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Case Report

Glanzmann thrombasthenia in a child manifesting after dengue infection

Maj Safal Muhammed^a, Gp Capt S.S. Dalal^{b,*}, Surg Capt K.M. Adhikari^b,
Surg Cmde Sheila S. Mathai^c

^a Clinical Tutor, Department of Pediatrics, Armed Forces Medical College, Pune 411040, India

^b Professor, Department of Pediatrics, Armed Forces Medical College, Pune 411040, India

^c Professor & Head, Department of Pediatrics, Armed Forces Medical College, Pune 411040, India

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Introduction

Glanzmann thrombasthenia is a rare, autosomal recessive disorder of platelets, characterised by failure of platelets to bind fibrinogen and aggregate after getting activated. Described for the first time in 1918, the historical importance of this rare disease is that the unravelling of its pathophysiology led to the development of antiplatelet drugs. In this article, we present a case of Type I Glanzmann thrombasthenia which manifested after an episode of dengue infection.

Case report

A 13-year-old male patient, fifth born of a non-consanguineous marriage, resident of Pune district (Maharashtra) with no past history of easy bruisability or bleeding tendency, presented

with history of recurrent gum bleeds and cutaneous petechial haemorrhages of seven months duration. This was associated with easy bruisability in response to trivial trauma. All the complaints seemingly started after hospitalisation for dengue fever (confirmed by serology) during which he received multiple platelet and packed RBC transfusions. There was no family history of bleeding or easy bruising. On examination, the patient was hemodynamically stable and had petechiae all over the body. General examination revealed pallor and gum hyperplasia. Liver was palpable 3 cm below right subcostal margin (span 11 cm) and was non-tender with smooth margins. There was no splenomegaly. Other systems were all normal. Investigations revealed microcytic hypochromic anaemia (Hb – 9 g/dL), normal platelet count (3.5 L/mm^3) and morphology. PBS did not show any atypical cells or blast cells or any evidence of hemolysis. PT, PTTK and INR were within normal limits. ANA, anti-dsDNA, RA factor, cANCA and pANCA were negative. Von Willebrand factor level was normal (131%). In view of normal platelet count and coagulation profile and no evidence of vasculitides, a diagnosis of a platelet function disorder was considered. Platelet aggregation testing using platelet function analyser showed ristocetin aggregation of 22% and no aggregation with ADP and collagen. Flow cytometry for platelet glycoprotein receptors revealed normal levels of GP Ib, GP IX and fibrinogen and negligible quantity of GP $\alpha\text{Ib}\beta 3$ (0.04%).

Based on the platelet aggregation pattern and low glycoprotein $\alpha\text{Ib}\beta 3$ on flow cytometry, a diagnosis of Glanzmann thrombasthenia was made. Gene mutation studies and screening of other family members were not done in view of financial constraints. Parents were counselled regarding the nature of the disease, avoidance of trauma and contact sports,

* Corresponding author. Tel.: +91 8412015551.

E-mail address: dalalshamsher@gmail.com (S.S. Dalal).

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NSAIDs and early medical consultation in case of any bleeding manifestation. The patient was started on iron supplementation (in view of iron deficiency anaemia), folic acid and vitamin C. On follow-up after one month, his haemoglobin increased to 12 gm% and platelet count decreased to 2.5 Lac/mm³. He has had no significant bleeding episodes at 6 months of follow-up.

Discussion

Glanzmann thrombasthenia is a rare, autosomal recessive disorder of platelets, characterised by failure of platelets to bind fibrinogen and aggregate after getting activated. It is the most common inherited platelet disorder, first described in 1918 by the Swiss Paediatrician Glanzmann when he noticed a certain bleeding disorder with normal platelet counts but abnormal platelet retraction. The defect is an abnormality of the genes encoding either chain of the integrin α IIb β 3 receptor. This receptor abnormality causes a failure to bind fibrinogen and other adhesive ligands.

