CASE REPORT

Glanzmann Thrombasthenia in a Newborn with Heterozygous *Factor V Leiden* and Heterozygous *MTHFR C677T* Gene Mutations

Nazli Dilay Gultekin[1], Fatma Hilal Yilmaz[1], Huseyin Tokgoz[2], Nuriye Tarakci[1] and Umran Caliskan[2]

From Departments of [1]Neonatology and [2]Pediatric Hematology and Oncology; Necmettin Erbakan University Meram Medical Faculthy, Konya, Turkey.

Correspondence to: Dr Nazli Dilay Gültekin, Department of Neonatology, Necmettin Erbakan University Meram Medical Faculthy, Konya, Turkey. dilayyenihan@hotmail.com
Received: December 31, 2017; Initial review: May 07, 2018; Accepted: December 12, 2018.

Introduction: Glanzmann thrombasthenia is a rare congenital platelet dysfunction. **Case characteristics:** A 2-day-old male neonate delivered at 35 weeks' gestation was referred with extensive bruising and jaundice. His elder sibling had Glanzmann thrombasthenia, and his mother had thrombophilic risk factors. Flow cytometric analysis revealed absent CD41/CD61. A molecular thrombophilia panel revealed the presence of heterozygous factor V Leiden *G1691A* and methylenetetrahydrofolate reductase *C677T* gene mutations. **Outcome:** General precautions to avoid injuries and spontaneous bleeding were advised. **Message:** Life-threatening bleeding may not be the first finding in cases of thrombasthenia accompanied by thrombophilic risk factors.

Keywords: *Bleeding, Jaundice, Neonate, Thrombocytopenia.*

Glanzmann thrombasthenia (GT) is an autosomal recessive disorder associated with severe platelet dysfunction, with prolonged bleeding time and normal platelet count. The classic disease state is characterized by decreased levels or decreased function of the anti-glycoprotein IIb-IIIa (GPIIb–IIIa) complex, leading to absent or severely reduced platelet aggregation that results in a defective consolidation phase of clot formation [1]. Clinical findings of GT are mainly limited to hemorrhage in various areas during infancy. We present the case of a newborn diagnosed with GT and subsequently found to be heterozygous for factor V Leiden and methylenetetrahydrofolate reductase (MTHFR) *C677T* mutations.

Case Report

A 33-year-old woman (gravidity 2, parity 2) delivered a male neonate at 35 weeks' gestation via cesarean section necessitated by premature rupture of membranes. The neonate weighed 2350 g, and had Apgar score of 7 at 1 min, and 8 at 5 min of birth. Immediately after birth, the baby had extensive bruising all over his body, and developed visible jaundice on the second day of life, for which he was referred to us. The mother had a pulmonary embolism during the pregnancy which was treated with enoxaparin that was continued after delivery. The patient's 10-year-old brother had GT, presenting with bruises without trauma from 2 months of age, but no history of excessive bleeding; his molecular thrombophilia panel had not yet been assessed.

Physical examination revealed icterus and ecchymotics patch measuring 5 × 3 cm^2 on the anterior aspect of the right thigh (the site of a vitamin K injection) and smaller ecchymoses on his face, back, legs, and arms. Rest of the examination was normal. Investigations showed a white blood cell count of 7.3×10^9/L, reticulocyte count 2.23% (normal 0.5-3%), platelet count 190×10^9/L, hemoglobin 20 g/dL (12.1-17.2 g/dL), hematocrit 56.3% (36.1-50.3%), total bilirubin 34.19 mg/dL, indirect bilirubin 33.45 mg/dL, G6PD enzyme level normal, activated partial thromboplastin time (aPTT) of 23.9 s. There were no Rh, ABO, or subgroup incompatibilities between the mother and infant. The peripheral blood smear did not reveal any dysmorphic erythrocytes or other findings to indicate hemolysis; neutrophils were 40%, lymphocytes 50%, and abundant, non-clustered, and normal-sized platelets. The abdominal and transfontanelle ultrasonographies were also normal. The baby underwent an exchange transfusion, after which his total bilirubin level dropped to 23.08 mg/dL, which was managed by phototherapy for another two days. In view of this family history, a molecular thrombophilia panel was tested. The results revealed that our index patient's mother had heterozygous factor V Leiden *G1691A* and homozygous *MTHFR C677T* gene mutations. The patient's flow cytometric analysis showed that the CD41/CD61 (anti-GPIIb–IIIa monoclonal antibodies) levels were undetectable. In addition, heterozygous factor V Leiden *G1691A* and heterozygous *MTHFR C677T* gene mutations were detected. Based on

the family history and investigations, our case was diagnosed as Glanzmann thrombasthenia.

