MEDVIX PUBLICATIONS

Journal of Medical and Clinical Case Reports
Case Report | Open Access | ISSN 2997-6022 | Volume 01 | Issue 03

Glanzmann's thrombasthenia presenting as post circumcision persistent bleeding in an apparently healthy boy.

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Received date: 07 May 2024; **Accepted date:** 20 May 2024; **Published date:** 23 May 2024

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Citation: Indre Zaparackaite, Shailinder Jit Singh, Swamy KB, Debashish Bhattacharya, Rafael Cavalcante Correia, Partap Kumar Midha, Ramnik V Patel. Glanzmann's thrombasthenia presenting as post circumcision persistent bleeding in an apparently healthy boy. Journal of Medical and Clinical Case Reports 1(3). https://doi.org/10.61615/JMCCR/2024/MAY027140523

Abstract: We report an otherwise normal, apparently healthy 9-year-old boy having no past or family history of bleeding who presented with persistent bleeding after a cultural circumcision. The patient had a history of consanguinity, a normal physical examination, and all the initial blood tests, including complete blood count {CBC} and first-line coagulation screens assay, were normal. Postoperatively, the bleeding time and peripheral smear studies were abnormal, suggesting qualitative platelet disorder. The patient did not respond to a combination of hemostatic agents, including local measures such as fibrin sealants, topical thrombin, and oral tranexamic acid therapy. A second-line coagulation assay was normal, but for the peripheral blood film for a qualitative study of the platelets, Platelet Function Analyzer (PFA-100) and Light Transmission Aggregometry {LTA) tests suspected Glanzmann's thrombasthenia, which was confirmed by Flow cytometry {FC} showing the absence of αIIbβ3. Treatment recommendations were made with recombinant activated factor VII, good control of persistent post-circumcision bleeding was achieved, and CBC remained stable; at follow, the patient is doing well.

Keywords: Autosomal recessive, bleeding time, circumcision, coagulation, Glanzmann thrombasthenia, hemorrhage, inherited qualitative platelet disorder, consanguineous, ITGA2B, ITGB3.

Abbreviations- GT- Glanzmann's thrombasthenia, PFA (100)- Platelet Function Analyzer, LTA- Light Transmission Aggregometry, FC- Flow cytometry Integrin αIIbβ3-Integrin Alpha II beta 3- Monoclonal antibodies, natural products, and small peptides, CBC-complete blood count, IPFD- Inherited platelet function disorders, Hb -Hemoglobin, MVC-Mean Corpuscular Volume, PLT-Platelets, INR-International ratio, APTT-Activated Partial Thrombin Time.

Introduction

Glanzmann's thrombasthenia (GT) is a rare congenital inherited autosomal recessive hemorrhagic platelet quantitative and qualitative abnormal functional disorder with prolonged bleeding time, decreased or absent clot retraction, and a marked reduction in platelet aggregation. GT has an incidence of 1 per 1 million population. GT is due to a deficiency of the receptor called platelet integrin alpha IIb beta3. Integrin is very much required for platelet aggregation and hemostasis, and the integrin is the platelet fibrinogen receptor. GT is caused by quantitative or qualitative defects of αIIbβ3, an integrin expressed on the platelet membrane, coded by the ITGA2B and ITGB3 genes. We wish to report an unusual case of persistent post-circumcision bleeding in an apparently healthy boy.

Case Report

An otherwise healthy 9-year-old boy, having consanguinity and no past or family history of bleeding, was brought to us for cultural circumcision. Blood tests performed at admission showed Hb 12.4 g/dl, MCV =70 fL, ferritin 9 ng/ml, PLT= 240000/mmc, INR=1.2, APTT= 27 sec, fibrinogen: 336mg/dL.

The circumcision was carried out uneventfully, but he developed persistent mild oozing at the circumcision site. Due to the persistence of bleeding, a

combination of hemostatic agents, including local measures such as fibrin sealants, topical thrombin, and oral tranexamic acid therapy, was tried without success. Repeat blood tests showed Hb 9.1 g/dl, MCV 69 FL, and ferritin 6. A hematology referral was made, and second-level coagulation assays were requested to rule out functional platelet defects or von Willebrand disease, and oral iron supplementation was for anemia.

PFA-100 showed abnormal platelet function for both collagen/epinephrine (208") and collagen/ADP (156"), while coagulation assays were normal: FVIII:c112% vWF: Rcof 50.2%, vWF: Ag 69%. LTA was then requested, showing a marked inhibition of platelet aggregation for all agonists except for ristocetin. Glanzmann's disease was then suspected and confirmed by FC, showing the absence of αIIbβ3. The following treatment recommendations were then performed: tranexamic acid therapy for mild mucocutaneous bleeding, recombinant activated Factor VII (rFVIIa), and platelet transfusion for severe bleeding.

Discussion

Among the inherited platelet disorders, Glanzmann thrombasthenia (GT) is the most frequently presented disease **[1]**. GT was first reported as "hereditary hemorrhagic thrombasthenia" in 1918 by a Swiss pediatrician called Eduard Glanzmann **[2]**. GT has a global prevalence of 1 in 1 million in general; however, in regions of high consanguinity, it is higher in particular **[3]**. In a recent study, 13 (86.7%) of 15 patients stated consanguinity reflected by homozygosity findings in 14 (93.3%) patients **[4]**.

