



Clinical and Biological Profile of Glanzmann Thrombasthenia in a Pediatric Cohort : A Report of Eight Cases

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ABSTRACT

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Introduction : Glanzmann's thrombasthenia (GT) is a rare bleeding disorder caused by quantitative or qualitative abnormalities of the platelet membrane glycoprotein IIb/IIIa, which is involved in platelet aggregation. This study aimed to describe the clinical and biological profiles of patients with GT and to evaluate the diagnostic performance of platelet aggregometry test in confirming this rare disorder.

Material and methods : This study involved 8 patients presenting with clinical symptoms of mucocutaneous bleeding and suspected inherited platelet disorder. Platelet aggregation test was performed on platelet-rich plasma (PRP) using a panel of physiological agonists, including adenosine diphosphate (ADP), collagen, epinephrine, and arachidonic acid. Ristocetin-induced platelet aggregation was assessed to differentiate GT from other macrothrombocytopenias.

Results : Hemorrhagic symptoms included mucocutaneous bleeding (epistaxis, ecchymosis, gingival hemorrhage). Both the platelet count and routine hemostasis tests showed normal physiological values. Platelet aggregometry test revealed a pathognomonic profile in all eight cases : a near-total absence of aggregation in response to physiological agonists, contrasted with a preserved or subnormal response to ristocetin.

Conclusion : Our study confirm that platelet aggregometry test remains the definitive gold standard for the biological diagnosis of GT. Despite its technical complexity necessitating centralization in specialized reference laboratories, it provides a reliable and essential functional assessment for the management and classification of this rare hemorrhagic disorder.

KEYWORDS:

Thrombasthenia, Platelet-Rich plasma, Platelet Aggregation Test, Blood Platelet Disorders, Ristocetin

INTRODUCTION

First described in 1918 by Swiss pediatrician Eduard Glanzmann, GT is a rare autosomal recessive congenital bleeding disorder. While the estimated global prevalence is approximately 1/1000 000 in the general population [1], its incidence rises significantly in regions with high rates of consanguinity, reaching 1/200 000 or higher [2].

It is a thrombopathy transmitted in an autosomal recessive manner, caused by mutations in the ITGA2B or ITGB3 genes located on chromosome 17q21 [3], leading to a quantitative or qualitative abnormality of the platelet integrin α IIb β 3, the fibrinogen receptor [4].

Clinical symptoms typically manifest early in life, occasionally during the neonatal period, with bleeding episodes involving skin and mucous membranes. This most commonly includes epistaxis, ecchymosis, and gum bleeding [5]. Gastrointestinal bleeding are less frequent, while some cases of GT remain clinically silent until they are incidentally diagnosed during invasive procedures or surgical interventions [6].

In Morocco, GT remains significantly under-documented, with the existing literature largely confined to isolated case reports. Consequently, the present study aims to provide a

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comprehensive characterization of the epidemiological, clinical, and biological profiles of GT within the Moroccan context, and to highlight the fundamental role of specialized laboratory tests in for a definitive diagnosis.

MATERIAL AND METHODS

A prospective descriptive study was conducted from August 2023 to February 2025. We included all patients suspected of GT, based on clinical presentation and suggestive personal or familiar history, regardless of age and sex. LTA was performed according to a standardized protocol to evaluate platelet functional integrity.

Patients were interviewed to collect demographic data (age, gender, geographical origin), clinical data (characteristics of bleeding episodes, their location, frequency), personal and/or family history of bleeding, rates of consanguinity, the presence of similar cases in the family, and medication use.

To prevent iatrogenic interference, a 10-day washout period was strictly observed for patients previously treated with antiplatelet agents or non-steroidal anti-inflammatory drugs (NSAIDs).

For each patient, coagulation tests were performed on SYSMEX CN-3000® analyzer, including prothrombin time (PT), activated partial thromboplastin time (aPTT), the measurement of fibrinogen and von Willebrand factor (vWF). Platelet count was performed on MINDRAY BC-6200® analyzer.

For LTA, venous blood samples were collected into 3.2% trisodium citrate tubes. To preserve platelet functional integrity, strict pre-analytical protocols were implemented, including a resting period, a 30-minute cessation of smoking and a 2-hour abstention from caffeine consumption. A control sample was taken under the same conditions from a healthy, untreated subject.

LTA was performed on SYSMEX CN-3000® analyzer within two hours of sample collection.

