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REVIEW ARTICLE

Platelets in Kawasaki disease: Is this only a numbers game or something beyond?

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Abstract Kawasaki disease (KD) is a medium vessel vasculitis with predilection to cause coronary artery abnormalities. KD is now the most common cause of acquired heart disease in developed countries. Thrombocytosis is consistently found in patients with KD, usually in 2nd to 3rd week of illness. Thrombocytopenia has occasionally been reported in the acute phase of KD. An increase or decrease in platelet number in patients with KD was initially considered to be a benign phenomenon. However, recent literature on platelet biology in KD has suggested that platelets are not only increasing but are rather activated. This phenomenon has been found to increase the risk of thrombosis in these patients. Similarly a fall in platelet counts during acute stage of KD has also been found to be associated with increased severity of disease. In this review, we update on the current best understanding about pathogenic role of platelets in patients with KD.

Introduction

Kawasaki disease (KD) is an medium vessel vasculitis that mainly affects children below 5 years.[1] KD is the most common cause of acquired heart disease in developed countries.[1,2] Japan records the highest incidence of KD in the world with an incidence of 308.0/1,00,000 children less than 5 years in 2014.[3] The incidence of KD in Korea and Taiwan is 194.7 and 69.5/1,00,000 children below 5, respectively.[4,5] Reliable nationwide data are not available for India and China. Hospital based data from Chandigarh suggest that the incidence of KD has been found to be increasing every year.[6] Similar trends on incidence of KD are discernible in several cities from China.[7,8]

Involvement of coronary arteries is a hallmark complication of KD and this may develop in approximately 15–25%

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of untreated patients. The risk of coronary artery complications is even higher in infants with KD and it may be as high as 60%. Approximately 3–5% may develop coronary artery abnormalities even after administration of IVIg.[1]

Thrombocytosis has consistently been reported in patients with KD and is often seen in 2nd to 3rd week of the illness.[1,2,9] It was initially thought to be a benign and reactive phenomenon secondary to underlying inflammation. However, recent knowledge about platelet biology (Table 1) has suggested that platelets are not only increasing in number but they are activated as well, thereby increasing the risk of thrombosis.[10–13] Thrombocytopenia has also been found in acute phase of KD[14] and has been documented to be a risk factor for CAAs.[15–20] In this review, we update on the current best understanding about pathogenic role of elevated platelets in patients with KD.

Thrombocytosis in childhood

Thrombocytosis is defined as an increase in platelet count above the upper limit of normal (usually $>400 \times 10^9$/L).[21] Incidence of thrombocytosis varies with age and is mostly seen in children younger than 2 years. Thrombocytosis in children may be a primary or secondary phenomenon. Secondary thrombocytosis, also known as reactive thrombocytosis, is commonly seen in children with infections, connective tissue diseases, trauma, iron deficiency anaemia, malignancies and after splenectomy.[21] Approximately two-thirds of thrombocytosis seen in childhood is believed to be secondary to respiratory tract infections.[22,23] Several rheumatological disorders (as for example systemic juvenile idiopathic arthritis, vasculitides) and inflammatory bowel diseases are also important causes of thrombocytosis. Thrombopoietin and other cytokines such as Interleukin (IL)-6, IL-8 and IL-11 are key regulators of thrombopoiesis.[21]

Literature review on natural course of platelets in patients with KD

The natural course of platelet counts in patients with KD may be divided into 3 distinct phases: First phase, where platelet counts remain normal and no platelet aggregation is seen. Second phase is characterized by activation of platelets and their numbers also start increasing. This typically happens when fever starts improving and desquamation starts. This occurs mainly in the 2nd to 3rd week of illness and is secondary to release of serotonin from platelets at this stage. The third and final phase is characterized by fall in platelet counts to normal range but children who have developed coronary artery aneurysms remain at risk of thrombosis.[1,9,24] A study by Laurito et al found activated platelets many months after initial

Table 1 Studies on platelets activation and CAA physiology in Kawasaki disease.

S. no.	Author, year and reference	Conclusion from study
1	Yokoyama et al (1980)[38]	Thrombocytosis in children of KD with CAAs increases the risk for thrombosis due to hyperaggregability
2	Levin et al (1985)[21]	Thrombocytosis in KD is associated with appearance of a circulatory factor that induces aggregation and serotonin release from platelets. Platelet derived vasoactive mediators may increase vascular permeability and facilitate further deposition of immune complexes in the tissues.
3	Hamaoka et al (1996)[33]	CAAs associated with KD significantly decrease coronary flow velocity and have abnormal flow profile with reduced coronary flow reserve.
4	Straface et al (2010)[42]	Platelets in KD patients are activated and aggregated with numerous platelet aggregates and also show heterotypic adhesion properties with leukocytes and red blood cells.
5	Yahata et al (2014)[43]	Platelets were found to be activated during acute phase of KD. Aspirin led to significantly fall in PDMP levels in patients with KD. PDMP levels showed a rebound increase when aspirin was discontinued
6	Pietraforte et al (2014)[8]	Two different subpopulations of platelets in the peripheral blood exists i.e.annexin V positive platelets and annexinV negative platelets. These considerably affect inflammatory responses in KD patients.
7	Ueno K et al (2015)[44]	Circulating platelet-neutrophil aggregates play a significant role in KD
8	Kim HJ et al (2017)[45]	PDMPs are measure of platelet activity in KD. PDMPs are useful as biomarker of antiplatelet therapy in KD.
9	Lu WH et al (2017)[47]	Platelet endothelial cell adhesion molecule-1 gene polymorphism was found to be associated with increased risk of coronary artery complications
10	Jin et al (2018)[48]	Increased PDMPs in patients with KD as compared to control. Rapid decrease in level of PDMPs after treatment with IVIG and aspirin. It was hypothesized that these platelet derived particles can directly stimulate granulocytes, macropahges, monocytes and vascular endothelial cells leading to expression of tissue factors and increased risk of thrombosis.

