Short Communication

Platelet indices in acute viral infections

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Abstract

An acute viral infection is characterized by rapid onset of disease, a relatively brief period of symptoms and resolution within days. There will be early production of infectious virion, accompanied by elimination of infection by the host immune system. Evaluation of haematological profile in acute viral infections serves as a clue for prognosis of disease per se. This includes RBC, WBC and platelet count and their indices. Platelet indices include the count, mean volume, distribution width and Platelet – large cell ratio. Though, Platelet indices could be done by a 3-part differential cell counter, it's usage in routine practice is not common. Hence, the role of platelet indices in acute viral infections has been explored in this article.

Key Words : acute viral infection, platelet indices

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Introduction

Acute viral infections begin with an incubation period, during which the genomes replicate and the host innate responses are initiated. The cytokines produced early in infection lead to classical symptoms such as aches, pains, fever, malaise, and nausea. Influenza and rhinovirus have incubation period as short as 1 day in which symptoms are produced by local viral multiplication near the site of entry. Incubation periods for some infections, such as HPV is 50-150 days and HIV 1-10 years and the symptoms are likely to be produced by virus- or immune-induced tissue damage far from the site of entry.

An example of a classic acute viral infection is uncomplicated influenza. Virus particles inhaled in droplets begins to replicate in ciliated columnar epithelial cells of the respiratory tract and produce symptoms within 48 hours. The infection is usually cleared by the innate and adaptive responses in 7 days. However, the patient usually feels unwell for several weeks, as a consequence of the damage to the respiratory epithelium and the cytokines produced during infection.

Six coronaviruses which can infect humans have been discovered, so far. HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1 cause common cold,

SARS-Co V causes severe acute respiratory syndrome and MERS-Co V causes Middle East respiratory syndrome. These viral infections can directly infect bone hematopoietic and bone marrow stromal cells causing hematopoietic dysfunction.

Usually, hematological profile carried out in these infections, guide the physician in treatment. Platelets are dynamic cells that participate in inflammation and pro thrombotic events in many viral infections.[1] In recent years, immune function of platelets is appreciated as it mediates a response to RNA viruses such as influenza.

Further, SARS-CoV-2 also can affect platelet count and platelet response to this virus is documented worldwide.[1-3]Though, platelets are involved in pathophysiology of disease per se in COVID 19 disease, dengue fever and flu, evaluation of platelet indices in these diseases as a protocol is lacking widely. Hence, the role of platelets and platelet indices in acute viral infections has been explored in this article.

Platelet indices

Platelet indices such as platelet count, mean platelet volume (MPV), platelet distribution width (PDW), and platelet large cell ratio (P- LCR) which can be done by any 3-part differential cell counter.[4]

1. Mean platelet volume

MPV is a calculated measure of platelet volume expressed in femto liter (fL). In hypo production of platelets, immature platelets are activated and increase in size by pseudopodia formation leading to increase in MPV(4). Hence, increased MPV can be used as a marker of production rate and platelet activation. Normal range of MPV is between 7.2 and 11.7 fL. High MPV with thrombocytopenia represents peripheral destruction. Low MPV indicates under production/bone marrow suppression. MPV is inversely related to platelet counts.[4]

2. Platelet distribution width

PDW measures variability in platelet size and reflects the heterogeneity in morphology of platelets. It changes with platelet activation and serves as an indicator of platelet anisocytosis. PDW is increased in the presence of platelet anisocytosis. PDW and P-LCR are analyzed from a histogram of platelet size distribution. The distribution width at the level of 20% (the peak of the histogram is 100%) is defined as PDW.[4]

3. Platelet larger cell ratio

The percentage of platelets of size more than 12fL was defined as P-LCR.(4). It is an indicator of circulating larger platelets (>12 fL), expressed as percentage (normal-15%–35%). It is used to monitor platelet activity. P-LCR is inversely related to platelet count and directly related to PDW and MPV. It is decreased in patients with thrombocytosis and increased in thrombocytopenia.[4]

Role of platelets in acute viral infections

Platelets detect and respond to pathogens in the vasculature. Platelets exhibit several pattern recognition receptors (PRR) such as Toll-like receptor, NOD-like receptor and C-type lectin receptor family. These receptors help in recognizing viral pathogens such as dengue, HIV-1 and influenza. Once platelets sense the invading

pathogens, they interact with neutrophils, monocytes and lymphocytes and causes amplification of immune response. Indirectly, through the release of cytokines and antimicrobial peptides further activation occurs. This is termed as Immune thrombosis.[3] It initiates adverse immunological and haemostatic processes and thereby contributes to adverse clinical outcomes such as vascular thrombosis, organ failure and death.

