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Glanzmann's Thrombasthenia: A Review Study

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Research Article

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ABSTRACT

Platelets are found in blood and they perform the functions of hemostasis whenever there is a damage in subendothelial happens platelets actives and aggregate to form a platelet plug in order to maintain hemostasis Glanzmann's thrombocytopenia is a disease discovered by Glanzmann's in 1918. It's a genetic platelet surface receptor defects of GPIIb / IIIa. Either qualitative or quantitative. It will result in abnormal platelet agreegation and clot retraction. Several bleeding episodes are symptoms of GT including epistaxis, gingival bleeding etc. the management of GT could be done by various local measures and many anti - fibrinolytic agents and desmopressin etc. Heeding to recent studies the treatment options included retiuximab, bevacizumab and rFVIIa etc bone marrow transplantation and stem cell therapy is a great option of treatment but very rarely using methods of treatment because have less chances of successful results and a painful and costly therapy it ishe objective of this study is to understand all about the Glanzmann's thrombasthenia its pathogenesis, discovery, treatment options and diagnostic tools etc . the study was based on previous published data obtained from PubMed , ncbi, elsevier and other publications of last 5 years was concluded that glanzmann's thrombasthenia is a platelet disorder it is very rarely occur and characterized by severe bleeding episodes hence, it's proper treatment and management is of great concern for all health care expertise.

INTRODUCTION

Platelets are found in blood and they perform the functions of hemostasis whenever there is a damage in subendothelial happens platelets actives and agreegate to form a platelet plug to maintain hemostasis. For the attachment of coagulation factors the phospholipids and surface is required which is also provided by platelets. After all of the coagulation mechanism a thrombus formation occurs. If any defect occurs in this pathway either by hereditary or inherited it may cause bleeding disordersne of the most common platelet disorder now a days is glanzmann's thrombasthenia. This disease is discovered by a scientist Eduard Glanzmann's in 1918 who was a swiss pediatrician. Heeding to the studies by a scientist the disease is consider to be as a hereditary autosomoal disorder characterized by defects in GPIIb / IIIa. This was a first disease that is characterized by platelet surface proteins their adhesion and activation defect. Now days this disease is a very keen of interest topic for research studies and to make therapeutic measures normal [1-3]. It is a recessive autosomal disorder that is very rarely occurs. This disease is mainly cause by the deficient levels in platelet GPIIb / IIIaecceptor on a platelet surface. Which helps platelets to agreegate and also cause activation of platelets by binding with fibrinogen, fibronectin and proteins [4].

The proteins GPIIb / IIIa is encoded by a gene that termed as ITGB3 and ITGA2B respectively. These genes are present within the 260 - kb segment of the q21 - 23 bands present on chromosome number 17. In either genes there is more than 100 mutations are reported. These mutational defects may happens due to splicing abnormalities, insertion and deletion, nonsense mutations and single amino acid substitution [5,6].

Glanzmann's thrombasthenia clinically represented as purpura, epistaxis, gingival bleeding. Epistaxis is the severe bleeding and normally cause in childhood rarely in adults. Purpura and petechial occurs normaly in 5 years old child. Gingival bleeding is mostly happen is a person with poor mouth hygiene. Due to extreme bleeding the iron deficiency and anemia is common in childrens. Mennorhagia may also reported in some cases. In association with angiodysplasia the gastrointestinal hemorrhages also observed in some patients. Hematuria also reported but hemarthosis rarely occurs. Intracranial hemorrhages reported unusually. Bleeding after a surgery procedure is more frequent. During pregnancy there are chances of bleeding rather than mennorhagia. Muco - cutaneous bleeding and spontaneous bruicing is also reported in some incidence. Fatal bleeding could also occur in the whole life span of patient [7-9].