Abbreviations: CAAs, coronary artery aneurysms; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; PDMP, Platelet-derived microparticles.

diagnosis in patients even without any obvious CAAs.[10] Thus platelets may remain active for many months after initial diagnosis of KD even though their numbers may normalize.

Thrombocytopenia is a rare finding in KD and has not been frequently reported in earlier literature. Thrombocytopenia associated with KD may occur in the acute stage of the disease on days.[19,20,25] In a study conducted by Nafech et al 31 KD patients were analyzed with thrombocytopenia and there was found to be female preponderance and a high incidence (14/31) of CAAs in these patients.[19] Niwa et al, found 10/303 patients of KD with concomitant thrombocytopenia and 6/10 patients developed CAAs, it was also noted that incidence of CAAs are higher as compared to that of controls.[26] The exact pathogenesis of thrombocytopenia in KD remains elusive but proposed mechanisms include coagulation mediated platelet consumption, destruction of platelets by immunoglobulin or as a consequence of macrophage activation syndrome (MAS). MAS has consistently been reported in KD and is cause of increased morbidity and mortality in these patients.[27–29]

Does thrombocytosis increase the risk of thrombosis?

It has been found that thrombocytosis seen in myeloproliferative disorders increases the risk of thrombosis due to giant platelets while in other diseases (such as infections) associated with reactive thrombocytosis there is no discernible increase in risk of thrombosis because of normal platelet size and function.[30] In a large cohort study by Subramaniam et al on 1000 children with reactive thrombocytosis secondary to various infections, none of the patients developed thromboembolism.[31] Several other studies have however, shown that reactive thrombocytosis also increases the risk of thromboembolism which is directly proportional to platelet count.[32–34] In a large cohort study by Ho et al on 1446 patients who were admitted to intensive care unit, 139 (9.6%) patients had reactive thrombocytosis and among these 29 (2%) patients developed venous thromboembolism. They found reactive thrombocytosis to be associated with an increased risk of subsequent venous thromboembolism after adjusting for other covariates and risk of venous thromboembolism had a linear relationship with thrombocytosis when the platelet counts were $>400 \times 10^9$/L.[32] Similarily Rinder et al showed that increased platelet turnover which is reflected by increased reticulated platelets in circulation, is a risk factor for thrombosis in patients with reactive thrombocytosis.[34]

What is the pathogenic role of platelets in patients with KD?

Increased risk of coronary artery abnormalities

Thromboytosis in children with KD and CAAs increases the risk for thrombosis due to hyperaggregability of platelets in coronary arteries. Hyperaggregability is secondary to vasculitis, immune complex platelet interactions and abnormal flow across aneurysmal vessels in patients with KD.[24,35,36] In a study on platelet functions in patients with KD by Straface et al, it was found that platelets obtained from blood samples of patients were aggregated and activated with formation of numerous platelet aggregates. Platelets in this study also showed heterotypic adhesion properties with WBCs and red blood cells as compared to platelets in control samples.[37] All these factors may promote thrombosis.

Variation in platelet homeostasis have long been hypothesized to be associated with damage to coronary arteries in patients with KD.[24,25] Levin et al showed that thrombocytosis is associated with appearance of immune complexes in the circulation that induces aggregation and release of serotonin from platelets and correlates with development of coronary artery aneurysms.[24] Autopsy findings in children with KD also suggest involvement of platelets in vasculitis and thrombosis in these children.[25] A study by Pietraforte et al on platelets of these patients found 2 separate subpopulations of platelets in the peripheral blood viz. annexin V positive platelets and annexin V negative platelets. According to the hypothesis both the sub-populations were involved in the inflammatory responses in patients with KD. Annexin V positive platelets are said to produce coagulation while annexin V negative platelets are inclined to become pro-coagulant when they come in contact with mediators such as adenosine diphosphate and thromboxane A2[11].

