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Case Report

Syncope as an atypical initial presentation of Glanzmann's thrombasthenia in an adolescent female: a case complicated by anti-Jka–mediated delayed haemolytic transfusion reaction

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ABSTRACT

Adolescents with Glanzmanns thrombasthenia (GT), a rare inherited disorder of platelet function characterized by defective platelet aggregation despite normal platelet counts, typically present with mucocutaneous bleeding; however, atypical manifestations may cause a delay in diagnosis. Case report describe a 15-year-old girl who had a syncopal episode due to severe iron-deficiency anaemia brought on by persistent menorrhagia. The initial coagulation levels were normal, prompting additional testing, and platelet aggregation tests confirmed GT. She needed coordinated hematology–gynecology care, anaemia correction, and menstrual bleeding stabilization; however, repeated transfusions caused a delayed hemolytic transfusion reaction because of the development of anti-Jka alloantibodies. Iron supplementation, antifibrinolytics, and customized menstrual control were used to treat the patient; alloimmunization required prolonged antigen matching for subsequent transfusions. She showed a good clinical recovery with no recurrence of syncope, highlighting the significance of early diagnosis, prevention of transfusion-related complications, and a multidisciplinary strategy for the best results, as well as the necessity of considering GT in adolescents with unexplained anaemia and normal coagulation profiles, especially in populations with high consanguinity.

Keywords: Glanzmann's thrombasthenia, Menorrhagia, Iron- deficiency anaemia, Syncope, Alloimmunization, Anti-Jka, Delayed haemolytic transfusion reaction

INTRODUCTION

Eduard Glanzmann first discovered Glanzmanns thrombasthenia (GT), an autosomal-recessive platelet-function disorder, in 1918. Defects of the platelet integrin αIIbβ₃ (formerly glycoprotein IIb/IIIa), which is necessary for fibrinogen binding and normal platelet aggregation, can be either qualitative or quantitative.[1] Platelet aggregation is severely damaged, which frequently causes a delay in diagnosis, even though routine coagulation parameters typically fall within acceptable limits and platelet count and morphology are normal. Although the disorder is rare worldwide, with an estimated incidence of about 1 per 1,000,000, the prevalence of GT is significantly higher in the population with common consanguinity; registry data from Al-Madinah, Saudi Arabia, reveal incidences as high as 1:10,000.[2,3] GT is slightly more prevalent in women (58%) than in men (42%).[4] The most common clinical manifestation of GT is lifelong mucocutaneous bleeding, which includes menorrhagia, gingival bleeding, epistaxis, and easy bruising. Adolescent females with GT frequently present with severe menstrual blood loss and secondary iron-deficiency anaemia. GT has a substantial

psychosocial and quality-of-life impact in addition to hemorrhagic symptoms, especially because of frequent hospital stays and activity limitations.[5,6] Alloimmunization to HLA or platelet antigens after repeated transfusions, which has been documented in up to 30% of patients and may cause platelet refractoriness and restrict treatment options, further complicates management.[7] Recombinant activated factor VII (rFVIIa), which has demonstrated safety and efficacy, has become a viable substitute in these refractory situations.[8] Therefore, given the genetic grouping of GT in the Middle East, South Asia, and other parts of Asia with high consanguinity, prompt hemostatic evaluation and increased clinician awareness are crucial to preventing serious complications, minimizing transfusion-related adverse events, and facilitating appropriate genetic counselling.[9,10] This case report aims to highlight the need for early recognition and tailored transfusion strategies in patients with Glanzmanns thrombasthenia.

CASE REPORT

A 15-year-old girl was admitted after experiencing an unexpected syncopal episode at school at around 8 AM. She lost consciousness for about 15 minutes and recovered on her own. No incontinence, tongue biting, tonic-clonic movements, or post-ictal deficits were present. She continued to experience menorrhagia (7-8 pads per day) for six days. Although she had previously experienced recurrent episodes of epistaxis, there was no history of bleeding during this episode. The parents were married to each other. Glanzmanns thrombasthenia was supported by platelet aggregation studies that revealed a preserved ristocetin response without ADP, collagen, or epinephrine aggregation. Both the brain CT scan and the neurological exam were normal. A laboratory evaluation showed normal morphology, a normal platelet counts of 2.62 lakhs/µL, and severe anaemia (Hb 5.2 g/dL) with a microcytic hypochromic picture indicating iron deficiency anaemia. Despite being pale, the patient's hemodynamics were stable.