Most cases of Glanzmann thrombasthenia are noted in specific populations or in the setting of consanguinity. Our patient was born through third degree consanguinity. The populations having relatively high incidence of the disease are South Indians, Arabs, Iraqi Jews and French Jews.¹

Spontaneous mucocutaneous bleeding is the most common presentation. Epistaxis and gastrointestinal bleeding are the most consistent features and may even necessitate iron supplementation in the patients. Five to ten percent lifelong mortality rate is accounted by intracranial and gastrointestinal haemorrhage. Rarely, patients may experience joint bleeding and muscle haematomas similar to haemophilia.²

The disorder has been divided into three types. Type I and Type II result from mutations of GPIIb or GPIIIa causing absent (<5% of normal) or reduced (10–20% of normal) expression of the α IIb β 3 complex on the platelet surface respectively. Expression of α IIb β 3 complex in asymptomatic heterozygotes is 50–60%. Type III results from rare mutations which results in a dysfunctional complex that is expressed at a normal or subnormal level. The severity of bleeding manifestation does not depend upon the type of disease.^{1,2} Our patient had negligible quantity of GP α IIb β 3 (0.04%) and thus fit into Type I disorder.

Investigations in Glanzmann thrombasthenia reveal normal platelet count and morphology. Bleeding time is prolonged and clot retraction is diminished or absent. The platelets show no or reduced response to physiological agonists of aggregation such as ADP, collagen, thrombin and adrenaline. They, however, demonstrate aggregation in response to ristocetin. Definitive diagnosis is made by flow cytometry and immunoblot analysis both of which can determine levels of α IIb β 3.¹ DNA sequencing for mutation analysis of gene encoding platelet glycoprotein alpha-IIb (ITGA2B) on chromosome 17q21.31 or the gene encoding platelet glycoprotein IIIa (ITGB3) on chromosome 17q21.32 is available and is required for genetic counselling.

Local compression strategies or application of thrombin can be useful during a bleeding episode. Platelet transfusions can be used for life-threatening haemorrhages, until resistance to platelet transfusions develop by formation of

antibodies.¹ Recombinant factor VII has been demonstrated to be a useful adjunct to platelet transfusions, particularly in the setting of refractoriness to platelet transfusions.³

In our patient, spontaneous bleeding started following dengue. Dengue is known to cause platelet qualitative and quantitative defects. Dengue causes platelet activation which manifests initially as increased expression of α IIb β 3, lysosomal marker CD63 and alpha granule marker CD62P (P-selectin). This activation, however, eventually leads to platelet function defects reflected by an overall reduction in activated α IIb β 3 and CD63 expression. This platelet dysfunction caused by dengue could have precipitated spontaneous bleeding in this child with pre-existing low α IIb β 3 expression due to underlying genetic defect of thrombasthenia.⁴ Secondly, dengue NS1 antigen has a tendency to elicit immune activation and antibody production against multiple platelet antigens and extracellular matrix proteins. Antiplatelet antibodies have been reported to have the capability to bind to dengue non-structural protein 1 (NS1).⁵

Production of antiplatelet antibodies in Glanzmann thrombasthenia is a well-known phenomenon after multiple platelet transfusions which our patient had received when he had suffered dengue. However, Ghosh et al. have described development of antiplatelet antibodies against α IIb β 3 in Glanzmann thrombasthenia in patients who have never had any platelet transfusions. In their study, 15 patients of Glanzmann thrombasthenia with no prior history of platelet transfusions were found to have antiplatelet antibodies. Molecular mimicry has been proposed as a probable mechanism for this. However, further studies are required before we can conclusively identify a cause for this antibody production.⁵

The unusual facet of this case meriting reporting is the role of dengue in causing persistent platelet dysfunction by functional depletion of α IIb β 3 which can precipitate bleeding manifestation in a child with a genetic deficiency.

Conflicts of interest

The authors have none to declare.

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