 96.4% had INR >1.1 and 91.1% had significant aPTT prolongation. This observation was important as impaired fibrinolysis and coagulation is considered to be a potential pathogenic mechanism of severe dengue.⁷⁻¹³ Khalil et al showed coagulopathy as a significant risk factor for mortality as well.¹⁴ the study conducted by Van Gorp et al and Isangkura et al also showed similar results.^{3,4} The hepatic involvement of dengue in our study is evidenced by the elevation of hepatic transaminases. Of 306 cases, majority (80.7%) had AST elevation in the range of 40-400. Only 9.2% had AST levels above 1000. Of 56 cases of severe dengue, 50% had AST levels above 1000, 38% had 40-400, 9% had 400-1000 and 3% below 40. Similarly, ALT elevation among the total cases also showed majority (67.3%) in the range of 40-400. Of the 56 cases of severe dengue, 51% had ALT levels 40-400, 30% had above 1000, 16% had 400-1000 and 2.5% below 40. AST was more sensitive than ALT. However statistical analysis showed significant difference in AST and ALT elevation among dengue fever without warning signs, dengue fever with warning signs and severe dengue. ($p < 0.001$). This was in accordance with other studies.^{5,15}

Thus, this study emphasizes on the role of coagulation in the pathogenesis and prognostication in severe dengue. The APTT prolongation occurs even before immunological changes starts. It can predict patients likely to develop complications. This simple cheaper blood investigation of other coagulation function PT, INR, and liver enzymes, can be used as a supporting evidence for severe dengue and thus helps in early intervention and management which can reduce the mortality of dengue fever.

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