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 genes.
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 \textit{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.

\textbf{Discussion}

\textit{GT} is an autosomal recessive disorder. The development of \textit{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 \textit{αIIbβ3}), which is an integrin complex acting as a receptor on platelets surface. The \textit{αIIb} and \textit{β3} subunits are encoded by separate \textit{ITGA2B} and \textit{ITGB3} 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.

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.

\textbf{Conclusion}

The present study reported a child (2 years) with novel pathogenic mutation c.985G>T in the \textit{ITGA2B} gene associated with \textit{GT} and reviewed its clinical management. The authors of the study put forward the following as a take-home message for \textit{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: \textit{GT} should be suspected in any child with significant recurrent bleeding. 4: When it comes to the treatment for \textit{GT}, we must have a hierarchical approach to avoid the excessive use of platelets, which may lead to antibodies production.

\textbf{List of Abbreviations}

\begin{itemize}
  \item ADP Adenosine diphosphate
  \item BMT Bone marrow transplant
\end{itemize}
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GT  Glanzmann’s thrombasthenia
GPIIb/IIIa  Glycoprotein IIb/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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References