In a study conducted by Jin et al, increased platelet-derived microparticles (PDMP) due to platelet activation were found in patients with KD as compared to control even when platelet count was normal in these patients. Levels of PDMPs were elevated in the acute phase of KD while there was a rapid decrease in levels of PDMP after treatment with IVIg and aspirin. It was seen that these platelet derived particles can directly stimulate granulocytes, macrophages, monocytes and vascular endothelial cells leading to expression of tissue factors and increased risk of thrombosis. PDMP may also be a useful biomarker for platelet activation and inflammation seen in patients with KD.[12]

Increased risk of peripheral gangrene

Peripheral gangrene is another complication seen rarely in children with KD. Some children with KD who developed gangrene also had moderate to high thrombocytosis.[38,39] Vasculitis and vasospasm are thought to be the predominant pathogenic mechanism of peripheral gangrene in patients KD but thrombocytosis in these patients may possibly perpetuate the formation of gangrene.[38,40]

Increased risk of sensorineural hearing loss

Sensorineural hearing loss (SNHL) is an uncommon but a known complication seen in patients with KD. It is considered to be a mild and transient manifestation. SNHL in patients with KD is perhaps under recognized as most young children may not communicate that they are having difficulty in hearing and it is difficult for parents to perceive it. This complication can only be detected by routine use of audiometry or brainstem auditory evoked potential assessment (BERA), this is however not routinely performed in all patients.[35] Although the mechanism of association

between thrombocytosis and elevated risk of SNHL is not known but in one study by Alves et al, persistence of SNHL (after 6 months) was seen in 11.3% of patients and thrombocytosis was found to be a significant risk factor for development of SNHL.[41]

Role of activated platelets and CD40 ligand

CD40 ligand is predominantly expressed on activated T cells and interacts with CD40 present on B cells. This interaction is essential for class switching and production of immunoglobulins by B cells. In addition, interaction of CD40L-CD40 is also involved in various inflammatory pathways including the inflammation in the acute stage of KD. However, secretory form of soluble CD40L is predominantly released from activated platelets and has been found to play important role in coronary artery disease. In preliminary study carried out at our centre, it was found that soluble CD40L seen in the acute stage even in patients who had received treatment with IVIg. Levels in the subacute stage of patients with KD were higher as compared to levels of CD40L in the acute stage, despite adequate treatment with IVIg in all patients (Unpublished data). It has also been found that patients with KD demonstrate abnormal vascular reactivity many years after the occurrence of KD even when they have no obvious coronary artery abnormalities.[10,42–44] This has been suggested by studies performed on abnormal brachial flow mediated dilatation and carotid intima media thickness in patients with KD. These results suggest that IVIg alone may not be sufficient for completely reversing the abnormal vascular changes in patients with KD. Role of activated platelets may at least partially be responsible for these vascular effects.

Treatment recommendations for elevated platelet counts

No treatment is recommended for reactive thrombocytosis unless patients have another risk factor for occurrence of thrombosis.[22,31] Aspirin is recommended to be given to all patients with KD in acute stage in anti-inflammatory dosages (30–50 mg/kg/day or 80–90 mg/kg/day) till the time of defervescence and in antiplatelet dosages (3–5 mg/kg/day) for at least 6 weeks.[1,45–47] The duration of aspirin therapy is recommended to be longer in patients with persistent coronary artery abnormalities.[1]The duration of therapy depends on the degree of coronary artery abnormalities present. There is controversy regarding the dosages and duration of aspirin therapy in KD. Few studies have shown that there is no significant outcome difference in low dose (3–5 mg/kg/day) and medium/high dose (30–50 or 80–100 mg/kg/day) aspirin therapy and high dose may lead to complications like anaemia and overt bleeding.[48–51] A recent review on treatment options in KD by Pilania et al has shown some concerns after use of high dose aspirin viz. negative impact on IVIG effects; increased expression of tumor necrosis factor-α and anemia.[52]

Yahata et al[13] showed that platelets are activated during the acute phase of KD and aspirin as an antiplatelet agent significantly change PDMP levels. PDMP levels rebounded when aspirin was discontinued after 2–3 months and duration of platelet activation varied among individual patients and persisted longer than previously thought. They also showed significant effect of IVIg in decreasing PDMP levels which may act secondarily by reducing platelet activation by suppressing inflammation. Other mechanism of immunomodulatory effects of IVIg hypostheized are, stimulation of the inhibitory FcgRIIb receptors, neutralization of conventional antigens or superantigens and intractions with dendritic cells, neutrophils and T cells.[53]

Conclusion

We conclude that, along with platelet number, platelet activation may be a major determinant of various complications associated with KD, which confirms the rationale of antiplatelet therapy in KD. PDMP level may be used as new a biomarker of platelet activation and vasculitis in KD. As recent literature suggests that platelet functions determines the risk of complications and there is no difference in outcome in low vs high dose aspirin therapy, low dose (3–5 mg/kg/day) aspirin therapy may come up as standard of care in these patients in future. As the dynamics of platelet activation and flow hemodynamics in vessels of patients with KD is not completely understood and so is the role of use of aspirin, further studies are needed to exactly define these. Furthermore, the decision of initiation and duration of antiplatelet and anticoagulant agents should also be based on combination of dynamics of platelet activation, hemodynamic parameters and geometric dimension of aneurysm in KD.

Conflict of interest

The authors declare no conflict of interest.

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