METHOD

Search criteria

The objective of this study is to understand all about the Glanzmann's thrombasthenia its pathogenesis, discovery, treatment options and diagnostic tools etc. the study was based on previous published data obtained from PubMed, ncbi, elsevier and other publications of last 5 years. A systematic review of the fact - based was passed out spending a unique search strategy. Databases scrutinized include Pubmed, Medline, Embase, Cinahl, and AMED. Preceding systematic reviews, Meta - observes and randomised trials were hand searched for extra references with the hunt lengthy to classify observational studies where correct. Internet examinations were also supported out on various websites. Review methods trials were included in the review if they were possible human trials gaging drugs in the dealing of hematological disorders and applied authenticated devices to measure participant appropriateness and clinical endpoints.

Inclusion and exclusion criteria

Assortment criteria of the study were clear and taken into thought. Treatments usually available to patients without prescriptions were chosen for inclusion. With the exception of criteria for studies was where there was no authorized diagnosis by the International Classification of Disease (ICD) 9, ICD 10,Diagnostic Statistical Manual (DSM)III or DSM - IV, or use of a recognized, validated and dependable dimension scale precisely for psychiatric symptoms. Extra, studies in patient groups with strong indicators of other platelets disorders.

RESULTS

Incidence and prevalence

Studies suggested that it is more commonly occurs in females as compared to males (58% versus 42%) (Figure 1). The peoples that have higher incidence of consiguency are more vulnerable to glanzmann's thrombasthenia such as Iraq, Palestinians, French gypsies etc. in France peoples there is a higher incidence of GT observed like 150 peoples from 300 individuals. The disease is hereditary and inherited so the patients with hereditary genetic defects are more vulnerable to disease [10].

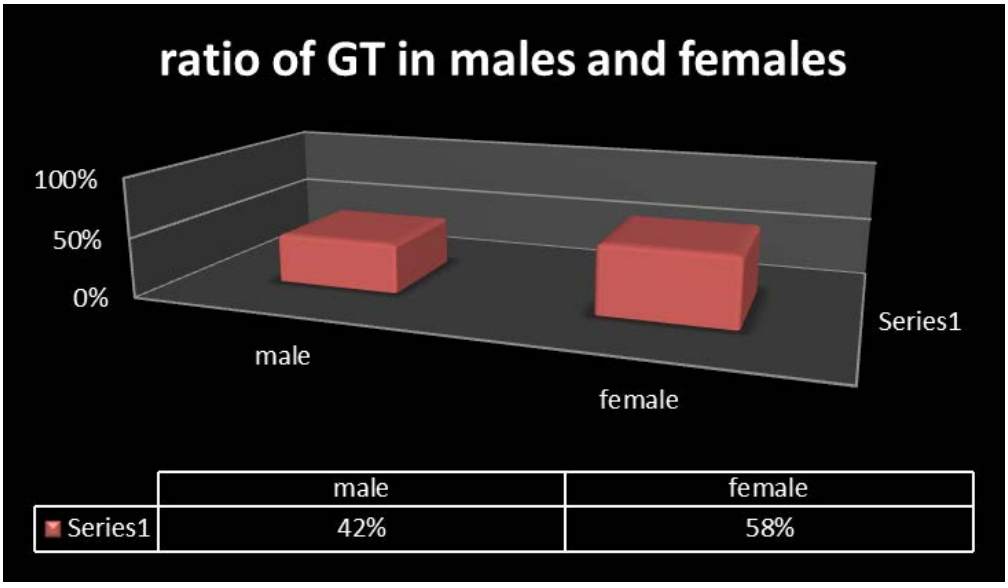

Figure 1. Ratio of GT in males vs females.

