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Capillary Leak Syndrome is Inversely Related to Platelet Count in Dengue

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Abstracts
Dengue is a mosquito borne viral disease caused by mainly four serotype of dengue virus (DEN-1,DEN-2,DEN-3,DEN-4). Infection with one type usually give lifelong immunity but short term immunity to other type. Subsequent infection with different type increases the risk of 'Dengue Hemorrhagic Fever (DHF) and 'Dengue Shock Syndrome'(DSS).
Pathophysiology of DHS and DSS is incompletely understood. But researchers suggested that it is due to cytokines production and activation of complement system. The endovascular system is the target organ in severe dengue and capillary leak syndrome is the main complication of severe dengue.
Probable pathogenesis of DHF or DSS is due to immune mediated platelet destruction which release massive cytokines, activate the complement system and lead to capillary leak syndrome. Severity of dengue is mainly depends upon number of platelet destruction. Secondary dengue is severe as it causes rapid and massive platelet destruction. Purpose of this study is to show at which level of platelet count causes capillary leak syndrome.
Key word: *Severe dengue ;massive platelet destruction; capillary leak syndrome.*

Introduction

Dengue is a mosquito borne human disease. Worldwide infected about 3.2 million/year.[1] Half of the world population is now at risk [2] India is a tropical country and endemic zone of dengue fever. Most commonly seen in rainy & autumn season. A number of people are affected by this disease. Most of them are non-complicated but some are fatal and may die. There is no specific treatment for severe dengue, only supportive treatment are available. An estimated 5 lakh people with severe dengue required hospitalization each year and 2.5% die.[2] Dengue can be diagnosed by NS1 antigen & IgM antibody. IgG antibody are not a good indication on endemic zone but only platelet monitoring is important guideline to prevent complication. Sensitivity of NS1Ag is89% and specificity is 79%.[3] When both test are done increase the specificity. Capillary leak syndrome is seen in severe dengue [4].

Regular monitoring of platelet count is an invaluable diagnostic tool in dengue. [5] It is the single most important factor in the treatment of Dengue fever. In Dengue fever, most affected cells are platelet & it is destroyed by dengue antibody. Due to molecular mimicry between dengue virus and platelet, the dengue antibody affect the platelet and destroy the platelet. It also affect the other cell like WBC, RBC. If the platelet destruction is less, treat it as simple viral fever. But if the platelet destruction is more it is complicated dengue. Because destructed platelet release a number of cytokine. Release of cytokines and other chemical mediator trigger the

plasma leakage.[6] This cytokines and other chemical mediator act on vascular endothelium & increase vascular permeability and lead to Capillary leak syndrome. So, it is suggestive that all the complication of dengue is due to platelet destruction. Dengue virus may causes simple fever like other viral fever. But depending upon the number of platelet destruction it may lead to systemic inflammatory response syndrome. And DHF & DSS are due to massive release of cytokines and activation of complement system. A number of cytokines are released from platelet like IL1,IL2,IL6,TN Falfa soluble CD8 which are mainly involved in capillary leak syndrome[7].

Elevation of TNF alfa, IL6,IL8,IL10,chokines, INF gama have been reported in the patients with serve dengue [8].

IL-1β, IFN-γ, IL-4, IL-6, IL-13, IL-7 and GM-CSF were significantly increased in patients with severe clinical manifestations of severe dengue [9]

Severe dengue is defined by one or more of the following: I) plasma leakage that may lead to shock and/or fluid accumulation, with or without respiratory distress; and/or ii) servere bleeding; and/or iii) severe organ impairment. [10]

The main pathogenesis in severe dengue is the cytokine which is released from destructed platelet. Platelet destruction is immune-mediated. Platelet transfusion is not the ideal treatment in severe dengue. But prevention of platelet destruct-ion and stoppage the release of cytokine are the mainstay of treatment in severe dengue. But it is very difficult. Mosquito control is easier method to control dengue. It not only protects from dengue but also protect from other mosquito borne disease.

We do not know the capillary leak syndrome is triggered by dengue virus itself or by antibodies to its antigen. But IL6 enhance the anti platelet antibody and anti endothelial antibody and destroy both cell. And these cell destruction further increase the cytokines level and further increase antibody level-- a vicious cycle starts. Ultimate effect of dengue virus is dysfunction endo-vascular system and lead to capillary leak syndrome.

Material and Method

The study was conducted in a private medical institute (ISO 9001:2008) at Kolkata, West Bengal. Study population was those who had been admitted with complaints of fever and NS1ag is positive.(kit- Dengue NS1Ag Microlisa, J Mitra and Co, New Delhi, India) Dengue IgM and IgG was done after admission.(IVD Micro well Dengue fever kit, IVD Research Inc, Carlsbad, CA USA).Number of subject was 30. Type of study was observational study. Study was conducted on July, 2015 to June 2016. Capillary leak syndrome is established (by using USG machine) by fluid in peritoneal space and pleural cavity. Also corroborated with high hematocrit value, low albumin level and low blood pressure and dependent oedema.