The assay is based on the turbidimetric principle, measuring the increase in light transmission through platelet-rich plasma (PRP) as aggregation occurs. Platelet activation was initiated using a panel of five agonists at the following final concentrations : ADP (1µM), collagen (2 µg/mL), arachidonic acid (1 mM), epinephrine (5 µM), and ristocetin

(1.2 mg/mL). The comparative aggregation rates for each agonist are illustrated in **Table 2**.

PRP was prepared via slow centrifugation at 1000 rpm for 10 minutes at room temperature. Following separation, the platelet count of the PRP was verified using a Mindray BC-6200® hematology analyzer. The mean platelet concentration of the PRP utilized was $280 \pm 35 \times 10^3/\mu\text{L}$.

Platelet-poor plasma (PPP) was obtained by a second, high-speed centrifugation step at 3000 rpm for 10 minutes. The aggregometer was calibrated using PPP as the 100% light transmission standard and PRP as the 0% transmission baseline.

Platelet agonists were introduced into the reaction cuvettes, and aggregation profiles were monitored over a 5- to 10-minute interval. Each patient's profile was validated and compared against a standardized healthy control to assess functional deviations.

Data were collected from the laboratory's platelet aggregation registry and laboratory information system (LIS). All statistical evaluations were performed using SPSS software (version 29.0) with a significance threshold set at $p < 0.05$.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Committee. Written informed consent was obtained from all study participants or their parents/guardians prior to inclusion in this study. All data were anonymized to ensure patient confidentiality.

RESULTS

During the period covered by our study, 192 platelet aggregation tests were performed. We identified 149 normal profiles and 43 thrombopathies, including 8 cases of TG, representing 18.6% of the thrombopathies documented in study.

The study population consisted of eight patients with a mean age of 5.87 years (range : 2–12 years). The cohort included six males and two females, resulting in a sex ratio (M/F) of 3.0.

Consanguinity was present in 80% of the cases. Two patients reported a positive family history of bleeding, specifically affecting siblings. Ecchymosis and epistaxis were the main bleeding manifestations reported (**Figure 1**).

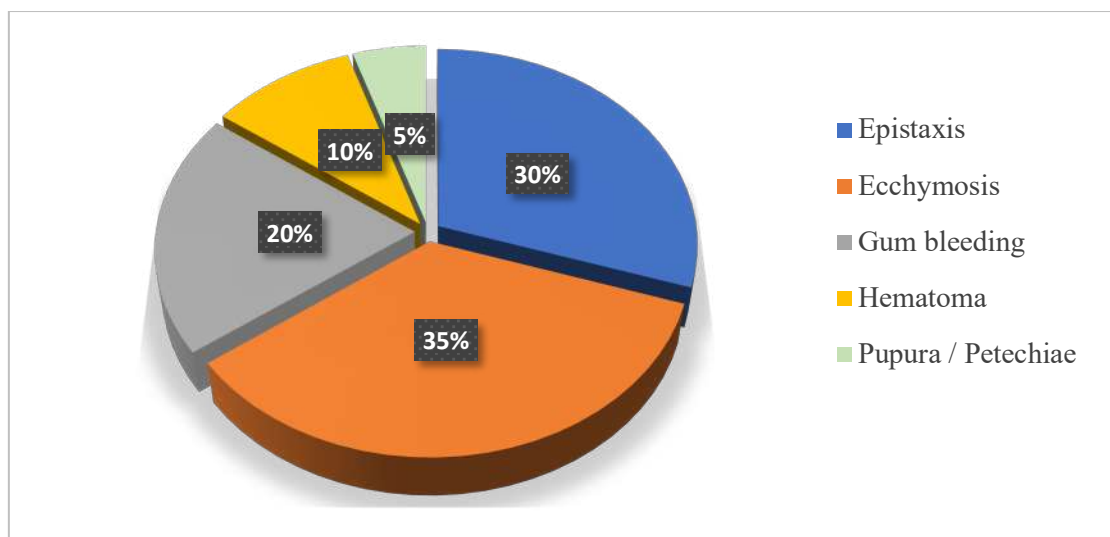


Figure 1 : Prevalence of bleeding symptoms among the patient population.

Baseline hematological parameters, including platelet counts and routine coagulation assays, were within reference ranges for all patients (Table 1). Peripheral blood smear examination

revealed normal platelet morphology in seven cases, with macrothrombocytes observed in only one patient.