The qualitative platelet disorders are described in **Figure 2.**

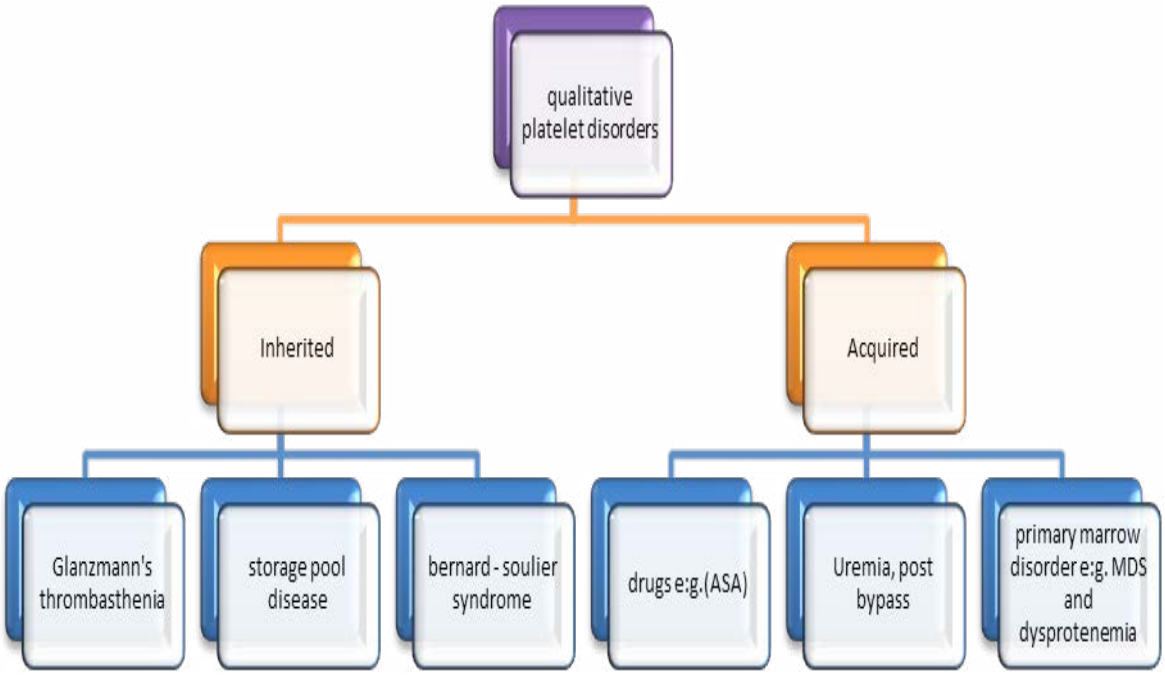

Figure 2. Qualitative platelets disorders.

Pathogenesis of GT

A large heterodimeric transmembrane receptor GPIIb / IIIa is consists of larger αIIb and smaller β3 sub units. The duplex between cell membrane and extracellular material is formed by the covalent linkages between these sub units. A large disulfide epidermal growth factor is present on β3 sub unit that activates the whole ITGαIIbβ3. On the β - propeller region of the αIIb sub unit a calcium site is present which helps in platelet adhesion. The formation of a thrombus, platelet aggregation, regulation of cell migration and cell to cell communication is controlled by the whole ITGαIIbβ3. Along a platelet surface roughly 100,000 copies of GPIIb / IIIa receptors expressed which differs by two folds solely. Mutations most commonly happens in ITGA2B gene the most frequent mutation that could happens are frameshifts, insertion, and non - sense and missense mutations also the deletion. The ITGαIIbβ3 biogenesis is arise from hematopoietic stem cells. The sub unit linkages are in this sense that αIIb is linked to megakaryocytes and β3 is linked to vitronectin receptor (αvβ3) this receptor is more abundant in patients with ITGA2B mutation gene. Variant form of GT cause or occurs when the αIIb subunit forms a partial complex that is in between the αIIb and β3 subunits. Due to many mechanisms of mutations platelet morphology and numbers will disturb with rough αIIbβ3 expression but it not leads to GT [11-15].

The stage or severness of GT is determine by the gene locus determination either homozygous or heterozygous mutations. Due to mutation subunit formation stops or inhibited and a complex formation occurs intracellular trafficking also inhibited by gene mutation. Residual subunits of αIIbβ3 is degraded when these complexes hindered. On the basis of functionality and expressions of residuals GT is characterized in 3 types: type 1 (>5% of residual αIIbβ3), type 2(5% - 20% of residual αIIbβ3) and type 3 (<20% of residual αIIbβ3) type 3 is very rarely ocuurs and it have some dysfunctional properties that leads to variant type of GT (Table 1). According to Fiore ITGB3 gene mutation could leads to phenotypic bleeding during disease progression [16].

