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## Feminizing Genitoplasty in a young girl with Glanzmann's thrombasthenia-management of haemostasis

Kashaf Khalid Turk,<sup>1</sup> Zafar Nazir<sup>2</sup>

### Abstract

We report peri- and post-operative management of haemostasis in a 11-year old girl with Glanzmann Thrombasthenia (GT) who had feminizing genitoplasty for genital ambiguity due to Congenital Adrenal Hyperplasia (CAH-21 Hydroxylase deficiency). A blend of Glanzmann Thrombasthenia (GT) and DSD 46XX due to CAH is not reported in literature. Surgery particularly genitourinary reconstruction in patients with GT is challenging due to risk of intra and post-operative bleeding. Haemostasis can successfully be achieved with platelet transfusions, antifibrinolytic (Tranexamic acid) and judicious use of recombinant factor VIIa (rFVIIa) even in a resource limited setting.

**Keywords:** Inherited Platelet disorders, Feminizing Genitoplasty, Disorders of Sexual Differentiation (DSD), Urogenital Sinus, Glanzmann's Thrombasthenia, Recombinant Factor VIIa (rFVIIa).

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### Introduction

Glanzmann's Thrombasthenia (GT) is a rare autosomal recessive disorder of platelet aggregation due to qualitative/quantitative defect of platelet membrane glycoproteins (IIb/IIIb). Reported incidence is 1: 1000,000 people worldwide.<sup>1,2</sup> GT may be frequent in South-East Asia where consanguinity is common.<sup>3</sup> In a series of 211 patients of Autosomal recessive inherited bleeding disorders (ARBDs) from Pakistan, 9.6% patients had GT.<sup>4</sup> Clinical manifestation includes easy bruising, tendency to bleed from muco-cutaneous surfaces e.g. epistaxis (bleeding from the nose), menorrhagia (abnormally heavy bleeding at menstruation), and bleeding after trauma or surgery.

In literature reports of children having GT undergoing minor procedures (e.g. dental extraction, herniorrhaphy) are common however, major surgical procedures particularly the genitourinary reconstructions are

sparingly reported.<sup>5-7</sup> In this report we share the experience of feminizing genitoplasty in a young girl with DSD 46XX due to CAH (Congenital Adrenal Hyperplasia-21 Hydroxylase deficiency), a rare autosomal recessive disorder (Incidence, 1: 15,000) who also had GT. We believe that blend of these two autosomal recessive disorders is rare and is not reported in literature before.

### Case Report

The patient was born to consanguineous parents. The mother was known to have Glanzmann's Thrombasthenia (GT) and delivered normally under the cover of platelet transfusions. Examination in nursery revealed ambiguous genitalia (enlarged clitoris, fused labio-scrotal folds and a single perineal opening. After the investigations which include serum electrolytes, 17-hydroxyprogesteron, Ultrasound Pelvis, karyotype and Genitogram, she was diagnosed CAH-21-hydroxylase deficiency and was categorized as DSD 46 XX. Steroid replacement (hydrocortisone and Florinef) was initiated. At 4.5 years she was diagnosed GT; after an episode of intractable epistaxis. Three further episodes of epistaxis were successfully managed by platelet transfusions and local measures. She was referred in June 2018 to Paediatric Surgery service at the Aga Khan University Hospital, Karachi (AKUH.K), Pakistan; at 11-years of age for feminizing genitoplasty.

Laboratory tests revealed Haemoglobin 12.5gm/dl, Hematocrit 34%, WBC count  $8 \times 10^9/L$ , platelets  $253 \times 10^9/L$ , prothrombin time (PT) :11 seconds, and activated partial thromboplastin time: 33 seconds. Bleeding time was > 14 minutes and platelet aggregation with collagen, adenosine diphosphate (ADP) and epinephrine was absent.

The patient was admitted electively for the reconstructive surgery and co-managed with Paediatric Haematology and Endocrinology. One hour prior to the procedure she received stress dose (3 times the maintenance dose) of hydrocortisone, 6 units of platelets concentrate and tranexamic acid (10mg/kg).

The technical details of Feminizing genitoplasty (flap Vaginoplasty, nerve-sparing clitoroplasty and labioplasty) are reported in literature.<sup>8</sup> Cystoscopy was the initial procedure which revealed the length of the common

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urogenital sinus (UG) to be 3.0 cm. The procedure continued for 3.15 hours. Excessive bleeding (>350 ml) was encountered particularly during dissection of UG and clitoroplasty. However, bleeding reduced (<50ml) remarkably after a bolus of recombinant factor VIIa (rFVIIa-Novo-sevenR), 90ug/kg. Additional dose of rFVIIa were administered in recovery room and at time of dressing change and removal of vaginal pack on 3rd postoperative day. Tranexamic acid (10mg/kg) 3 times a day was continued, and she received 6 units of platelets concentrate twice daily for 7 days and once daily for the next 5 days. The patient recovered well and was discharged from the hospital on the 12th post-operative day. She did not experience any adverse effects of rFVIIa treatment or further oozing from the wound during hospitalization and on 8-week follow-up.

## Discussion

Both GT and CAH are autosomal recessive inherited disorders and caused by mutation of genes (TGA2B/ITGB3 and CYP21A2) located on Chromosome 17 and 6 respectively. Mechanism of presence of these rare disorders in one patient is unknown and is not reported in literature. Perhaps it can be explained by uniparental disomy (maternal or parental) i.e. inheritance by offspring of two copies of a homologous chromosome from one parent and none from the other.

Surgical procedures in patients with GT are challenging due to increased risk intra- and post-operative bleeding and haematoma formation. In a series of 112 GT; 77% patients required blood transfusion.<sup>1</sup> Prophylactic or therapeutic platelet transfusions preferably from single donor and/or HLA compatible along with local and general measures e.g. desmopressin, fibrin glue, and antifibrinolytics (e.g. Tranexamic acid) are usually utilized to manage bleeding episodes and to support surgical interventions in GT patients.<sup>2,9,10</sup> However, immunity to glycoproteins IIb-IIIa and/or HLA may develop and render the platelet transfusions ineffective. Moreover, blood products carry risks e.g. infection, allergic reaction etc., and preferred HLA compatible platelets and single donor platelets may not be readily available. Recombinant activated factor VIIa (rFVIIa, NovoSevenR, Novo Nordisk A/S, Bagsvaerd, Denmark) is currently used as an alternative or adjuvant to platelet transfusions to reduce bleeding during surgical and invasive interventions in patients with disorders of platelet dysfunctions. e.g. Bernard-Soulier syndrome and GT.<sup>2,11</sup>

None of the currently available treatment protocols are supported by tangible evidence. In the reported patient haemostasis was achieved through platelet transfusions and antifibrinolytics (tranexamic acid) and restricted use of rFVIIa

as the cost of one dose of rFVIIa is US\$ 560.00 in Pakistan where per capita income is around US\$ 5500. It was effective in controlling intra and post-operative bleeding episodes.

The exact mechanism of rFVIIa as haemostatic agent is not known. It is reported to bind activated platelets and boost local thrombin generation and adhesion of GP IIb/IIIa deficient platelets. As Fibrin is an active participant in platelet aggregation; antifibrinolytics such as tranexamic acid may have a role in management.<sup>2</sup>

In conclusion, surgical procedures particularly genitourinary reconstructions in patients with GT can be carried out safely by careful planning and coordination between haematologist and the surgeon. rFVIIa is effective as an adjuvant to platelet transfusions; in reducing bleeding. The reported approach may also be applicable in children and adolescents with GT having minor, major surgical and obstetric procedures.

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**Conflict of Interest:** None to declare.

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