DISCUSSION

The incidence of GT is significantly higher in countries where consanguineous marriages are widespread [2]. Therefore, details about family history and age at onset are important in making the diagnosis and choosing the appropriate treatment. Patients of GT often tend to bleed throughout their lives. GT is divided into three subtypes based on the GP IIb–IIIa levels: type-I (<5% of normal), type-II (5-20%), and those with normal or near-normal GP levels but with defective functioning are classified as type III.

In terms of the differential diagnosis, due to the absence of thrombocytopenia and giant platelets, Bernard-Soulier syndrome and other giant platelet disorders were not considered. As blood coagulation parameters were normal, hemophilia was excluded. Von Willebrand factor (VWF) levels were not examined because there was no family history of the disease. We think that the lack of severe bleeding during the neonatal period in this patient with type 1 GT may have been due to an increased tendency to thrombosis. Evidence strongly suggests that the bleeding phenotype in GT cases is multifactorial as the frequency, timing, and severity of bleeding have been shown to vary among siblings in the same family [5]. Thrombophilic mutations such as factor V Leiden are thought to have a potentially protective effect as it has been observed that such mutations are more frequent in GT cases with less bleeding. However, there is no conclusive evidence to support this hypothesis [6,7].

Factor V Leiden and *MTHFR* C677T mutations are among the screening tests used to screen for thromboembolism in neonates. As in our case, it is increasingly common to test infants whose families are known to have hereditary thrombophilia. The necessity for these tests varies according to the clinical condition of the patient. Furthermore, it has been shown that thrombosis may occur in GT cases where there are also thrombophilic risk factors, even in the absence of severe platelet aggregation disorders [8,9].

Family education is the highest priority in terms of treatment options. Nonsteroidal anti-inflammatory drugs or aspirin should be avoided. While platelet transfusion is the standard treatment for severe bleeding, topical measures such as compression for superficial bleeding on accessible areas may suffice in most instances. In recent years, the use of recombinant factor VIIa has yielded good results in the prevention and treatment of bleeding [10]. The use of anticoagulant therapy is also indicated when an unexpected thrombosis develops in GT cases, accompanied by thrombophilic risk factors. As there was no history of bleeding or thrombosis in our case, no treatment apart from general precautions was recommended.

In conclusion, life-threatening bleeding may not be the first finding in thrombasthenia cases accompanied by thrombophilic risk factors. Family history can be a guide for the early diagnosis of such cases.

Contributors: NDG and FHY: managed the case and drafted the manuscript; HT: helped in diagnosis and manuscript writing; NT: manuscript revision; ÜÇ: helped in management and manuscript writing.
Funding: None; *Competing interest*: None stated.

REFERENCES

1. George JN, Caen JP, Nurden AT. Glanzmann thrombasthenia: the spectrum of clinical disease. Blood. 1990;75:1383-95.
2. McGuinn C, Bussell JB. Disorders of Platelets. *In*: Lanzkowsky P, Lipton J, Fish J, editors. Manual of Pediatric Hematology and Oncology. 6th ed. London: Academic Press; 2016. *P*. 262-301.
3. Coller BS, French DL. Hereditary Qualitative Platelet Disorders. *In*: Beutler E, Lichtman MA, Coller BS, Kipps TJ, Seligsohn U, editors. Williams' Hematology. 6th ed. New York: McGraw-Hill Co; 2001. *P*. 1551-60.
4. Nurden AT, Didry D, Kieffer N, McEver RP. Residual amounts of glycoproteins IIb and IIIa may be present in the platelets of most patients with Glanzmann's thrombasthenia. Blood. 1985;65:1021-4.
5. Nurden AT, Pillois X, Nurden P. Understanding the genetic basis of Glanzmann thrombasthenia: Implications for treatment. Exp Rev Hematol. 2012;5:487-503.
6. Nurden AT, Pillois X, Wilcox DA. Glanzmann thrombasthenia: State of the art and future directions. Semin Thromb Hemost. 2013;39:642-55.
7. Nurden AT. Should studies on Glanzmann thrombasthenia not be telling us more about cardiovascular disease and other major illnesses? Blood Rev. 2017;31:287-99.
8. Rezende SM. Secondary prophylaxis with warfarin for recurrent thrombosis in a patient with Glanzmann thrombasthenia and F5 G1691A. Br J Haematol. 2012;156:144-5.
9. Ten Cate H, Brandjes DPM, Smits PHM, Van Mourik JA. The role of platelets in venous thrombosis: A patient with Glanzmann's thrombasthenia and a factor V Leiden mutation suffering from deep venous thrombosis. J Thromb Haemost. 2003;1:394-95.
10. Solh T, Botsford A, Solh M. Glanzmann's thrombasthenia: Pathogenesis, diagnosis, and current and emerging treatment options. J Blood Med. 2015;6:219-27.