1. Platelet indices in influenza

Recently, it has been noted that platelets can phagocytose influenza virus. It can be rapidly adsorbed onto human blood platelets at 4˚C and completely eluted at 37˚C. Ozcelik et al compared platelet indices of influenza and COVID 19 affected patients and revealed influenza pneumonia and COVID pneumonia were similar in many aspects and that there is no statistically significant difference between these two diseases both radiologically and symptomatically.[5]However, they observed mean platelet levels in influenza patients are lower than those of COVID-19 patients.

2. Platelet indices in Dengue

Dengue is the most common haemorrhagic viral disease, causing seasonal outbreak in Tamil Nadu annually. Its Spectrum of clinical manifestations ranges from mild self-limiting dengue fever (undifferentiated febrile illness) to life-threatening dengue haemorrhagic shock syndrome due to hemodynamic dysfunction including coagulopathy and vasculopathy. Thrombocytopenia is an alarm marker in dengue fever and serially monitored in these patients. The drop in platelet count coincides with hemodynamic instability and progression to severity and platelet count recovery associates with clinical improvement.[3] Following are the probable pathophysiologic mechanisms documented in literature.[3,6]

1. Increased levels of cytokines and pro-inflammatory mediators targeting the vascular endothelium as a consequence of viral entry.

2. Lymphocytes, monocytes, macrophages and dendritic cells amplifying the immune response.

3. Profound platelet activation caused by surface markers of activation such as P-selectin and CD63 expression, phosphatidylserine exposure and inside-out activation of αIIbβ3 integrin.

4. Activated platelet deposition in the microvascular bed in the peripheral vessels.

Thrombocytopenia in dengue patients in first week of illness could be the result of

1. Direct bone-marrow suppression of thrombopoiesis

2. Modulation of endothelial cell by dengue virus

3. Destruction of platelets by Anti-NS1 antibodies directed against the virus cross-reacting with the platelets.[3,4]

Increase in MPV in dengue is due to platelet activation, pseudopod formation and increased immature platelets (larger in size) released from bone marrow. When platelet production is decreased, young platelets become bigger and more active, and MPV values increase. Increase in MPV together with a stable platelet count indicates recovery whereas a persistently elevated MPV together with ongoing thrombocytopenia is suggestive of active disease. P-LCR is inversely related to platelet count and an increased P-LCR is seen

in destructive thrombocytopenia. PDW is reported to be higher in dengue fever. Low platelet count and high PDW may be used as predictors of severity of dengue infection.[4]

3. Platelet indices in COVID 19

Manne et al, for the first time found that the platelet transcriptome are altered in COVID-19 patients, as compared to healthy donors. Further, hundreds of platelet transcripts were differentially expressed during COVID-19 and were distinctly different from those transcripts altered during pandemic influenza A/H1N1 or sepsis. This suggests there may be unique aspects of COVID-19 infection on platelets that are distinct from those changes triggered during sepsis and pandemic influenza A/H1N1.[7]

Guclu et al in Turkey studied oxygen saturation and MPV at the time of admission, Day 1 and Day 3 during hospitalization in COVID 19 patients. They showed that mortality was 8.4 times higher in patients with oxygen saturation lesser than 90 % and 1 unit increase in MPV between Day 1 and day 3 of hospitalization, increased mortality by 1.76 times. They have stressed that MPV may be used as an auxiliary test in predicting the mortality in COVID-19 patients.[8]

Zaid et al documented SARS-CoV-2 RNA inside platelets in COVID-19 affected patients and revealed the modulation of platelet-associated cytokine levels in them. Further, they demonstrated the release of contents from alpha and dense granules and extracellular vesicles in platelets. From this, it is evident that platelets contribute to cytokine storm by their inflammatory action.[9]

Hypothesis put forth for decreased platelet count in COVID 19 disease [6, 7, 10, 11]

1. Bone marrow suppression caused by the infection and the decrease in the production of the platelets.
2. Destruction of the platelets as a result of the increased immune response
3. Consumption of the platelets by the formation of the micro thrombi in the lungs and other organs

Conclusion

Estimating Platelet indices gives clue whether there is ongoing platelet destruction or there is bone marrow suppression. Yet, Platelet indices are still underutilized parameters both by the laboratory personnel as well as the clinicians due to various reasons like variability or lack of standardization in testing and reporting and difficulty in determination of reference values. Involvement of platelets in acute viral infection signifies the importance of evaluating platelet indices at the earliest.

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