ORIGINAL ARTICLE

Congenital thrombopathies in southern Tunisia : A multicenter study

Les thrombopathies congénitales dans le sud Tunisien : Etude multicentrique

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Abstract

Introduction : congenital thrombopathies (CTs) are rare bleeding disorders resulting from platelet dysfunction which may also be associated with thrombocytopenia. To date, the prevalence of CT in Tunisia has not been established.

Aim : The aim of this study was to describe the various types of CT and the associated hemorrhagic manifestations observed in a cohort from southern Tunisia.

Methods : We retrospectively collected clinical and laboratory data of patients with CT who were followed up over 43 years (1982 - 2024) in the pediatric and hematology departements of a university hospital center in southern Tunisia. The diagnosis of thrombopathy was established based on flow cytometry analysis and/or light transmission aggregometry and/or molecular analysis.

Results : We identified 60 patients (35 men and 25 women). The mean age at diagnosis was 61.7 months (1 month-70 years). Consanguinity was noted in 71.6% of cases (n=43). A family history of thrombopathy was reported in 51.6% of cases (n=31). The presenting symptoms at diagnosis were spontaneous or provoked bleeding (n=56) and easy bruising associated with thrombocytopenia within the first 48 hours of life (n=1). The etiologies of the thrombopathies were as follows : Glanzmann thrombasthenia (n=54), Bernard Soulier syndrome (n=5) and Wiskott Aldrich syndrome (n=1).

Conclusion : Glanzmann thrombasthenia was the most prevalent thrombopathy
in our cohort, likely attributed to the high rate of consanguinity in our region.

Keywords: Thrombopathy; hemorrhage; Glanzmann thrombasthenia; Bernard Soulier syndrome; Wiskott Aldrich syndrome

Résumé

Introduction: les thrombopathies congénitales (TC)sont maladies hémorragiques qui résulte d'un dysfonctionnement plaquettaire qui peut être associé à une thrombopénie. jusqu'à nos jours, la prévalence des TC en Tunisie n'a pas été établie.

Objectif: décrire les différents types de TC et les manifestations hémorragiques associées dans une cohorte du sud Tunisien

Méthodes: nous avons collecté rétrospectivement les données cliniques et biologiques des patients atteints d'une TC durant une période de 43 ans (1982-2024) dans les services de pédiatrie et d'hématologie du sud Tunisien.

Le diagnostic de TC était basé sur la cytométrie en fluc et/ou l'aggrégométrie et /ou sur l'analyse moléculaire

Résutats: Nous avons colligé 60 patients (35 de sexe masculin et 25 de sexe féminin). La moyenne d'age au moment du diagnostic était de 61,7 mois (1 mois-70 ans). La consanguinité a été notée dans 71,6% des cas (n=43). Des antécédents familiaux de TC ont été rapportés dans 51,6% des cas (n=31). Les symptomes au moment du diagnotisc étaient des saignements spontanés ou provoqués (n=56) et des ecchymoses associés à une thrombopénie néonatale dans un cas.

Les étiologies des TC étaient: une thrombasthénie de Glanzmann (n=54), syndrome de Bernard et Soulier (n=5) et syndrome de Wiskott Aldrich (n=1)

Conclusion: la thrombasthénie de Glanzmann était la thrombopathie la plus fréquente dans notre cohorte, attribué probablement aux taux élevé de consanguinité dans notre région

Mots clés: Thrombopathie, hémorragie, thrombasthénie de Glanzmann, syndrome de Bernard et Soulier, syndrome de Wiskott Aldrich

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Introduction

Congenital thrombopathies (CT) are a heterogenous group of bleeding syndromes resulting from platelet dysfunction which may also be associated with thrombocytopenia (1). In Tunisia, the prevalence of these disorders remains unknown due to the absence of a national registry of thrombopathies.
The hemorrhagic symptoms observed in patients with thrombopathies are mostly muco-cutaneous and of variable severity (1,2).
The diagnosis of thrombopathies is not always easy. It can be challenging due to similarities in the clinical presentation with other hemostatic disorders (3). Moreover, these conditions are rare and may coexist with other hemostatic abnormalities, such as coagulation factor deficiencies, Von Willebrand disease, or thrombocytopenia (4,5).
The diagnosis of CT follows a stepwise approach based on clinical history, laboratory analysis of platelet morphology, platelet aggregation in response to specific agonists, flow cytometry assessment of platelet glycoproteins and genetic analysis. These biological analyses allow for the diagnosis of major thrombopathies, mainly Glanzmann's thrombasthenia (GT) and Bernard-Soulier syndrome (BSS). However, other thrombopathies (such as secretory thrombopathies) present significant diagnostic challenges necessitating specialized tests like electron microscopy.
The management of patients with CT primarily relies on local hemostatic measures and/or antifibrinolytic therapy (6,7). If these initial measures fail to control bleeding, platelet transfusion and/or recombinant, activated Factor VII (rFVIIa) may be administered. Additionally, education of patients and their families is essential in preventing the occurrence of bleeding and optimizing disease management.
The aim of this study was to describe the various types of CT and the associated hemorrhagic manifestations observed in a cohort from southern Tunisia.

