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Thrombocyte: the prime target of dengue virus – A review

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ABSTRACT

Dengue fever is an endemic infectious disease caused by dengue virus (DENV). A sustained increase in the incidence of dengue infection is clear in tropical and subtropical areas of the world. Clinical manifestations in dengue ranges from fever on 2^{nd}-3^{rd} day to thrombocytopenia on 4^{th} day. Initial stage of dengue fever may progress to potentially fatal Dengue hemorrhagic fever (DHF) and Dengue shock syndrome (DSS). The main targets of DENV are platelets, as a result thrombocytopenia is regarded as the potential indicator in the diagnosis of dengue. There is no particular therapeutics for the treatment of dengue infection. Acetaminophen is generally given to reduce pain and fever. Platelet transfusion was performed in some hospitalized patients, but its effectiveness is controversial. This article also specifies on unnecessary platelet transfusion therapies which are now considered harmful more than having beneficial effects in patients with dengue.

Keywords: Dengue Fever, Thrombocytopenia, Platelet Transfusion.

INTRODUCTION

Dengue is an acute infectious disease caused by a genus flavivirus of species dengue virus. It is transmitted by Aedes mosquito. Dengue fever is also called The Break Bone fever. Dengue viruses (DENV's) are the most common at the same time most dangerous human arboviruses. They occur worldwide with increased incidence in tropical and subtropical areas of the world. An estimated 50-100 million cases of dengue are recorded every year worldwide. [1]

Dengue viruses

Dengue viruses (DENV's) are the members of Flaviviridae family. They are ss-RNA viruses containing 11,000 nucleotides that code for a single polyprotein. This polyprotein is divided into 3 structural proteins namely C, prM/M, E and 7 non structural proteins namely NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5.[2][3]

Structural proteins

C: It refers to capsid protein. It binds the viral RNA.
M: Refers to membrane protein. It is found in mature viral particle.
E: It refers to envelope protein. It mediates the viral attachment, membrane fusion and virion assembly.[5]

Out of the above 3 structural proteins, envelope protein is the most important protein as it is expressed on the surface of the viral particle. This exposure triggers the protective immune responses in the host and thus leads to the production of neutralizing antibodies in the host. Envelope protein contains 3 domains:

Domain 1- It contains central region of the protein.
Domain 2- It assists viral mediated membrane fusion.
Domain 3- It interacts with the cell receptors and has epitopes which are recognized by these neutralizing antibodies. [4]

Non Structural Proteins

These are involved in viral replication, transcription and translation.

NS1

It is 46 kDa protein involved in RNA replication of virus. It is expressed on the surface of viruses infected cells. Serum levels of NS1 have been used as a diagnostic tool for dengue infection. [8]

NS2A

It is a 22 kDa protein involved in RNA replication and packaging. It is also involved in interferon type-I antagonism.[7][8]

NS2B

It is a 14 kDa protein. It serves as a cofactor for NS3 to form a viral protease complex.[9][10]

.NS3

It is a multifunctional protein involved in unwinding the ds-RNA replicative form. It is also involved in RNA replication.

NS4A & NS4B

These are small hydrophobic proteins that functions as interferon signaling inhibitors.[7][8]

NS5

It is a huge multifunctional 103 kDa protein. It has an RNA dependent polymerase activity and acts as a potential type I interferon production antagonist. [11][12]

All the above serotypes are capable of causing dengue with symptoms ranging from undifferentiated fever called dengue fever (DF) to potentially fatal Dengue hemorrhagic fever (DHF) or Dengue shock syndrome (DSS). [13]

CLINICAL PRESENTATIONS

Patients with dengue infections presents with the following symptoms:

- High fever 40^{o}C or 104 F.
- Liver enlargement
- Circulatory failure (hypotension and shock)
- Pleural, abdominal, cardiac edema
- Internal bleeding

More severe forms include:

- Plasma leakage
- Thrombocytopenia with or without hemorrhage.

WHO classified the symptoms of DHF into 4 severity grades based on laboratory data:

Grade I

Fever with positive tourniquet test.

Grade II

+ mild spontaneous bleeding.

Grade III

Presence of weak and rapid pulse.
Grade IV: Profound shock with undetectable pulse. [14]

THROMBOCYTOPENIA – Potential Indicator Of Dengue Infection

Thrombocytopenia is defined as a rapid decrease in the platelet count or a platelet count less than 1,50,000 per microliter of blood [15]. The normal blood platelet count is 150-400 x 10^{9} per liter of blood. In DHF/DF a significant decline of platelets count was observed on the 4th day of illness. In children there is minor interrelation between platelet count and bleeding manifestations. In adults, platelet count of 5 x 10^{9} L^{-1} and packed cell volume (PCV) > 50 are presented with bleeding manifestations.

