

CASE REPORT

**CONTROL OF SEVERE BLEEDING EPISODE IN CASE OF
GLANZMANN'S THROMBASTHENIA REFRACTORY TO PLATELET
TRANSFUSION THERAPY BY ADMINISTERING RECOMBINANT
FACTOR VIIa**

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Glanzmann's thrombasthenia is an autosomal recessive inherited platelet function defect. Though, quantitatively normal, the aggregation ability of platelets is reduced leading to bleeding episodes requiring transfusion of platelet concentrates. We describe a case of 13-year-old girl who had recurrent episodes of epistaxis since birth and was managed with multiple platelet concentrate transfusions and recently admitted with severe epistaxis refractory to platelet transfusion. At this stage administration of recombinant activated factor VII (fVIIa) was considered, which was initially given at 90 µg/kg dose with little control of bleeding but subsequent second dose of 120 µg/kg was administered with excellent response and immediate control of bleeding.

Keywords: Glanzmann's thrombasthenia, autosomal recessive, platelet disorder, recombinant factor VIIa, epistaxis

INTRODUCTION

Glanzmann's thrombasthenia (GT) is a rare disorder of platelet function. The basic pathology in this disease is the quantitative or qualitative deficiency of glycoprotein IIb-IIIa (GP IIb-IIIa) complex, causing inability of platelets to form haemostatic plug. This leads to bleeding episodes. It was described for the first time by Glanzmann in 1918 as 'hereditary hemorrhagic thrombasthenia'. A prolonged bleeding time and an isolated, rather than clumped, appearance of platelets on a peripheral blood smear were used as the early diagnostic criteria.¹ It is an inherited disorder of platelet function characterised by recurrent bleeding episodes. The laboratory studies show prolonged bleeding time (BT) with a normal platelet count. The global profile of coagulation is normal. Platelet aggregometry shows no response to agonists like Adenosine dinucleotide phosphate (ADP), collagen, and arachidonic acid. The molecular basis of GT is linked to quantitative and/or qualitative abnormalities of α IIb β 3 integrin receptor which mediates the binding of adhesive proteins that attach aggregating platelets and ensure thrombus formation at the sites of injury in blood vessels. Platelet α IIb β 3 deficiency should always be confirmed in new patients, preferably with monoclonal antibodies and flow cytometry.^{2,3}

Clinical presentation in patients with GT is not uniform. Some patients have only minimal bruising while others present with frequent, severe and potentially fatal haemorrhages. The site of bleeding is mucocutaneous with purpura, epistaxis, gingival haemorrhage, and menorrhagia being the most frequent features. Mostly the bleeding symptoms appear early after birth as seen in this case.

Occasionally it is diagnosed in later life. The patients are also at an increased risk of severe bleeding during pregnancy and perinatal period. Visceral bleeding in the form of haematomas is usually not a feature of GT. Patients with absent platelet aggregation and no clot retraction have been classified as having type I disease and those with absent aggregation but preserved residual clot retraction as type II disease.⁴

CASE REPORT

We present a case of 13-year-old girl who was brought to paediatrician at the age of 11 months with history of continuous oozing of blood from her vaccination site. Her physical examination did not reveal any abnormality. Her blood counts showed Hb 6.4 g/dl (hypochromic microcytic) and a platelet count of 334,000/mm³. Bleeding time was more than 15 minutes but rest of the coagulation profile including, prothrombin time and activated partial thromboplastin time were all within normal limits. Platelet aggregation studies were performed which showed no response to agonists like collagen, ADP and adrenaline but exhibited normal platelet aggregation in response to ristocetin. Based on platelet function studies a diagnosis of Glanzmann's thrombasthenia was made.

She had 4 elder siblings who were all healthy. Her parents were first cousins. There was no known history of any bleeding disorder in the family. Since the day of her diagnosis she kept on having spontaneous episodes of mucosal bleeds like epistaxis or gum bleeds and easy bruising, almost every 1–3 months. Mostly the bleeds were minor and managed at home by applying local pressure, and giving anti-fibrinolytic agents but at times hospitalisation was required for platelet transfusion.