Dengue was diagnosed by history of fever with generalised body ache specially headache, retro orbital pain and joint pain. Some of the patient presented with morbilliform skin rash all over the body. Routine investigation of NS1Ag was done before hospitalized or immediately after admission. Then sent for dengue antibody like IgM and IgG . Study subject were whom platelet count was below one lakh. Two important tool of this study were:

1. Daily platelet count and (Automatic cell counter;MS4; Part5)
2. Daily USG screening.

And in some patient needed 12 hourly platelet monitoring .Others cause of fever are excluded by total count of WBC, MP.MP antigen, Typhidot M, CXR. USG of abdomen, Urine RE&CS,. Others routine test were Complete hemogram, LFT, Serum urea /creatinine, NA+/K+,CRP . But not excluded the others viral fever in which NS1Ag may be positive. Others flavivirus like yellow fever is not found in our country. Japanese encephalitis and KFD are excluded clinically. West Nile is not reported in West Bengal.

Result and Analysis

Sl. No.	Platelet count & USG screeing	5th day of fever	6th day of fever	7th day of fever	8th day of fever
1	Platelet count & USG screeing(ascites&effusion)	98,000/cmm	70000/cmm	42000/cmm	56000/cmm
		Nil	+	++	++
2	Platelet count & USG screeing(ascites&effusion)	74,000/cmm	70,000/cmm	98000/cmm	---
		Nil	Nil	nil	---
3	Platelet count & USG screeing(ascites&effusion)	70000/cmm	56000/cmm	45000/cmm	52000/cmm
		Nil	+	++	++
4	Platelet count & USG screeing(ascites&effusion)	86000/cmm	62000/cmm	38000/cmm	25000/cmm
		Nil	+	+++	+++
5	Platelet count & USG screeing(ascites&effusion)	60000/cmm	45000/cmm	38000/cmm	48000/cmm
		Nil	+	+++	+++
6	Platelet count & USG screeing(ascites&effusion)	96000/cmm	70000/cmm	56000/cmm	62000/cmm
		Nil	Nil	nil	Nil
7	Platelet count & USG screeing(ascites&effusion)	70000/cmm	48000/cmm	42000/cmm	36000/cmm
		Nil	Nil	+	++
8	Platelet count & USG screeing(ascites&effusion)	56000/cmm	48000/cmm	36000/cmm	38000/cmmm
		Nil	+	++	++
9	Platelet count & USG screeing(ascites&effusion)	60000/cmm	50000/cmm	45000/cmm	80000/cmm
		Nil	+	+	+
10	Platelet count & USG screeing(ascites&effusion)	76000/cmm	56000/cmm	42000/cmm	36000/cmm
		Nil	Nil	++	++
11	Platelet count & USG screeing(ascites&effusion)	90000/cmm	60000/cmm	45000/cmm	58000/cmm
		Nil	Nil	+	+
12	Platelet count & USG screeing(ascites&effusion)	70000/cmm	52000/cmm	39000/cmm	28000/cmm
		Nil	Nil	++	+++
13	Platelet count & USG screeing(ascites&effusion)	62000/cmm	42000/cmm	45000/cmm	76000/cmm
		Nil	+	+	--
14	Platelet count & USG screeing(ascites&effusion)	58000/cmm	38000/cmm	33000/cmm	25000/cmm
		Nil	++	++	+++
15	Platelet count & USG screeing(ascites&effusion)	62000/cmm	38000/cmm	25000/cmm	17000/cmm
		Nil	++	+++	++++
16	Platelet count & USG screeing(ascites&effusion)	80000/cmm	58000/cmm	43000/cmm	48000/cmm
		Nil	Nil	+	+
17	Platelet count & USG screeing(ascites&effusion)	77000/cmm	63000/cmm	52000/cmm	45000/cmm
		Nil	Nil	+	+
18	Platelet count & USG screeing(ascites&effusion)	50000/cmm	38000/cmm	33000/cmm	38000/cmm
		Nil	+	+	+
19	Platelet count & USG screeing(ascites&effusion)	90000/cmm	72000/cmm	65000/cmm	68000/cmm
		Nil	Nil	nil	Nil
20	Platelet count & USG screeing(ascites&effusion)	70000/cmm	55000/cmm	45000/cmm	49000/cmm
		Nil	Nil	nil	Nil
21	Platelet count & USG screeing(ascites&effusion)	56000/cmm	47000/cmm	42000/cmm	38000/cmm
		+	+	++	++
22	Platelet count & USG screeing(ascites&effusion)	80000/cmm	51000/cmm	43000/cmm	38000/cmm
		Nil	Nil	+	++
23	Platelet count & USG screeing(ascites&effusion)	950000/cmm	60000/cmm	52000/cmm	47000/cmm
		Nil	Nil	nil	Nil
24	Platelet count & USG screeing(ascites&effusion)	63000/cmm	47000/cmm	39000/cmm	30000/cmm
		+	++	+++	+++
25	Platelet count & USG screeing(ascites&effusion)	78000/cmm	55000/cmm	40000/cmm	58000/cmm
		Nil	+	++	+++
26	Platelet count & USG screeing(ascites&effusion)	56000/cmm	38000/cmm	30000/cmm	33000/cmm
		Nil	++	+++	+++
27	Platelet count & USG screeing(ascites&effusion)	90000/cmm	67000/cmm	50000/cmm	38000/cmm
		Nil	Nil	+	+++
28	Platelet count & USG screeing(ascites&effusion)	82000/cmm	60000/cmm	45000/cmm	32000/cmm
		Nil	Nil	+	+++
29	Platelet count & USG screeing(ascites&effusion)	42000/cmm	36000/cmm	28000/cmm	25000/cmm
		+	++	+++	++++
30	Platelet count & USG screeing(ascites&effusion)	85000/cmm	67000/cmm	48000/cmm	57000/cmm
		Nil	Nil	+	+

