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CASE REPORT

Glanzmann's thrombasthenia due to a novel mutation in *ITGA2B* gene

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ABSTRACT

Background: Glanzmann's thrombasthenia (GT) is a rare congenital bleeding disorder clinically presented with mucocutaneous bleeding associated with trauma and/or surgery. Patients with GT have normal platelet count but prolonged bleeding time. GT is been reported to be associated with mutations in the genes, which encode for glycoprotein IIb/IIIa (GPIIb/IIIa).

Case presentation: A 2-year-old male patient with a history of recurrent nasal bleeding for 1 year was presented to us. Bleeding time was found prolonged (9 minutes), while activated partial thromboplastin time was 37 seconds, prothrombin time (PT) was 13.5 seconds and remained within the normal range. Platelet aggregation assays were defective when using adenosine diphosphate, adrenaline, collagen, and arachidonic acid. Genetic analysis found a novel likely pathogenic homozygous mutation c.985G > T in the *ITGA2B* gene. The subjects were controlled by using 1 g of aminocaproic acid twice daily for 10 days, which improved the bleeding time was improved to 6 minutes.

Conclusion: The present study reported a child (2 years) with novel pathogenic mutation c.985G > T in the *ITGA2B* gene associated with GT and reviewed its clinical management.

Keywords: Glanzmann's thrombasthenia, mutation, bleeding, platelets aggregation.

Introduction

Glanzmann's thrombasthenia (GT) was first reported in 1918 by a Swiss Pediatrician Eduard Glanzmann, who described it as a functional abnormality of platelets with defective clot retraction [1]. GT was later studied to be associated with a defect in glycoprotein IIB/IIIa, leading to abnormal aggregation. GPIIb/IIIa is a receptor complex on platelets, which is responsible for mediating platelets binding to fibrinogen. There is no or decreased platelet aggregation in the presence of adenosine diphosphate (ADP), epinephrine, thrombin, and collagen. In GT, the platelet count is usually normal. Platelets are abundant in number, but their function is impaired. GT is inherited as an autosomal recessive disorder. Due to the deficiency of platelet function, GT manifests a bleeding disorder characterized by mucocutaneous hemorrhage of varying severity. The *ITGA2B* gene responsible for GT was found to be located on the long arm of chromosome 17 at q. The incidence of GT is about 1 in 1,000,000 with an equal sex predilection. It has been reported a high incidence in populations where intermarriages are common [2].

Case Presentation

A 2-year-old male patient with a history of recurrent nasal bleeding for 1 year was presented to us. The subject was screened based on platelet counts and morphology. Medical histories and demographic characteristics of the patient were recorded. Platelet aggregation tests were performed at Umm Al-Qura hospital laboratory using ristocetin, epinephrine, ADP, and collagen. Bleeding time measurements were performed and compared with reference values: 0–4 years, 4 ± 1 min; boys >4 years, 5 ± 1 min; girls >4 years, 5.5 ± 1 min. Bleeding time was found prolonged (9 minutes), while activated partial thromboplastin time was 37 seconds, prothrombin time (PT) was 13.5 seconds and remained within the normal range. Platelet aggregation assays were defective when using ADP, adrenaline, collagen, and arachidonic acid. Genomic DNA was extracted from peripheral blood leukocytes isolated from whole blood obtained from the patient. Exon polymerase chain reaction (PCR) was used to amplify all coding regions of the *ITGA2B* and *ITGB3*

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genes (using reference sequences NM_000419 and NM_000212, respectively). PCR products were purified and Sanger sequenced. The ExAC database was used to determine the pathogenicity of novel mutations.

Genetic analysis found a novel likely pathogenic homozygous mutation c.985G>T, p.Val329Phe in the *ITGA2B* gene. This missense variant replaces a valine by phenylalanine. The detected polymorphism has not been reported with clinical significance in the scientific literature and was not found in the ExAC database. Based on the current knowledge, it was classified by the reference laboratory as likely pathogenic. The subjects were controlled by using 1 g of aminocaproic acid twice daily for 10 days, which improved the bleeding time was improved to 6 minutes.