The autoimmunity or autoantibody attacks on platelet αIIbβ3 subunit that leads to acquired GT. The patients who have lupus erythmatosis syndrome are greater vulnerable to gene mutation on GPIIb / IIIa receptor. Transient GT type state could develop by the use of anti thrombic therapies during coronary disease events e., abciximab, tirofiban and eptifibatide [17].

Table 1. Ratio of residual αIIbβ3 gene respective to different types of GT.

Types of GT	Residual αIIbβ3
• Type 1	>5%
• Type 2	5 - 20%
• Type 3	<20%

Causes

The disease is mainly cause due to heredity and genetic defects in platelet surface receptors that is GPIIb / IIIa. It may cause by auto immunization and immune compromise patients have a great susceptibility to GT. The very dominant cause included mutation of genes ITGA2B etc [18,19].

Symptoms

The symptoms of GT involved severe bleeding episodes epistaxis, gingival bleeding, intracranial bleeding, menorrhagia, post-

partum hemorrhage, menrrache. More than normal bleeding during surgery, labor and after any injury, less platelet aggregation etc. these are the major symptoms of GT [20].

Diagnosis

The diagnosis first shuld be start with the patient history of bleeding disorders or hereditary platelet disorders. The laboratory diagnostic findings should be done very carefully because there is a normal platelet count in GT no variation is occurs in number of platelets. During the complete blood cells laboratory findings all the cells may be in normal count but iron deficiencies could present in patients with GT. PTT & thromboplastin time is also normal but prolongs bleeding time triggers further investigation [21].

A gold standard diagnostic tool for GT is considering the light transmission agreegometry (LTA) to analyse platelet functions. In this method the platelet rich plasma sample first centrifuge than it is before and after the addition of agonist like collagen. Thromboxane A2, arachidonic acid and ADP. It will assess the lag phase aggregation of platelets, deaggregation, percent of aggregation and platelet shape changes. This test is highly specific for GT because in positive results no aggregation will occurs with agonist except the ristocetin. The two drawback of this method is that it require expert labs and it is very difficult to obtain platelet rich sample in pediatrics and thrombocytopenic patients [22-24].

Platelet function analyzer (PFA) the more prominent method to diagnose GT. In this test collagen+ADP and collagen+epinephrine embede cartridges are used to mimic a endothelial vessel damage. The blood than flows by a strong shear stress rate through cartridges platelets then bind and form a plug. The patients with GT have more prolong PFA [25].

Flow cytometry is another diagnostic tool for GT. Because it measures the platelet receptor densities by using various monoclonal antibodies to those receptors. Then it will signaling out the deficient αIIBβ3 he patients with GT have decrease or absent levels of CD41 & CD61 while the normal levels of CD42 are present and the identification of defective or deficient αIIBβ3 are also observed in patients with GT low cytometry is easy to perform in peads because a small volume of sample could be used in this methodutation analysis is the best way to diagnose GTIIBβ3 , ITGB3 and ITGA2B gene should be carefully examine during the procedure and should be then confirmed through second DNA sample analysis [26, 27].

The overall diagnostic procedure of GT include prolong bleeding time, prolong PFA, diminished and absence of clot retraction and absence of platelet aggregation during LTA these all situations indicates the disease progression [28, 29].

Management of GT

Management of minor to moderate bleeding

Minor to moderate bleeding episodes could be encounter by local measures or used of anti fibrinolytic drugs. The local measres include gelatin sponge, topical application on skin and also application of thrombin etc., anti fibrinolytic agents include tranexamic acid, aminocaprolic acid and epsilon. These agents could be used alone or in combination with rFVIIa. Both of these be given orally or IV. They easily cure gingival bleeding, epistaxis and mennorr agia. The all of the anti - fibrinolytics are prohibited in patients with hematuria because of clot presence in urine. Above agents could also used as a prophylaxis of surgical procedures.

Management of epistaxis

Epistaxis could also cure by local thrombin application and anti fibrinolytic drugs, nasal packages etc. according to studies epistaxis more efficiently cure by the use of prothrombotic agents. The last choice to cure epistaxis is platelet transfusion and rFVIIa treatmentith salt pork strips nasal packings are reported as a cure to severe epistaxis.

