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CAPILLARY LEAK SYNDROME IN SEVERE DENGUE

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A R T I C L E I N F O

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A B S T R A C T

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. Material and Method: 30 dengue patient whose platelet was below one lakh were taken in this study.Regular monitoring of platelet and daily USG screening were the tool of this study.Results:Out of 30 patient 25 patient had sign of capillary leak .Conclusion :Capillary leak syndrome seen in severe dengue and inversely related to platelet count.

INTRODUCTION

Dengue is a mosquito borne human disease. worldwide infected about 3.2 million/year.(1) Half of the wold populatio is now at risk.(2)There are four serotype of dengue virus (DEN-1, DEN-2, DEN-3, DEN-4).(2) 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).(2 &3)

Pathophysiology of DHS and DSS is incompletely understood. Two popular theory are (a) Antibody dependend enhancement (b) Virulence theory.(4) 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. 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)organ impairment. (5)

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 capillary leak syndrome in dengue with low platelet count.

Capillary leak syndrome (CLS) otherwise called as capillary permeability syndrome was first described by Clarkson in 1960. Thus, it is also known as Clarkson's syndrome.(6)It is characterized by-

1. Hypotension with hemoconcentration,
2. hypoalbuminemia without albuminuria and
3. generalized edema.

This syndrome is due to capillary hyperpermeability with massive extravasation of plasma containing macromolecules smaller than 200kD and sometimes upto 900kD. Capillary leak may occur as a part of the systemic capillary leak syndrome (SCLS) or secondary to the systemic inflammatory response syndrome (SIRS). This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following toxemias, poisoning shock syndromes, low-flow states, or ischemia-reperfusion injuries. It can lead to generalized edema and multiple organ failure associated with oxidation injury.(6)

Capillary leak are

1. Primary/idiopathic systemic capillary leak syndrome.
2. Secondary capillary leak syndrome are Venomous snake bite (ophitoxemia), Viral hemorrhagic fever (dengue, hantan virus), Toxin related (abrin ricin, sanguinarine), Adverse drug reaction (interleukin-2, interferon β-1b, gemcitabine) and Sepsis related CLS. Capillary leak syndrome is seen in severe dengue but the exact cause in not known.(7)We do not know the capillary leak syndrome is triggered by dengue virus itself or by antibodies to its antigen. (8) But IL6 enhance the anti platelet antibody and anti endothelial antibody and destroy both cell (8) 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. The endothelium is the primary fluid barrier of the vasculature and

ultimately the effects of *dengue* virus infection that cause *capillary leakage*.(9)

MATERIALS AND METHODS

The study was conducted in a private medical institute. 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 Microwell 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.