Discussion

GT is an autosomal recessive disorder. The development of GT is associated with defects in the genes encoding for the two subunits of the receptor glycoprotein IIb/IIIa (GPIIb/IIIa, also known as integrin αIIbβ3), which is an integrin complex acting as a receptor on platelets surface. The αIIb and β3 subunits are encoded by separate genes (*ITGA2B* and *ITGB3*) that are closely located on chromosome 17q21-23 [3]. The stimulation of platelets is required to allow the αIIbβ3 receptor to mediate platelets aggregation by binding to soluble fibrinogen and von Willebrand factor. Platelet stimulation usually occurs after vessel wall injury [4]. Understanding the biology and the pathophysiology of this receptor is crucial in understanding the disease mechanisms in GT. Integrins are unique transmembrane heterodimer cellular structures that mediate crucial biological cellular function and cell-to-cell interaction roles. GT is classified into three types. Type I quantitative defect with GP IIb/IIIa level < 5%. Type II is also a quantitative defect with GP IIB/IIIa level 10%–20%. Type III GPIIb/IIIa level is normal but functionally abnormal. No relationship has been reported to date between disease subtype and bleeding severity [2]. The incidence of GT worldwide is about 1:1,000,000. It occurs slightly more frequently in females than in males (60%:50%). There is increased frequency reported in consanguineous marriages. It has been reported more frequently in Iraq, India, Turkey, and France [5]. In Saudi Arabia, GT has been reported by several studies. A. M. Bashawri reported a higher incidence of GT in the Eastern province of Saudi Arabia. It was found to be the second inherited bleeding disorder in Saudi Arabia; however, the exact cause for the disease in different parts of Saudi Arabia is not exactly known [6]. Previous studies have reported many cases of GT in Riyadh and Madinah, Tarek regions of Saudi Arabia. Owaidah et al. [7] reported a novel mutation in the *ITGA3B* gene among four Saudi families with GT [8].

Currently, there are at least 200 mutations identified in the ITGA2B gene and at least 130 mutations identified in the ITGA3B gene [8]. The present case was found to be due to a novel likely pathogenic homozygous mutation c.985G > T, p.Val329Phe in the *ITGA2B* gene. The symptoms of GT usually begin at birth or shortly thereafter and include the tendency to bruise and bleed easily and sometimes profusely, especially after surgical procedures. Other symptoms may include susceptibility to easy bruising, nosebleeds (epistaxis), bleeding from the gums (gingival), intermittent gastrointestinal bleeding, and/or variably large red- or purple-colored spots on the skin that are caused by bleeding in the skin (purpura) [9]. Regarding the present case, it was 2-years-old male patient with a history of recurrent nasal bleeding for 1 year.

The management of GT follows a hierarchical approach. First, the use of antifibrinolytics such as tranexamic acid or aminocaproic acid. Second, if antifibrinolytics are unsuccessful, the clinicians use more potent measures such as recombinant activated factor VII (rFVIIa). Novoseven was approved in July 2014 for the treatment of bleeding episodes, especially perioperative in adults and children with GT [10]. Third, the use of 106 platelets transfusion, especially for significant bleeding. Although it is the gold standard therapy, it is very less used for mild to moderate bleeding to avoid the development of antiplatelets' antibodies [11]. To reduce platelet alloimmunization, only leukocyte-depleted blood products should be used in patients with GT. Also, only HLA-matched platelets should be used. Fourth, for severe refractory GT, bone marrow transplant (BMT) could also be considered. BMT in GT was performed in 1994 for a 2-year-old girl with severe type I GT with frequent hospitalizations who had an HLA matched sibling. On 19 months follow-up, she was in good condition with no more bleeding episodes. Generally, two indications for BMT are reported in GT. The first indication is the development of antiplatelet antibodies. The second indication involves severe refractory bleeding episodes [12]. Other treatment for GT includes the avoidance of antiplatelet drugs (such as Non-Steroidal Anti-Inflammatory Drugs. Also, the use of combined oral contraceptives for menstruating girls who have menorrhagia has been reported in the previous studies [13]. The present study subject was controlled by using 1 g of aminocaproic acid twice daily for 10 days, which improved the bleeding time was improved to 6 minutes.

Conclusion

The present study reported a child (2 years) with novel pathogenic mutation c.985G > T in the *ITGA2B* gene associated with GT and reviewed its clinical management. The authors of the study put forward the following as a take-home message for GT clinical diagnosis: 1: Epistaxis in children is not always due to local causes. 2: Platelets functional disorders are important causes of bleeding in children. 3: GT should be suspected in any child with significant recurrent bleeding. 4: When it comes to the treatment for GT, we must have a hierarchal approach to avoid the excessive use of platelets, which may lead to antibodies production.

List of Abbreviations

ADP	Adenosine diphosphate
BMT	Bone marrow transplant

GT	Glanzmann's thrombasthenia
GPIIb/IIIa	Glycoprotein IIb/IIIa GPIIb/IIIa
PT	Prothrombin time
rFVIIa	Recombinant activated factor

Conflict of interest
The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent for publication
Informed consent was obtained from all the participants.

Ethical approval
Ethical Approval is not required in our institute for publishing anonymous case report.

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