Recently she presented to us with persistent epistaxis. Her Hb was 5.1 g/dl, platelet count of 189,000/mm³ and a bleeding time of more than 15 minutes. Nasal packing was done and she was given 24 units of platelet concentrates, 7 units of red cell concentrates and antifibrinolytic agents but her oozing persisted for the next 2 days. At this stage administration of recombinant activated factor VII (rFVIIa, Novo Seven, Novo Nordisk) was considered and initially given at 90 µg/kg dose with little control of bleeding but subsequent second dose of 120 µg/kg was administered with excellent response and immediate control of bleeding. Nasal packing was removed and patient was discharged the next day.

DISCUSSION

This disease is named after Glanzmann who described it for the first time in 1918 as 'hereditary haemorrhagic thrombasthenia'. A prolonged bleeding time and scattered appearance of platelets on peripheral blood smear were the early diagnostic criteria.¹ GT is an inherited disorder of platelet function characterized by bleeding episodes manifesting usually in early life.

A review of 177 patients with GT showed that 102 (58%) of the patients were females and the disease had an increased incidence in populations where marriage among close relatives was common.⁴ Despite variations in the severity and frequency of bleeding episodes, most GT patients receive blood transfusions.^{5,6} Local bleeding can be treated by local measures, such as fibrin sealants. Epistaxis and gingival bleeds are successfully controlled in most patients by nasal packing or using antifibrinolytic agents. The fact that most patients receive frequent platelet transfusions resulting in the production of alloantibodies against αIIbβ3, Human platelet antigen (HPA)-1 and HPA-3 are localised on GPIIb and GPIIIa, respectively, which are defective in GT, and refractoriness due to alloimmunisation may develop with recurrent platelet transfusions.⁴⁻⁶ The development of anti-HPA 1a antibodies in GT patients requires platelet transfusion from donors that lack specific antigen and may result in a variable response to subsequent platelet transfusions.^{7,8} In this case, an acceptable response to platelet transfusions was demonstrated in the previous bleeding episodes because the bleeding time always became normal and bleeding stopped, however repeated platelet transfusions administered in the last episode were not effective to stop bleeding likely due to development of anti-HPA 1a antibodies.

The treatment of GT is a challenging issue, especially when repeated platelet transfusions have induced anti-GPIIb/IIIa antibodies. Antibodies have been successfully removed prior to surgery by immunoadsorption on Protein A Sepharose.⁹ Plasmapheresis followed by platelet transfusions have

been successfully used for prevention and treatment of intra and postpartum bleeding in cases of Glanzmann's disease.¹⁰ These are complex procedures and their use is limited to specialized centres. In few patients, the condition has been thought to be sufficiently serious to consider allogeneic bone-marrow transplantation. Recombinant factor VIIa (rFVIIa) (NovoSeven) has been successfully used in cases of platelet functions defect and represents an alternative approach for early cessation of bleeding, especially for patients with antibodies and/or a history of refractoriness to transfusion.^{5,11-13} It is often used in combination with anti-fibrinolytic agents. The drug is still fairly expensive, making it a difficult choice in developing countries.

The exact mechanism of action of recombinant factor VIIa in achieving haemostasis in GT is not fully understood. FVIIa plays a key role in the initiation of haemostasis. In fact, according to a cell based model of coagulation following injury to the vessel wall, tissue factor (TF) is exposed to circulating blood and TF-FVIIa complexes are formed on the TF-bearing cells, where they activate factor X (FXa), leading to the conversion of prothrombin to thrombin.¹⁴ The limited amount of thrombin formed subsequently activates the co-factors V, VIII and XI, as well as platelets accumulated at the site of injury. The activated platelets expose negatively charged phospholipids, such as phosphatidyl serine on their membrane and FIXa, FVIIIa, and FXIa bind to this surface leading to further FX activation and full thrombin generation.¹⁵ The most important observation in this case report is that rFVIIa was not effective at low dose 90 µg/kg but excellent response was observed with dose escalation to 120 µg/kg. Further studies are needed to elucidate the mechanism resulting in activation of platelets at higher doses of rFVIIa.