(+ =only ascites; ++=ascites and one sided pieural effusion; +++ =ascites with bilateral effusion;++++ = ascites with bilateral effusion and pericardial effusion.)

Number of patient was 30. There is no age prediction of dengue fever. Complications are seen two cases whose age were above 65yr. One young, age 23yr also complicated with hemoptysis and needed blood transfusion. There is no sex preference in dengue. Feature of capillary leak syndrome seen whose platelet count at 70000/cmm in one patients in the form of ascites. But the result show most of the cases, ascites and pleural effusion are developed when platelet count is below 50,000/cmm. Thrombocytopenia and hemo concentration are seen in mild form of dengue. Although severe dengue seen in children of south-east Asia but was no scope to proved it because all the patient are above 18yr in this study.

Discussion

Capillary leak syndrome in dengue is not due to viral invasion but due to high level of cytokines which activate the complement system. Same pathogenesis is seen in Septicaemia, systemic inflammatory response syndrome, SLE. In Dengue, there is not only massive platelet destruction but also destruction of RBC, WBC. From these cell huge amount of cytokine are released. But more cytokine released from destructed platelet as platelet is thought as a tiny pharmaceutical bag.[11] Due to molecular mimicry between dengue virus and platelet; more platelet are destructed than others cell. First time, Dengue cause less platelet destruction but second time dengue cause massive platelet destruction due rapid formation of antibody & more complication arises. Conclusion is massive destruction of platelet lead to huge released of cytokines result is increase vascular permeability and capillary like syndrome. Most common accepted hypothesis is 'Antibody depended enhancement' in pathogenesis of severe dengue.[12]

Result found that percentage of platelet destruction is inversely related to Capillary leak syndrome. But it is not proved that platelet destruction is the only cause of capillary like syndrome. We proved it indirectly. We have not estimated the viral load because it is very difficult and costly. Some virus may direct cause of increased vascular permeability, may not though the destruction of platelet. In this study, the sample size is very small. So, the conclusion is that Capillary like syndrome is inversely related to platelet destruction is not gladly accepted. We have not estimate the cytokine level and do not know at which level it increased vascular permeability. We have not identified specific cytokine which increase vascular permeability. But it is proved that destruction of platelet release a number of cytokines, which increases the vascular permeability.[13] DHS and DSS may be prevented by blocking the cytokines. Biologic therapy in may be the future treatment option in severe dengue specially DHS, DSS, where mortality is 20% [2]. As it is suggested that immune-mediated platelet destruction is the pathogenesis of severe dengue, so, platelet monitoring is the single most important factor in severe dengue. Platelet destruction usually started from the 4^{th} or 5^{th} day of dengue fever & upto 14^{th} day. A large Brazilians study included 543 dengue patients show thrombocytopenia started from 3^{rd} day of fever in uncomplicated cases, while thrombocytopenia started from 1st or 2^{nd} day in severe dengue [14].

This period is crucial for dengue patient and also for doctor. Effect of cytokines is not only limited to vascular endothelium but also involve others organ like liver. Purpose of this study is at which level of platelet count started complication of severe dengue. Basically it depend upon the level of dengue antibody present in the blood, destruction of platelet, level of cytokines in the circulation and response of body to cytokine. In my study it is found that the complication arises when platelet count fall around 70,000 /cmm to downward. Mild complication is seen when platelet count is around 70,000/cmm and severe complication seen when it is 20000 to 30000/cmm. Platelet transfusion was done when count fall below 20,000/cmm. Platelet transfusion is not a treatment of severe dengue. It is transfused to prevent bleeding disorder which may cause of death. It is for time being. The immune

system of body will recovered from this complication by the time. Bleeding disorder are due to platelet destruction, hepatic involvement, and alteration of coagulation system.

Conclusion

In severe dengue, huge number of platelet are destructed and released enormous amount of cytokines which act on endovascular system and activate the complement system. The resulted effect is increased vascular permeability and lead to capillary leak syndrome . The pathogenesis of severe dengue is same as severe bacterial infection. It is the systemic inflammatory response syndrome (SIRS) and involved all the system of body. But most commonly affect the Endo-vascular system; the largest surface area of body; more than the skin. Due largest surface area of the endovascular system dengue causes rapid complication. So, complication of dengue may be prevented either by prevention of platelet destruction or by blocking the cytokines.

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Consent

Written consent was taken from the proper authority of that private medical institute for the publication of this study .Informed consent is taken from each patient.

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