CAUSES OF THROMBOCYTOPENIA

The mechanisms involved in thrombocytopenia and bleeding due to DENV infection are not clearly understood. The following are known to profoundly cause thrombocytopenia:

a. Bone marrow depression.
b. Increased destruction of platelets.
c. Platelet dysfunction.

Bone mass depression: Dengue associated bone mass suppression evolves rapidly through several phases

- Onset of bone marrow suppression within 3 to 4 days of dengue viral infection.
- Direct lesion of platelet progenitor cells by DENV. [16][17]

- DENV is found to infect and kill stromal cells of bone marrow.
- Destruction of megakaryocytes by DENV, thus limiting the production of platelets.

Increased destruction of platelets

- Thrombocytopenia occurs as a result of consumption of platelets during ongoing coagulopathy process.
- Activation of complement system [18] and increased peripheral sequestration [19][20] are also known mechanisms to cause thrombocytopenia.
- In patients with secondary DENV infections, platelets undergo phagocytosis by macrophages as a result of uncharacterized mechanisms.
- In addition patients with DENV infections develop anti platelet antibodies which cause lysis of platelets.

Platelet Dysfunction

- Studies conducted on skin biopsy specimens of infected patients revealed the presence of DENV antigens on the surface of platelets.
- Reverse transcription (RT) PCR and Electron transmission microscopy (EM) analysis have been performed on platelets and plasma of some hospitalized individuals.
- Dengue viral RNA was detected in platelets and plasma by these techniques, which confirmed the presence of dengue viral particles inside the platelets which is associated with dengue dysfunction.
- Atomic force, scanning, ETM analysis revealed several morphological changes in platelets such as altered platelet membrane architecture, degranulation, presence of filopodia and dilation of open canalicular system. [21]

PLATELET TRANSFUSION

Transfusion of platelets is of 2 types

- Prophylactic platelet transfusion is defined as transfusion of platelets without clinical bleeding.
- Therapeutic platelet transfusion is defined as transfusion of platelets with clinical bleeding. [22]
- Most of the clinical guidelines recommend that the platelet transfusion must be given to patients who develop serious hemorrhagic manifestations, that is who have platelet levels falling below $10\text{-}20\text{x}10^9\ \text{L}^{-1}$ without hemorrhage or $50\text{x}10^9\ \text{L}^{-1}$ with hemorrhage.
- But the outcome effect of platelet transfusion is very controversial. [26]
- Some studies indicate that there was no difference in hemorrhage between patients who received platelet transfusion compared to those who did not receive.
- Platelet transfusion is known to cause pulmonary edema and increased length of hospitalization and many other side effects.

Is Platelet Transfusion Necessary for most of the dengue cases??

- It is a myth that all dengue patients need platelet transfusion.
- Indeed unnecessary platelet transfusions cause more damage and puts the individual at risk of several complications. [23]
- Platelet transfusion must only be done in patients with platelet count less than 10,000 with hemorrhage.
- Most of the dengue cases can be prevented by using supportive care and medications like acetaminophen (tylenol) to alleviate pain and reduce fever.
- NSAID's like aspirin, ibuprofen must be avoided which can increase bleeding complications. [24]

Latest development in the treatment of dengue

- There are no specific medications for dengue infection.
- Therefore a dengue vaccine would represent a major advancement in the disease control.
- Dengvaxia (CYD-TDV) is the first dengue vaccine put forward by Sanofi Pasteur.
- It was first registered in Mexico in December-2015.
- Dengvaxia is a live recombinant tetravalent dengue vaccine which is evaluated as a 3- dose series in phase III clinical studies.
- It has been registered to be used in individuals from 9-45 years of age living in endemic areas.[25]

CONCLUSION

In dengue infection the hospitalized individuals are divided into high, moderate, low and no risk patients based on the severity and platelet count.

Moderate and low risk patients can be treated with drugs and natural therapy. In high risk patients the treating physician must take the decision whether to opt platelet transfusion or not. Majority of the studies conducted prove that harmful effects of platelet transfusion overthrown the benefits of it in patients with thrombocytopenia. Therefore unnecessary platelet transfusions must be avoided and supportive care and preventive measures are to be followed. There is a need for further research and development on patients without affecting the progenitor cells, in order to control the complications of thrombocytopenia.

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