IV ferric carboxymaltose 500mg, tranexamic acid, pantoprazole, ondansetron, paracetamol, and two PRBC units were administered to her. A diet high in protein and iron was included in, nutritional counseling. By Day two, her menstrual bleeding had stopped, her Hb had improved to 8.3g/dL, and she was still asymptomatic. After Eight and sixteen days she was scheduled to receive IV iron therapy and discharged with antiemetics, and tranexamic acid as needed. After receiving a PRBC transfusion and taking ibuprofen on her own for a fever episode, she was readmitted after Eight days, with cola-colored urine, groin pain, and jaundice. Examination revealed noticeable pallor and icterus. Recurrent anaemia (Hb 6.1 g/dL), thrombocytopenia (1.23 lakhs/µL), hemoglobinuria, elevated total bilirubin (2.35 mg/dL), elevated indirect bilirubin (1.65 mg/dL), LDH (320 U/L), and elevated reticulocyte count were all found during investigations. Indirect Coombs was positive, direct Coombs was negative, and USG revealed mild splenomegaly. The anti-Jka alloantibody was found.

Based on evidence of hemolysis and a spontaneous improvement in haemoglobin and platelet counts, a diagnosis of delayed hemolytic transfusion reaction (DHTR) was made. In order to ensure antigen-negative blood for use in the future, additional transfusions were stopped, and the blood bank was informed of the anti-Jka alloantibody. The patient was treated conservatively with IV ferric carboxymaltose 500 mg as prescribed, folic acid 5mg once daily, and normal saline at a rate of 2-3 mL/kg/hour to maintain urine output. No further PRBC transfusions were needed, and NSAIDs were avoided. On Day three, the patient was discharged with instructions to continue iron therapy, dietary support, avoid NSAIDs, and monitor for anaemia and bleeding episodes after serial monitoring revealed that jaundice and hemoglobinuria had resolved.

DISCUSSION

Platelet integrin α IIbβ$_3$ (formerly known as glycoprotein IIb/IIIa) receptor defects, either quantitative or qualitative, cause GT, a rare autosomal-recessive inherited platelet-function disorder.[11] This receptor is necessary for platelet cross-linking and fibrinogen binding, which allows aggregation.[12] Although the prevalence increases in areas with a high consanguinity (e.g., ~1 in 200,000) due to autosomal-recessive inheritance, the incidence in the general population is estimated at ~1 in 1,000,000.[13,14] Despite normal platelet count and morphology, GT usually manifests in early childhood as mucocutaneous bleeding, including epistaxis, gingival bleeding, menorrhagia, and easy bruising.[15] This 15-year-old girl demonstrated that GT may manifest indirectly through bleeding complications like anaemia because, in contrast to the majority of documented cases, she had menorrhagia, prior epistaxis, and an atypical initial of syncope due to severe iron-deficiency anaemia (Hb 5.2 g/dL) from chronic heavy menstrual bleeding.

The presenting feature of this case was syncope, which is uncommon in GT and typically indicates severe iron-deficiency anaemia from prolonged bleeding rather than primary hemostatic impairment.[16] Although transfusion-dependent anaemia and menorrhagia frequently appear in adolescents with GT, syncope or pre-syncope as a first presentation is rarely documented, highlighting the diagnostic challenge.[17] The case is particularly noteworthy because of a delayed hemolytic transfusion reaction brought on by anti-Jka alloimmunization, underscoring the significance of careful observation, prudent transfusion procedures, and prolonged antigen matching in adolescents with GT who receive transfusions regularly. When serious bleeding occurs despite normal platelet count, PT, and aPTT, especially in the context of consanguinity, as in our case, a high index of suspicion is necessary. Key diagnostic tests continue to

be flow cytometry, which shows decreased αIIbβ3 expression, and platelet aggregation studies that show no responses to ADP, epinephrine, and collagen with preserved ristocetin response.[18] Even patients with minor laboratory abnormalities may experience significant bleeding, and there is no consistent correlation between bleeding severity and residual receptor expression or aggregation.[19] It is important to distinguish between Glanzmanns thrombasthenia and Bernard-Soulier syndrome, which manifests as thrombocytopenia and giant platelets because of a GPIb–IX–V complex defect that impairs platelet adhesion instead of aggregation.[20] Patients with GT are more likely to develop alloimmunization to both platelet and red-cell antigens because they frequently need repeated transfusions for bleeding episodes. Kidd antibodies, including anti-Jka as in our case, are among the most prevalent causes of delayed hemolytic transfusion reactions, and reported rates of RBC alloimmunization range from 10 to 30%.[21] To reduce these risks, genotypic matching or extended antigen phenotyping should be used before transfusion.