Table 1 : Hemostasis parameters

Parameters	Observed Range (Min – Max)	Reference Range
Prothrombin Time (PT) (%)	75 -120	70 - 140 %
Activated Partial Thromboplastin Time (APTT) (ratio)	0.90 – 1.10	0.80 – 1.20
Fibrinogen (g/L)	2.58 – 3.61	2.0 – 4.0
VWF:Ag (Antigen) (%)	100 - 160	50 - 150 %
VWF:RCo (Ristocetin Cofactor) (%)	95 - 120	50 - 150 %
Platelet count (10 ³ /μL)	160 - 361	150 - 450

Table 2 : Agonist-induced maximal platelet aggregation rates in the study population

Agonists	Aggregation rate (%)
Ristocetin	61,05 ± 23,38
Epinephrin	3,85 ± 7,21
Arachidonic Acid	15 ± 24,67
Collagen	1,81 ± 0,98
ADP	5,76 ± 12,24

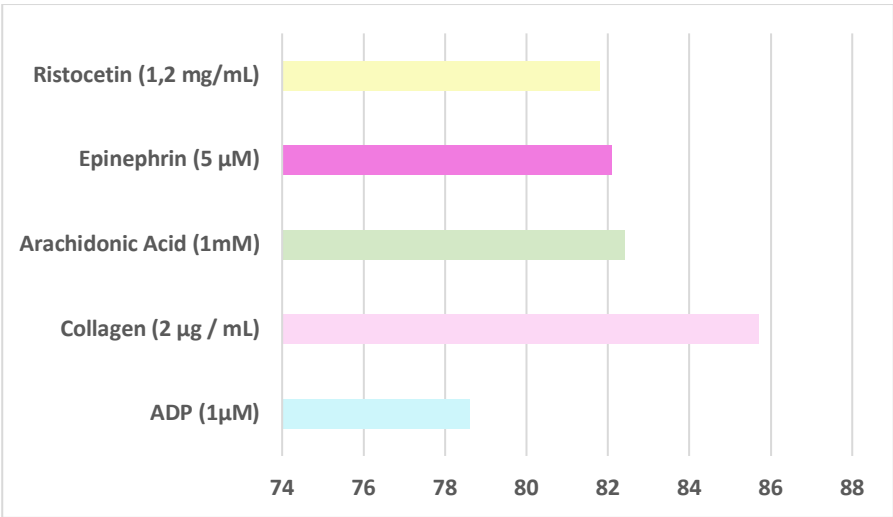


Figure 2 : Platelet aggregation rate in a healthy subject

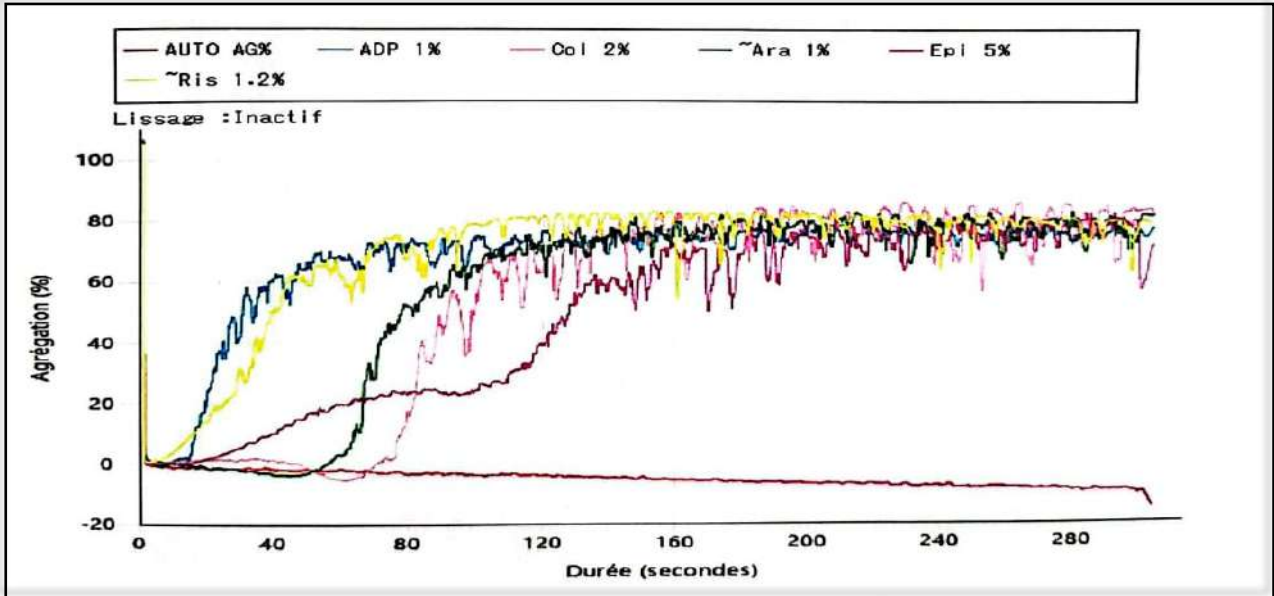


Figure 3 : Platelet aggregation profile in a healthy subject

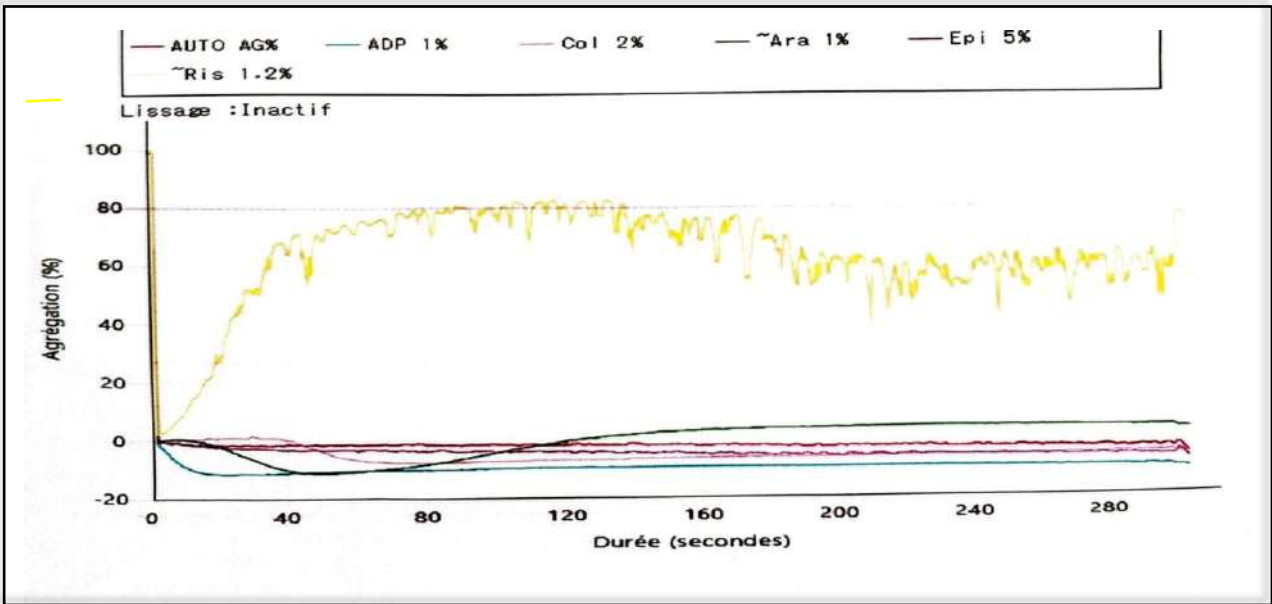


Figure 4 : Pathognomonic platelet aggregation profile of Glanzmann's Thrombasthenia.

DISCUSSION

Glanzmann's Thrombasthenia (GT) is a rare inherited platelet function disorder characterized by an autosomal recessive pattern. The molecular basis of GT involves a quantitative or qualitative deficiency of the integrin $\alpha\text{IIb}\beta 3$ which is known as the GPIIb/IIIa complex. This integrin functions as the predominant surface receptor for fibrinogen, with a density of approximately 80,000 copies per platelet [7].

GT is considered as a rare disease with a global estimated prevalence of 1 in 1,000,000 [8]. However, its incidence increases significantly in countries with high rates of consanguinity. In Morocco, studies report a high prevalence of GT, which correlates with consanguinity rates ranging from 54.5% to 81% across major hospital-based cohorts [9,10]. Due to these epidemiological factors, GT represents the most prevalent inherited platelet function disorder in Morocco. In the present study, consanguinity was documented in almost all patients, a result that closely aligns with the observations reported in previous clinical studies [11,12]. Two patients reported similar symptoms among older relatives, in whom bleeding episodes significantly regressed during adulthood. This observation supports earlier studies suggesting a potential improvement in clinical severity with age [13].

