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A case series on Glanzmann thrombasthenia in adolescent girls with puberty menorrhagia

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Abstract
Background: Glanzmann thrombasthenia is a genetic disorder which is rarely seen in which the platelets have qualitative and quantitative deficiencies of fibrinogen receptor. Patients with Glanzmann thrombasthenia present with mucosal bleeding, petechaie, ecchymosis, menorrhagia, gastrointestinal bleeding. Presenting here a series of 3 cases of Glanzmann thrombasthenia who presented to obstetrics and gynaecology department with gynaecological complaints. One had a large ovarian haemorrhagic cyst and the other two had severe menorrhagia. All these three cases were managed conservatively.
Material and Methods: Retrospective Observational Study was conducted at a tertiary care centre over a period of 2 years in our unit. All the three patients were diagnosed with Glanzmann thrombasthenia with gynaecological complaints and their case record were analysed.
Results: we had total three cases of Glanzmann thrombasthenia presenting to gynaecology department. All were in adolescent age group. One had a large ovarian haemorrhagic cyst and the other two had severe menorrhagia. All three had severe anaemia due to blood loss. All required factor VII, platelets and blood transfusion and one required immunoglobulin. All cases were managed conservatively.
Conclusions: Patients with Glanzmann thrombasthenia present with spontaneous episode of bleeding, which can be severe and even life threatening. Medical management is the mainstay of treatment. Platelet transfusion is the recommended treatment. Newer modalities of treatment like factor VIIa may also be beneficial to these patients.

Keywords: Glanzmann thrombasthenia, puberty menorrhagia

Introduction
Glanzmann thrombasthenia is a rare genetic disorder with autosomal recessive type of inheritance. [1, 2] It was first documented by a Swiss paediatrician, Dr Eduard Glanzmann in 1918. He described it as a platelet function disorder with defective clot retraction. The incidence of Glanzmann thrombasthenia is 1 in 1 million. Glanzmann thrombasthenia is a platelet disorder with deficient or dysfunctional platelet glycoprotein complex (GP IIb/IIIa). Patient with Glanzmann thrombasthenia present with prolong bleeding time and poor platelet aggregation that results in bleeding manifestations. These patients may present with life threatening menorrhagia at menarche requiring multiple blood transfusion.
Patients commonly present with purpura, petechial haemorrhages, gingival bleeding, epistaxis and menorrhagia. Less common manifestations of the disease are haematuria, hemarthrosis, gastro intestinal bleeding and haemorrhagic ovarian cysts. Menorrhagia is seen in most female patients from the time of menarche and is a serious concern as they often present with severe haemorrhage and severe anaemia require blood and blood products transfusion and also at times immunoglobulins.

Aims and Objectives
1. This case series was done to study the clinical presentation in patients with Glanzmann thrombasthenia.
2. To study the management in these patients.
3. To study the outcome of these patients.

Material and Methods:
Retrospective Observational Study was conducted at a tertiary care centre at Seth G.S M.C and KEM Hospital over a period of 2 years in our unit. The history of these patients was collected from indoor papers. There were three patients diagnosed with Glanzmann thrombasthenia with gynaecological complaints in adolescent age group and their case records were analysed.