Management of menorrhagia

Anti - fibrinolytic therapy is best to manage menorrhagia but if in case it will fail then hormonal therapy should be used either progesterone alone or in combination with estrogen. medroxyprogesterone acetate once every 3 months should administer as an IM depot is enough to cure menorrhagia in womens with GT. Intrauterine devices could also be used in control of bleeding. The high - dose conjugated estrogen IVfor 24–48 hours is consider to stop menarche and severe bleeding. And it is followed with high doses of estrogen - progestin orally. The rFVIIa could also used in menorrhagia. In most severe cases the hysterectomy is prefer for that women who are no more desire to be a pregnant.

Management of Postpartum Hemorrhage

Pregnancy along with GT is associated with a high risk of fetal bleeding and postpartum bleeding. So rFVIIa in combination with anti - fibrinolytic agents and platelet transfusion should be done as a prophylaxis of vaginal delievery. All of the women with GT should be monitor for platelet alloantibodies throughout the duration of pregnancy [30].

Management with desmopressin

The release of VWF, tissue plasminogen activator and FVIIa into the plasma is trigger by desmopressin. It has no directly effected to platelets. But Desmopresin is successfully consider as a treatment option for various platelet disorders. There is not enough data supports the usage of desmoprresin in GT [31].

Role of transfusion in management of GT

Platelet transfusion is more prominently prefer when anti - fibrinolytic therapy and other local measures are fail to control the severe type of bleeding. It could also used as a prophylaxis just some time before to the surgery. After platelet transfusion 30 - 70% of the patients develop isoantibodies to GPIIb / IIIa isotopes or HLA isotopes. The Platelet alloimmunization may leads to platelet refractionaries and failure to platelet transfusion. HLA matched platelets could give the possible results for transfusion of platelets. The patients who did not respond to platelet transfusion then rFVIIa is recommended for those patients. immunoadsorption on protein A sepharose could remove platelet alloantibodies prior to surgical procedures [32].

The management of various symptoms of GT is describe below in summarize view as shown in **Table 2.**

Table 2. The symptoms of GT and their management respectively.

Symptoms	Management of symptoms
• Mild to moderate bleeding	• Local measures and anti - fibrinolytic agents
• Epistaxis	• Local thrombin, nasal packages
• Menorrhagia	• Hormonal therapy, anti - fibrinolytic therapy and hysterectomy rarely
• Postpartum hemorrhage	• rFVIIa, fibrinolytic agents and platelet transfusion
• Bleeding during surgery	• Prophylaxis by rFVIIa, platelet alloantibodies and immunoadsorption protein A sepharose.

TREATMENT of GT

The patients of GT need no treatment on regular basis but they require treatment therapy before any surgery or after any injury in which bleeding is cause. The agents used in the treatment of GT describe as below:

rFVIIa

It is used very commonly and first by the patient of GT in 1996. After that it is successfully used in the bleeding management of GT. But it is not so effective in all of the patients. Novoseven RT is a product available in japan , north America and Europe. It is a recombinant activated human FVIIirstly, it was used in many bleeding disorders but now FDA approved its use in severe bleeding cases of GT.

Mechanism of action

The factor rFVIIa is binds to platelet surface and activate factor IX and X and so what increases in thrombin formation. At the dose of 90mcg / kg or more heeding to studies considerations is enough to thrombin generation. The increase in thrombin formation stimulates platelet adhesion and platelet aggregation also included the GPIIb / IIIa lacking platelets.

Uses of rFVIIa

It is not 100% efficacious but could use in various bleed disorders including GT and those patients who are refractory to platelet transfusion. In hemorrhages when local measures and anti - antifibrinolytic therapy is failed to respond them rFVIIa should prefer to use. The exact dose for GT patients is not yet established but bolus injections of 90 mcg / kg IV every 2 hours for 3 doses or until bleeding stops is consider as a normal dose for GT patients that is followed by a single or more maintanence dose. rFVIIa have a short half - life so repeated dosing is prefer. Its use is recommended by the UK Haemophilia Centre Doctors' Organisation for minor surgical prophylaxis having dental extractions etc. it should use as early to the bleeding as possible because on the basis of clinical trials within 12 hours bleeding could stop by the usage of rFVIIa.