GT results from mutations in the ITGA2B or ITGB3 genes, preventing the assembly, intracellular transport or binding function of integrin [7]. Under physiological conditions, platelet activation triggers inside-out signaling, inducing a conformational rearrangement of the integrin $\alpha\text{IIb}\beta 3$. This transition shifts the receptor from a low-affinity to a high-affinity state, exposing the binding pocket for soluble plasma fibrinogen [7]. Fibrinogen then acts as a molecular bridge between the $\alpha\text{IIb}\beta 3$ complexes of adjacent platelets, allowing platelet aggregation and the formation of the hemostatic plug [14]. In GT, the lack of fibrinogen bridging makes platelet aggregation impossible, despite preserved initial adhesion to the subendothelium, which is mediated by the GPIb/IX/V complex (the platelet receptor for von Willebrand factor).

The GPIIb/IIIa complex plays a crucial role in outside-in signaling and the subsequent retraction of the fibrin clot through its direct linkage to the actin cytoskeleton, which explains the weak platelet plug and the severity of bleeding manifestations observed in GT's patients [15].

GT is categorized into three distinct clinical types based on the surface expression and functional integrity of the GPIIb/IIIa complex:

- Type I: Severe deficiency (<5% of normal expression), usually associated with absent clot retraction.
- Type II: Moderate deficiency (5–20% of normal levels), with residual clot retraction.

- Type III (Variants): Near-normal expression levels (>50%), but the receptor is functionally defective [16].

The clinical phenotype of GT typically emerges during the neonatal period or early infancy, manifesting as a mucocutaneous bleeding disorders including recurrent epistaxis, gum bleeding, spontaneous or post-traumatic purpura and ecchymoses [7].

In females of reproductive age, heavy menstrual bleeding is a major clinical complication that often serves as the inaugural manifestation of the disorder. This condition can be life-threatening, frequently resulting in severe iron-deficiency anemia [17].

Gastrointestinal bleeding and hematuria are less common, but generally correlate with severe clinical phenotypes. In contrast to hemophilia, hemarthroses and deep-seated hematomas are exceptionally rare in GT, typically occurring only as a consequence of significant mechanical trauma. Significant phenotypic heterogeneity is observed in GT. The intrafamilial variability in bleeding manifestations among individuals with identical mutations, suggests a dissociation between genotype and clinical expression, likely mediated by epigenetic factors or modifier genes [15]. In our study, ecchymosis was the predominant clinical sign, likely attributable to the pediatric age of our patients and their increased susceptibility to minor trauma. Epistaxis represented the primary mucosal manifestation and was the inaugural symptom in two patients. Other documented bleeding signs included gum bleeding, hematomas, and petechiae. However, no gastrointestinal bleeding has been reported.

The biological diagnosis of GT is primarily based on the prolonged platelet occlusion time. In contrast, the platelet count, morphology on peripheral blood smear, and routine coagulation profile (PT, aPTT, and Fibrinogen) typically remain within reference ranges [17]. These findings align closely with the observations documented in our study.

LTA is the gold standard for GT's diagnosis. However, it is a technically demanding procedure that requires strict pre-analytical standardization and specialized expertise to interpret aggregation profiles. Consequently, it is typically centralized in reference laboratories. It is performed on PRP. The pathognomonic profile consists of a near-total absence of aggregation in response to physiological agonists—including ADP, collagen, epinephrine, and arachidonic acid—while the response to ristocetin remains preserved or subnormal [7]. This differential response to ristocetin is a critical diagnostic hallmark, effectively excluding Bernard-Soulier syndrome and von Willebrand disease.

The management of GT involves a dual strategy focusing on prophylactic measures and the acute control of bleeding episodes. The first-line treatment for acute episodes relies on platelet transfusions, although recurrent administration

carries a significant risk of platelet alloimmunization [17]. Consequently, recombinant activated factor VII (rFVIIa) has emerged as a safe and effective therapeutic alternative for immunized patients [7]. Although hematopoietic stem cell transplantation currently represents the only definitive curative treatment, the significant risk of procedure-related morbidity limits its use to the most clinically severe cases [8]. As part of a family investigation, LTA was performed on both parents. The mother showed a normal aggregation profile. In contrast, the father showed low aggregation across all agonists, suggesting a potential GT variant. Consequently, further investigations, including flow cytometry and molecular genetic testing, are required to definitively characterize the GT subtype and differentiate between heterozygous and homozygous profiles [18].

CONCLUSION

GT is a rare bleeding disorder characterized by significant mutational diversity, resulting in a broad spectrum of clinical severity. Although functional assays proved reliable in our patient series, access to molecular genetic diagnosis remains a primary challenge, limiting the precise identification of underlying mutations. Nevertheless, genetic characterization is essential for resolving atypical cases, providing accurate genetic counseling, and facilitating prenatal diagnosis, particularly in regions with high rates of consanguinity.

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