REFERENCES

1. Glanzmann E. Hereditäre hamorrhagische thrombasthenie. Ein Beitrag zur Pathologie der Blutplättchen. J Kinderkranken 1918;88:113.
2. Wilcox DA, Wauthier JL, Pidard D, Newman PJ. A single amino acid substitution flanking the fourth calcium binding domain of αIIb prevents maturation of the αIIbβ3 complex. J Biol Chem 1994;269:4450-7.
3. Ruiz C, Liu CY, Sun QH, Sigaud-Fiks M, Fressinaud E, Muller JY, *et al.* A point mutation in the cysteine-rich domain of glycoprotein (GP) IIIa results in the expression of a GPIIb-IIIa (αIIbβ3) integrin receptor locked in a high affinity state and a Glanzmann thrombasthenia-like phenotype. Blood 2001;98:2432-41.
4. George JN, Caen JP, Nurden AT. Glanzmann's thrombasthenia: The spectrum of clinical disease. Blood 1990;75:1383-95.
5. Nurden AT, George JN. Inherited abnormalities of the platelet membrane: Glanzmann thrombasthenia, Bernard-Soulier syndrome, and other disorders. In: RW Colman, VJ Marder, AW Clowes, JN George, SZ Goldhaber. (eds). Hemostasis and Thrombosis, Basic Principles and Clinical

- Practice. 4th edition. Philadelphia: Lippincott, Williams & Wilkins; 2005. p.987–1010.
6. Bellucci S, Caen J. Molecular basis of Glanzmann's thrombasthenia and current strategies in treatment. *Blood Rev* 2002;16:193–202.
 7. Martlew VJ. Peri-operative management of patients with coagulation disorders. *Br J Anaesth* 2000;85:446–55.
 8. Monte S, Lyons G. Peripartum management of a patient with Glanzmann's thrombasthenia using Thrombelastograph. *Br J Anaesth* 2001;87:734–8.
 9. Martin I, Kriaa F, Proulle V, Guillet B, Kaplan C, D'Oiron R, *et al.* Protein A Sepharose immunoabsorption can restore the efficacy of platelet concentrates in most patients with Glanzmann's thrombasthenia and anti-glycoprotein IIb-IIIa antibodies. *Br J Haematol* 2002;119:991–7.
 10. Ito K, Yoshida H, Hatoyama H, Matsumoto H, Ban C, Mori T, *et al.* Antibody removal therapy used successfully at delivery of a pregnant patient with Glanzmann's thrombasthenia and multiple anti-platelet antibodies. *Vox Sang* 1991;61:40–6.
 11. Poon MC, D'Oiron R, Von Depka M, Khair K, Negrier C, Karafoulidou A, *et al.* International Data Collection on Recombinant Factor VIIa and Congenital Platelet Disorders Study Group: Prophylactic and therapeutic recombinant factor VIIa administration to patients with Glanzmann's thrombasthenia: results of an international survey. *J Thromb Haemost* 2004;2:1096–1103.
 12. Bellucci S, Devergie A, Gluckman E, Tobelem G, Lethielleux P, Benbunan M, *et al.* Complete correction of Glanzmann's thrombasthenia by allogeneic bone-marrow transplantation. *Br J Haematol* 1985;59:635–41.
 13. Fujimoto TT, Kishimoto M. Glanzmann thrombasthenia with acute myeloid leukemia successfully treated by bonemarrow transplantation. *Int J Hematol* 2005;81(1):77–80.
 14. Hoffman M. A cell-based model of hemostasis. *Blood Rev* 2003;17:S1–5.
 15. Monroe DM, Hoffman M, Oliver JA, Roberts HR. Platelet activity of high dose factor VIIa is independent of tissue factor. *Br J Haematol* 1997;99:542–7.

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