DHTR, which usually happens 5-14 days after transfusion as a result of an anamnestic immune response, was the cause of the second hospitalization in this instance. Consistent with our results, Kidd antibodies, especially anti-Jka, are referred to as causing severe DHTR with little DAT positivity.[22,23] Hemoglobinuria, jaundice, indirect hyperbilirubinemia, elevated LDH, and reticulocytosis all supported the diagnosis, highlighting the significance of early detection given its potentially fatal course. Furthermore, the patient self-administered NSAIDs like ibuprofen, which have rarely been connected to immune-mediated hemolysis and may exacerbate platelet disorders and mucosal bleeding in GT, potentially increasing the severity of DHTR.[24-27] The patient was treated conservatively with supportive care instead of further transfusions, in line with published research. In order to prevent haemoglobin-induced renal damage in delayed haemolytic transfusion reactions, adequate intravenous hydration (2-3 mL/kg/hour) is frequently advised.[28] The use of oral folic acid and intravenous iron to support erythropoiesis in this instance is consistent with previously documented treatment approaches for patients exhibiting clinical and haematological improvement without additional transfusion.[29,30]

The complicated treatment of Glanzmanns thrombasthenia (GT) necessitates a multidisciplinary strategy to stop bleeding, treat anaemia, and prevent recurrence. Antifibrinolytics like tranexamic acid for mucosal bleeding, packed red-cell transfusions or parenteral iron for anaemia, and platelet transfusions—ideally HLA-matched single-donor units—for severe bleeding or surgical procedures are all part of the treatment; however, repeated transfusions can cause alloimmunization and platelet refractoriness.[31] Recombinant activated factor VII (rFVIIa) is a safe and effective substitute in these circumstances; about 100 patients have reported positive results.[32] Although human trials are still pending, preclinical lentiviral correction of ITGA2B/ITGB3 has demonstrated restored platelet function, and curative options such as gene therapy and hematopoietic stem cell transplantation are emerging but still under investigation.[33]

Menorrhagia makes management more difficult for teenage girls. Hormonal treatments, such as combined oral contraceptives and the levonorgestrel-releasing intrauterine system (LNG-IUS), are frequently used when antifibrinolytics are insufficient. LNG-IUS significantly reduces menstrual blood loss and improves haemoglobin in adolescents with GT, according to case series.[34,35] These results are corroborated by more general evidence in inherited bleeding disorders, which shows amenorrhea in about 60% of women and improved iron parameters.[36,37] However, the majority of the data come from small studies, which highlights the need for larger prospective trials to elucidate its role in GT management.[38] Haemoglobin stabilization and rapid clinical improvement were the outcomes of immediate care with packed red-cell transfusion, intravenous iron, and antifibrinolytics. On follow-up, menorrhagia was reduced, and the patient was advised regarding long-term care, such as genetic counselling and avoiding antiplatelet agents.[39] A multidisciplinary strategy involving haematology, gynaecology, and clinical pharmacology is necessary for the ongoing management of Glanzmanns thrombasthenia in order to monitor haemoglobin and iron stores, optimize menstrual control, prevent anaemia recurrence, and address psychosocial impact, which has a substantial impact on quality of life.[40]

Although the lack of genetic confirmation and prolonged follow-up limit this single-case report, it emphasizes the significance of taking GT into account in teenage girls who have heavy menstrual bleeding and unexplained anaemia despite having normal coagulation profiles. Increased clinical awareness is necessary for atypical presentations like syncope from chronic anaemia. To avoid serious complications and transfusion-related events like DHTR, early diagnosis, coordinated medical treatment, genetic counseling—particularly in areas with high consanguinity—and prolonged red-cell antigen matching in patients receiving continuous transfusions are crucial.

CONCLUSION

Adolescents with unexplained iron-deficiency anaemia and standard coagulation profiles should be evaluated for Glanzmanns thrombasthenia, despite its rarity, especially in areas with high consanguinity. This case shows an unusual presentation in which anaemia caused by chronic menorrhagia led to syncope. Recurrence prevention still depends on early detection and coordinated haematology-gynaecology care. Long-term care is further strengthened by incorporating iron-repletion techniques, assessing the necessity of hormonal therapy or antifibrinolytics, and

ensuring prompt access to HLA-matched platelets during acute bleeding episodes. Optimising results and quality of life requires structured follow-up, genetic counselling, and patient education on avoiding bleeding risks.

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