Methods

As part of the development of a registry for congenital bleeding disorders, we restropectively collected medical records of patients diagnosed with CT over a 43-year period (1982-2024) in the pediatrics and hematology departements at Hedi Chaker Hospital.
For each patient, clinical data were collected, including family history, sex, age at presentation, bleeding severity and sites, as well as findings from the clinical examination. Laboratory investigations included a complete blood count, blood smear analysis, mean platelet volume (MPV) measurement, prothrombin time (PT), activated partial thromboplastin time (APTT), bleeding time, closure time (PFA-100/200) , Von Willebrand factor antigen (VWF) quantification, platelet aggregation studies using adenosine diphosphate, collagen,arachidonic acid and ristocetin, as well as flow cytometry analysis.

Inclusion criteria

patients diagnosed with GT, BSS and Wiskott Aldrich syndrome (WAS) were included. The diagnosis of GT was based on normal platelet count, prolonged bleeding time and/or closure time, lack of aggregation in response to ADP, collagen and arachidonic acid and reversible aggregation with ristocetin. Deficient αIIbβ3 integrin expression is detected via monoclonal antibodies targeting CD41 (αIIb) and CD61 (β3) using flow cytometry. The diagnosis of BSS was based on the presence of thrombocytopenia, giant platelets in the blood smear and the absence of aggregation in response to ristocetin and/or on flow cytometry. WAS was confirmed by genetic testing.
We excluded other inherited platelet disorders such us:
- Congenital thrombocytopenia
- Thrombopathy observed in Arthrogryposis, cholestasis and renal dysfunction (ACR syndrome) and in chediak Higaschi syndrome.
- Aquired disorders of platelet function.

Since 2020, the ISTH-SSC Bleeding Assessment Tool (ISTH-BAT) has been introduced as a standardized method for retrospective symptom evaluation. This tool comprises 14 categories. A high bleeding score (>6) is indicative of an inherited bleeding disorder. This tool has been systematically applied to patients newly diagnosed over the past four years (2020-2024) (8).
This score was used for patients newly diagnosed in the last four years

Statistical analysis

Data were entered and analyzed using the computer software Statistical Package for Social Sciences (SPSS), version 23.
Qualitative variables were expressed as absolute frequencies (N) and proportions (%), while quantitative variables were analysed using means for normally distributed variables. For non-normally distributed variables, data were presented as medians. The Kolmogorov-Smirnov test was used to assess the normality of quantitative variables.

Results

General results

We identified 60 patients with CT, of whom 35 were males (58%) and 25 were females. originated from southern Tunisia. The distribution of thrombopathy subtypes in our cohort was as follows: GT (n=54), BSS (n=5) and WAS (n=1).
The age at diagnosis ranged from one month to 70 years (median: 5.1 years). Forty-one patients (71.6%) were born to consanguineous parents, and thirty-one patients had a family history of CT (51%). A family history of death due to severe bleeding was reported by 15 patients (25%).
The most common presenting symptom at diagnosis was bleeding (n=56), while three patients were diagnosed through family screening (n=3), and one patient presented

with bruising and neonatal thrombocytopenia (n=1). Initial clinical manifestations included skin and mucosal bleeding in 37 patients (61.6%). (Table 1)

Table 1. sites of bleeding at presentation in our cohort

Bleeding sites	Number (%)
Skin + mucosal bleeding	37 (61,6)
Skin + mucosal+ gastrointestinal bleeding	15 (25)
Visceral bleeding : gastrointestinal bleeding/ caesarien section	4 (6,6)
Hemorrhagic circumcision	4 (6,6)

Glanzmann Thrombasthenia

Among the 60 patients, 54 were diagnosed with GT, including 32 males and 22 females. Consanguinity was noted in 39 cases (72.2%). The mean age at diagnosis was 5.1 years, ranging from one month to 70 years.
A family history of GT was reported by 31 patients (57%). Hemorrhagic manifestations at initial diagnosis were spontaneous in 47cases and provoked in seven cases. (Table 2)