Case report 1

A 19 year old, nulligravida, married since one year presented to gynaecology outpatient department with complaint of abdominal pain and nausea since 2 days. She also had menorrhagia since puberty, episodes of epistaxis, gum bleeding and easy bruisability since childhood. Her brother also had similar history and was diagnosed with Glanzmann thrombasthenia. On clinical examination her vital parameters were stable, systemic examination was within normal limit. Abdominal examination revealed a midline mass arising from three pelvis corresponding to 22 weeks size firm in consistency. Vaginal examination revealed a right adnexal mass of 15 x 10 cm with restricted mobility with uterus normal size and retroverted. Ultrasonography was suggestive of a large heterogeneous mass of 14x11x10 cm in the midline with haemorrhagic changes on right adnexa. CT scan done was suggestive of a large multicystic lesion of 11x 14x 17 cm in the right adnexa with subacute haemorrhage within. Her haemoglobin was 8gm%, platelet count was 4 lacs/mm3 with PT INR, aPTT and serum fibrinogen within normal limit. Tumour marker were within normal limit with CA125 raised 66 IU/L. Haematology reference was taken in view of history of menorrhagia, easy bruisability, epistaxis and gum bleeding with positive family history. Platelet aggregation with ristocetin was normal and was decrease with epinephrine, collagen and adenosine Di Phosphate. Glycoprotein IIb/IIIa level were 92.22% on platelet glycoprotein receptors by flow cytometry study with normal clot retraction time. A diagnosis of platelet function disorder, variant Glanzmann thrombasthenia was made. In view of above diagnosis surgical intervention was deferred as she was a very high risk for surgery and patient was managed conservatively. Two doses of factor VII 2mg were administered intravenously with six unit of platelet transfusion. She was also started on injectable tranexamic acid 500 mg thrice a day for 3 days and later was shifted to oral and on oral contraceptive pill. Within one weeks the size of the ovarian mass reduced on clinical examination from 22 weeks to 16 weeks size. At the time of discharge the mass was just palpable. Hence patient was discharged. On her follow up visit after a month to OPD, ultrasonography done revealed right ovarian mass of 5x6 cm. patient was advised to continue oral contraceptive pill for 3 months. (This was published in IJRCOG) [3]

Case report 2

A 13 year unmarried girl presented to emergency obstetrics and gynaecology department with heavy menstrual bleeding. This was her first menstrual cycle. She was diagnosed case of Glanzmann thrombasthenia diagnosed who she was 8 year old during screening as her brother died of same disease. She had history of easy bruisability and epistaxis. She was admitted at a peripheral hospital in view heavy menstrual bleeding and started on injectable tranexamic acid. Her menorrhagia was not controlled with tranexamic acid, hence she was referred to our hospital. On clinical examination, she was very pale, her vital parameters were stable and there was no evidence of organomegaly on abdominal examination. She was admitted in haematology ward and started on abdominal examination. She was started on injectable tranexamic acid 500 mg tds, tab medroxyprogesterone acetate 10 mg tds. Her haemoglobin 5.6 gm%, coagulation profile, hepatic and renal function was within normal limit. Haematological opinion taken. Novo 7 (factor VII) was given in the dose of 90 mcg/kg in divided doses. Single dose of 2500 mcg (half-life is 3 hours) was given 3 hourly for 5 days up to total dose of 50 mg (20 doses). Patient did not respond and was started on combined oral contraceptive pills 2 tablet tds and injectable Ethamsylate. Patient received multiple blood transfusion. Bleeding had reduced but was still persistent hence she was given Inj. testosterone enanthate 50 mg IM for total 4 doses over 4 hour. Since her bleeding did not respond to the above management, she was Inj. Leuprolide acetate 3.75 mg, in a view to completely suppress her hypothalamo-pituitary ovarian axis. Leuprolide acetate is actually contraindicated for her age, but it was used as a life saving measure. Her bleeding stopped within 2 days after giving Inj. leuprolide. At the time of discharge, her general condition improved and her haemoglobin had increased to 7.7 mg%. Total 25 blood transfusion were given to her along with parenteral albumin for her hypoproteinaemia over a period of 19 days. She was later discharged with advice to start tab tranexamic acid 500 mg thrice a day from day 1 of her menses and to follow up immediately if bleeding is not controlled. (This was published in IJRCOG) [4]

Case report 3

A 13 year unmarried girl presented to emergency department with bleeding per vaginum since 9 days with passage of clots. She attend her menarche in January 2017 bleeding for 6 days which had stopped spontaneously. She was diagnosed with Glanzmann thrombasthenia at 6 month of age GP2b/3a-0.1%. She had history of bleeding during tooth extraction was given platelet transfusion with Tab. tranexamic acid at the age of 6 years. History of haematuria at the age of 6 years at that time also she was given platelet transfusion and Tab. tranexamic acid No family history of bleeding disorder. On clinical examination at our institute her pulse was 110/min, blood pressure was 100/60 mm Hg, pallor ++, no abnormality detected on systemic examination. On abdominal examination there was no guarding, rigidity, tenderness or any organomegaly. Patient was started on Inj. Tranexamic acid 500mg 8 hourly and oral contraceptive pill thrice a day. She was also given NOVO 7 2.5mg over 3 hour for 2 days. In view of her severe pallor she was given total 5 unit of blood transfusion. She still had bleeding per vaginum her the dose of Ovral-G was increased to 2 tab trice a day and Inj. testosterone 50mg IM was given after which her bleeding stopped. Patient was then discharged with advice to continue tab Ovral-G 2 tab trice a day for 2 days and 1 tab trice a day 7 days and 1 tab twice a day.