Inheritance is usually autosomal recessive. Pathogenic variants in the receptor-coding genes ITGA2B and ITGB3, located on the long arm of chromosome 17 (q21–22), have been implemented as causative factors. ITGA2B has 17 kb and 30 exons; ITGB3 has 46 kb and 15 exons. The receptor's pathogenic variants may cause qualitative or quantitative disorders in the expression of the αIIbβ3 receptor.

GT can be classified as type 1 (<5% of normal αIIbβ3 level) or type 2 (5–25%) depending on the αIIbβ3 expression. In addition, the receptor may be normally expressed; however, functionally impaired, resulting in defective binding of fibrinogen **[5]**.

GT is occurring in populations with a high incidence of consanguineous marriages. Ours is a population with very low consanguinity; the history of consanguineous marriage is a very important clue. In our case, consanguinity was ignored initially, and normal initial standard coagulation basic series being normal gave us a false sense of security, delaying the detailed study. Moreover, bedside laboratory with peripheral smear study and bedside bleeding time tests would have given some clues to the qualitative defects of the platelets as the platelet count was normal in the study.

GT clinically presents with a moderate to severe bleeding tendency with a normal platelet count. It is associated with recurrent mucocutaneous bleeding, mucosal gum bleeding, epistaxis, purpuric skin rash, and menorrhagia in females. Bleeding episodes are usually not fatal; however, life-threatening bleeding can occur in case of surgery in mucocutaneous regions, like circumcision in our case.

Inherited platelet function disorders (IPFDs) are heterogeneous in severity, mechanisms, and frequency in general, and GT, in particular, can be challenging for diagnosis and treatment due to the difficult access to clinicians and laboratories with the required expertise and resources. There is no standardized protocol for the diagnosis of IPFD, and many laboratory techniques used for assessment are insufficiently standardized, technically challenging, and poorly reproducible. Several surveys have shown a significant heterogeneity in diagnostic approaches. Consequently, only a minority of patients investigated for mucocutaneous bleeding are currently diagnosed with IPFD **[8]**.

For the diagnosis of GT, it is essential to evaluate the personal and family history. The occurrence of spontaneous cutaneous or mucosal bleeding, such as petechiae, purpura, or easy bruising, needs to be evaluated. Conventional tests, including complete blood cell count (CBC) and first-level coagulation assays, are usually normal, even if platelets may have an increased volume. In some centers, a Platelet function analyzer (PFA-100) is performed to preliminary evaluate the platelet's function as a low-specificity test for screening purposes. Confirmatory diagnosis of GT is made by light transmission aggregometry (LTA), the gold standard method due to its high sensitivity and specificity, in which platelet aggregation is absent for all agonists (ADP, collagen, thrombin, arachidonic acid), but the response to ristocetin is maintained. Flow cytometry (FC), performed with monoclonal antibodies specific for platelet membrane receptors, rapidly confirms the deficiency of αIIbβ3. FC allows us to distinguish three types of GT: type I, in which αIIbβ3 is absent; type II, in which reduced αIIbβ3 is observed; and type III/variant, in which αIIbβ3 may be expressed but is not functional. Genetic diagnosis can help to improve disease management by directing genetic counseling, prenatal diagnosis, and carrier screening in asymptomatic family members, especially in regions with high consanguinity, even if it is expensive.

Management of bleeding is based on a combination of topical and systemic therapies. Localized bleeding can be treated with conservative local measures such as the application of gauze pads and/or fibrin sealants containing fibrinogen, thrombin, factor XIII, and aprotinin, or fibrin-coated collagen fleece. Systemic therapy includes oral tranexamic acid therapy, with antifibrinolytics or desmopressin, recombinant activated factor VII with or without platelet transfusions **[8]**. Refractory bleeding and platelet alloimmunization are common complications. A potential reduction in platelet refractoriness, therefore, is treated by favoring transfusions of platelets from HLA-matched donors. Unfortunately, the short half-life of platelets and platelets availability makes it difficult to obtain HLA-matched donor platelets, particularly in emergency cases.

Conclusion

IPFDs should be suspected, especially in male patients with consanguinity, bleeding symptoms, a normal quantitative platelet count, in the absence of coagulation alterations and an abnormal bleeding time, and qualitatively poor platelets on peripheral smear. Clinical bedside research is crucial due to the rarity of the disease. The absence of specific therapies, especially in young children with excessive post-circumcision bleeding, is another consideration. Diagnosis should be established promptly to enact an effective bleeding

control, mainly based on a combination of accurate, detailed, comprehensive targeted history, simple bedside tests such as peripheral smear and bleeding time, and advanced level two or three laboratory assays. Management should be tailored to the severity and response to various measures undertaken. The prognosis is usually good.

Compliance with ethical standards:

Acknowledgments

We are grateful to Dr. Jitendra G Govani, Primary Care Physician, for referring the patient to us and to Dr. Anil Kumar Trambadia, MD, DCH, and Dr. Kavita Trambadia, MD, DCH consultant pediatricians monitoring the growth, development, and follow-up care.

Conflict of interest

The authors have no conflict of interest to declare. No funding source was involved in this study.

Ethical approval

All procedures performed on human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from the parents and all the relatives involved prior to all the procedures. Parents and all involved parties were informed about the procedure.

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