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	98,000/cmm	70000/cmm	42000/cmm	56000/cmm
	screeing(ascites&effusion)	Nil	+	++	++
2	Platelet count & USG	74,000/cmm	70,000/cmm	98000/cmm	---
	screeing(ascites&effusion)	Nil	Nil	nil	---
3	Platelet count & USG	70000/cmm	56000/cmm	45000/cmm	52000/cmm
	screeing(ascites&effusion)	Nil	+	++	++
4	Platelet count & USG	86000/cmm	62000/cmm	38000/cmm	25000/cmm
	screeing(ascites&effusion)	Nil	+	+++	+++
5	Platelet count & USG	60000/cmm	45000/cmm	38000/cmm	48000/cmm
	screeing(ascites&effusion)	Nil	+	+++	+++
6	Platelet count & USG	96000/cmm	70000/cmm	56000/cmm	62000/cmm
	screeing(ascites&effusion)	Nil	Nil	nil	Nil
7	Platelet count & USG	70000/cmm	48000/cmm	42000/cmm	36000/cmm
	screeing(ascites&effusion)	Nil	Nil	+	++
8	Platelet count & USG	56000/cmm	48000/cmm	36000/cmm	38000/cmmm
	screeing(ascites&effusion)	Nil	+	++	++
9	Platelet count & USG	60000/cmm	50000/cmm	45000/cmm	80000/cmm
	screeing(ascites&effusion)	Nil	+	+	+
10	Platelet count & USG	76000/cmm	56000/cmm	42000/cmm	36000/cmm
	screeing(ascites&effusion)	Nil	Nil	++	++
11	Platelet count & USG	90000/cmm	60000/cmm	45000/cmm	58000/cmm
	screeing(ascites&effusion)	Nil	Nil	+	+
12	Platelet count & USG	70000/cmm	52000/cmm	39000/cmm	28000/cmm
	screeing(ascites&effusion)	Nil	Nil	++	+++
13	Platelet count & USG	62000/cmm	42000/cmm	45000/cmm	76000/cmm
	screeing(ascites&effusion)	Nil	+	+	--
14	Platelet count & USG	58000/cmm	38000/cmm	33000/cmm	25000/cmm
	screeing(ascites&effusion)	Nil	++	++	+++
15	Platelet count & USG	62000/cmm	38000/cmm	25000/cmm	17000/cmm
	screeing(ascites&effusion)	Nil	++	+++	++++
16	Platelet count & USG	80000/cmm	58000/cmm	43000/cmm	48000/cmm
	screeing(ascites&effusion)	Nil	Nil	+	+
17	Platelet count & USG	77000/cmm	63000/cmm	52000/cmm	45000/cmm
	screeing(ascites&effusion)	Nil	Nil	+	+
18	Platelet count & USG	50000/cmm	38000/cmm	33000/cmm	38000/cmm
	screeing(ascites&effusion)	Nil	+	+	+
19	Platelet count & USG	90000/cmm	72000/cmm	65000/cmm	68000/cmm
	screeing(ascites&effusion)	Nil	Nil	nil	Nil
20	Platelet count & USG	70000/cmm	55000/cmm	45000/cmm	49000/cmm
	screeing(ascites&effusion)	Nil	Nil	nil	Nil
21	Platelet count & USG	56000/cmm	47000/cmm	42000/cmm	38000/cmm
	screeing(ascites&effusion)	+	+	++	++
22	Platelet count & USG	80000/cmm	51000/cmm	43000/cmm	38000/cmm
	screeing(ascites&effusion)	Nil	Nil	+	++
23	Platelet count & USG	950000/cmm	60000/cmm	52000/cmm	47000/cmm
	screeing(ascites&effusion)	Nil	Nil	nil	Nil
24	Platelet count & USG	63000/cmm	47000/cmm	39000/cmm	30000/cmm
	screeing(ascites&effusion)	+	++	+++	+++
25	Platelet count & USG	78000/cmm	55000/cmm	40000/cmm	58000/cmm
	screeing(ascites&effusion)	Nil	+	++	+++
26	Platelet count & USG	56000/cmm	38000/cmm	30000/cmm	33000/cmm
	screeing(ascites&effusion)	Nil	++	+++	+++
27	Platelet count & USG	90000/cmm	67000/cmm	50000/cmm	38000/cmm
	screeing(ascites&effusion)	Nil	Nil	+	+++
28	Platelet count & USG	82000/cmm	60000/cmm	45000/cmm	32000/cmm
	screeing(ascites&effusion)	Nil	Nil	+	+++
29	Platelet count & USG	42000/cmm	36000/cmm	28000/cmm	25000/cmm
	screeing(ascites&effusion)	+	++	+++	++++
30	Platelet count & USG	85000/cmm	67000/cmm	48000/cmm	57000/cmm
	screeing(ascites&effusion)	Nil	Nil	+	+

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

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 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

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 hemoconcentration 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

A hallmark of severe dengue disease is the presence of elevated levels of cytokines and chemokines including IP-10, ITAC, IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12, IL-13, TNFα, IFNα, IFNγ, MIF, RANTES, histamine.(9) Elevated C3a, C5a, and histamine have been associated with severe permeability deficits in dengue virus patients and in the development of DHF and DSS (9) Their presence in the blood of patients with severe dengue disease is significant since these anaphylatoxins direct lysis of infected cells and mast cell degranulation, leading to histamine release.

Importantly, cytokines, chemokines, and complement-activating factors can all be secreted by and act on the endothelium, influencing endothelial cell regulation of fluid barrier function and vascular leakage. Recent analysis dengue virus strongly induces secretion of immune cell activating cytokines, chemokines, and complement factors that are likely to contribute to an immune enhanced disease process [10]. Since permeability is ultimately the result of responses that act on the endothelium, dengue infected endothelial cells are key elements in DSS and DHF that must be considered more fully within animal and in vitro models. On the otherhand, autopsy samples do not take into account contributions of dengue virus infection of the endothelial cell.(10)

So it is suggested that capillary leak syndrome in dengue is not due to viral invasion but due to high level of cytokines. In severe cases, this "cytokine release syndrome" turns into a "cytokine storm," unleashing a tsunami of inflammation that quickly leads to organ dysfunction.(11) Same pathogenesis is seen in Septicaemia, systemic inflammatory response syndrome,envenomation, drug(gemcitabine)(12) and toxins

In Dengue, there is massive platelet destruction & 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(13). Due to molecular mimicry between dengue virus and platelet; more platelet are destructed than others cell. (14)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.

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 leak 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 pathogenesis of capillary leak syndrome is 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.(15) This two fatal condition may be prevented by blocking the cytokines. In future we may use some biologic in case of severe dengue and, Dengue shock syndrome. Biologic therapy 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 3rd of fever in uncomplicated cases, while thrombocytopenia started from 1st or 2nd in severe dengue (16).

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.(17) 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 this 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 70000/cmm and severe complication seen when it is 20000 – 30000/cmm. Platelet transfusion is not a treatment of severe dengue. It is transfused to prevent bleeding disorder which may cause of death. 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 destruction and released enormous amount of cytokines, activate the

complement system which increased vascular permeability and ultimately lead to capillary leak syndrome e.g.complication of dengue. It is the systemic inflammatory response syndrome 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 cause rapid complication.

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Consent

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

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