Table 1: Summary shown in tabulated form

	Case 1	Case 2	Case 3
Age	**19**	**13**	**13**
Presentation	Haemorrhagic ovarian cyst	Menorrhagia	Menorrhagia
Marital status	Married	Unmarried	Unmarried
Family History of Glanzmann Thrombasthenia	Brother	Brother	None

Results

All the three patients presented in adolescent group, all three had menorrhagia. One of them had haemorrhagic ovarian cyst. All three were given multiple blood transfusions and Factor VII and their bleeding responded to medical management.

Discussion

Glanzmann thrombasthenia is a rare genetic disorder with autosomal recessive type of inheritance, commonly seen in patient with consanguineous marriages. Heterozygotes are

asymptomatic with normal platelet function test. In normal coagulation pathway, glycoprotein complex binds to fibrinogen and bridges the platelet in presence of calcium to form platelet aggregates responsible for clotting. In Glanzmann thrombasthenia, this complex is deficient. Glanzmann thrombasthenia is classified into 3 types. [5]

Table 2: Classification of Glanzmann Thrombasthenia

Type I	less than 5% of the normal GP IIb/ IIIa complex and clot retraction is absent
Type II	5-20% of the normal complex and clot retraction is impaired.
Type III	are variants who have normal receptor levels but defective receptor function

Patient with Glanzmann thrombasthenia present with mucosal bleeding, petechaie, ecchymosis, menorrhagia, gastrointestinal bleeding. On laboratory evaluation, there is prolonged bleeding time, normal platelet count and morphology. Abnormal clot retraction time is seen. When the test is performed using collagen and ADP epinephrine then platelet aggregation test results are abnormal due to dependence of these agents on fibrinogen. Fibrinogen attachment to platelet is essential for these factors to cause aggregation. Platelet aggregation occurs in response to ristocetin because of its independence from fibrinogen. [6] Receptor assay using flow cytometry is done using monoclonal antibodies to detect the presence of glycoprotein IIb/IIIa complex, glycoprotein IIb (CD 41), glycoprotein IIIa (CD 61) and fibrinogen. The above method can also be used to diagnose carrier status. [7] The management of patient with Glanzmann thrombasthenia requires multidisciplinary approach and is very challenging. The goal of treatment is to control bleeding. Platelet transfusion is the recommended treatment. About 15-30% of patient develop antibodies to glycoprotein IIb/IIIa and/or HLA antibodies and hence they do not respond to these transfusion. They also develop refractoriness to these transfusion. If the patient present with menorrhagia initial should be managed with anti-fibrinolytics (tranexamic acid and Ethamsylate) and the followed by hormonal therapy. Blood and blood product transfusion should be given to correct anaemia, as every transfusion increases the risk of alloimmunization, which in future can lead to massive haemorrhage. Newer modalities of treatment like factor VIIa may also be beneficial to this patient. [8, 9] Factor VIIa is given for prevention of bleeding during surgery or invasive procedures. It can be given in acute episodes of bleeding. The recommended dosage is 90 mcg/kg intravenous. In patients who have already developed alloimmunization the only treatment option is plasmapheresis. Intramuscular injections and medications affecting platelet function like NSAIDS should be avoided. These patients should be immunised against hepatitis B.

Conclusion

Glanzmann's thrombasthenia patients do well with necessary supportive care. Spontaneous bleeding is not uncommon. Post traumatic bleeding can occur, which can be serious and even life threatening. The need for immediate and appropriate individualized medical measures forms the mainstay of management in rare coagulation disorders like Glanzmann thrombasthenia.

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