Retuximab

Rituximab is anti - CD20 agent. It is a human - mouse chimeric monoclonal antibody that binds with B - cells CD20 antigen and is used in the acquired immune cytopenia and other bleeding disorders. For patients with GT The use of systemic corticosteroids, chemotherapy, protein A Sepharose immunoadsorption, plasma transfusion and IVIG, rFVIIa, and rituximab is approved to admirably in the treatment of GT. The usual dose dose of 375 mg / $m^{2/}$ week for 4 weeks is consider as enough dose to treat GT and also leads to cessation of disease symptoms and normal platelet aggregation [5,33].

Bevacizumab

Bevacizumab (avastin) it is an anti VEGF antibody that is used in a variety of cancers in combination with chemotherapy dose of 5 mg / kg infusion of bevacizumab was first given every 2 weeks followed with a maintanence dose in every 4 weeks is consider to be reduction in GIT bleeding cause by angiodysplasia and also in other bleeding disorders. It was reported that patents who are fail to respond to tranexamic acid and aminocaproic acid are well respond to the bevacizumab therapy. It cess the bleeding in many cases efficiently.

Hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation (HSCT) is not too effective treatment option for GT. Infact it is done very rarely and

reserved as a last choice of therapy. The successful HSCT or bone marrow transplantation was first performed on a 4 year old boy in 1985. Glanzmann's discovered the disease but there is no satisfactory treatment is available yet for GT. Further studies and more advocate treatment options could develop for severe bleeding episodes during the disease progression [34].

DISCUSSION

Platelets are one of the cells found in plasma of blood it plays many role in blood coagulation pathway and other hemostatis maintanence systems. If there is any abnormality occurs in these hemostasis pathways it will leads to a diasease progression. Glanzmann's thrombocytopenia is one of that disease which are caused by platelet functional abnormalities, the global frequency or ratio of disease is very rare however it is common in UK, Europe, Japan etc. the major cause of disease including genetic defects. Its pathogenesis starts by a platelet surface receptor abnormality i:e. GPIIb / IIIa hat will cause by a mutation of genes found in that platelet cell. GT is characterized by a various bleeding disorders including gingival bleeding, epistaxis, menorrhage etc. the proper management of each symptom is require either by local measures, anti - fibrinolytic drugs, tranexamic acid and aminocaproic acid. GT could not diagnose by platelet count because platelet is normal in a patient with GTo, it could diagnose by prolong bleeding time, prolong PFA results, flow cytometry technique and by LTA. The satisfactory treatment is not yet available for GT but rFVIIa is consider a best choice to cess disease progression and its symptoms it binds with platelet and activates factor IX and X which further stimulates platelet aggregation. Other treatment options included rituximab that is human - mouse chimeric monoclonal antibody it binds with B - cells CD20 antigen to perform its functiont was first used in the treatment of acquired immune cytopenia then later approved to treat GT at a dose of 375 mg/m^2/week for 4 weeks. Another agent is bevacizumab that is anti VEGF antibody and was used in cancerous patients along with chemotherapy. It will respond on those patients even who fail to respond on aminocaproic acid, tranexamic acid therapies etc. the last choice of treatment is bone marrow transplantation which is very rarely used in very rarely casesther treatment options include systemic corticosteroids but it have various adverse effects so not used as a treatment tool in GTt was suggested that there's should be a medicines involved in GT treatment therapy that blocks the mutation of genes on genetic level so that the disease progression stops sucessfully and its further pathogenesis could also encounter in a patients.

CONCLUSION

Heeding to the studies introductory it was concluded that glanzmann's thrombasthenia is a platelet disorder it is very rarely occur and characterized by severe bleeding episodes hence, it's proper treatment and management is of great concern for all health care expertise.

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