Table 2. Sites of spontaneous and provoked bleeding in patients at diagnosis

Spontaneous bleeding	
Type of bleeding	**Number of patients**
Epistaxis	36
Gingival bleeding	20
Bruising	11
menorrhagia	10
Gastrointestinal bleeding	5
Provoked bleeding	
Type of bleeding	**Number of patients**
Circoncision	3
Caesarean section	2
Scalp hematoma	1
False aneurysm	1

Most patients (95%) had a normal platelet count (91000-400 000/mm3). PT, APTT and VWF assays were within normal limits in all patients.
Thirty patients had prolonged bleeding time or occlusion time (platelet function analyser PFA100). Platelet aggregation testing, performed in 42 patients, revealed absent aggregation in response to ADP, arachidonic acid and epinephrine. Flow cytometry analysis was conducted in 26 patients, enabling disease classification in 25 patients: type 1 (76%) and type 2 (24%). Familial screening was performed in only 7 families identifying three asymptomatic carriers, including two members from the same family (father and sister).
Management of the initial bleeding event was based on local measures such as nasal packing (27,7%), intravenous tranexamic acid (74%), ethamsylate (57,4%). Forty-nine patients received leukocyte-free platelet transfusion (90,7%). Recombinant activated Factor VII was indicated during the course of the disease in eight patients (14,8%) (Table 3).

Table 3. Indications of rFVIIa in patients with Glanzmann Thrombastenia

Indication	Number of patients
Immunization anti HLA	2
Bleeding refractory to platelet transfusion without immunization	2
Unknown reason	2
Ovarian hemorrhage with hemoperitoneum	1
Hemorrhagic choc related to gastrointestinal bleeding	1

Twelve (12/22/) female patients (54,4%) were treated with high doses of progesterone to prevent menorrhagia. During follow-up, 49 patients (90,7%) had at least one bleeding episode (1-29). The mean follow-up was 24.8 years. The mean age at last visit was 23.4 years (2-74 years). Four patients developed alloimmunization, one patient developed thrombosis, and we recorded three deaths due to refractory epistaxis, severe gastrointestinal bleeding and excessive gingival bleeding complicated by disseminated intravascular coagulation.

Bernard Soulier Syndrome

The epidemiological, clinical, biological and follow-up data of patients with BSS are summarized in Table 4.

Wiskott Aldrich syndrome

A three-month-old boy presented to our department with bruising and epistaxis. He was born to unrelated parents and was the third child in the family, with two older sisters who appeared to be healthy. Thrombocytopenia had been noted since the neonatal period (day 2 of life), leading to an initial diagnosis of thrombocytopenia secondary to maternal alloimmunization. He received intravenous immunoglobulin and platelet transfusion. At the age of 7 months, he was admitted for epistaxis and severe eczema. Complete blood count showed microcytic non-regenerative anemia (Hb of 8.8 g/dl), platelets count of 29000/mm3 and a mean platelet volume of 4.9 fl (normal limits: 8-11). His blood smear showed microthrombocytopenia. His immune work up showed normal IgG levels, decreased serum IgM, elevated serum IgA (1.93 g/L, normal range for age: 0.13-0.82) and IgE of 2500 UI/L. Whole exome sequencing revealed a novel mutation in the WASP gene and functional tests are underway. During the course of the disease, the patient presented with recurrent bronchitis, otitis and severe infection (candidemia). He developed hemolytic anemia at the age of 16 months, which was
managed with oral corticosteroids. He is proposed for geno-identical hematopoietic stem cell transplantation.

Evaluation of the bleeding score (ISTH BAT).

Since 2020, the ISTH-BAT has been used to assess the bleeding score in newly diagnosed patients. In this study, a total of 17 patients underwent assessment including

14 cases of GT, 2 cases of BSS and one case of WAS. The mean value of ISTH BAT was 7,57 in patients diagnosed with GT. The two patients diagnosed with BSS had ISTH BAT values of 7 and 4 respectively. The patient with WAS had a value of 8.

Table 4. Epidemilogical, clinical, and biological data in patients with BSS

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at diagnosis (months)	19	24	48	168	24
sex	M	F	F	F	M
Presenting symptoms	Hemorrhagic circumsion	Bruising, gingival bleeding	Epistaxis gingival bleeding	menorrhagia	Bruising , epistaxis
Platelet count (mm3)	7000	33000	7000	20000	5000
Blood smear	Giant platelet	ND	ND	ND	Giant platelet
Aggregation test	+	+	+	+	+
Cytometry on flow	CD42 : 0% CD61 : moderete deficiency	ND	ND	ND	CD42A : 0,9%, CD42B : 0,1%
Platelet transfusion	yes	yes	yes	yes	yes
Desmopressine	Yes but inefficient	-	-	-	-
rFVII a	Yes	No	No	No	No
Evolution	Recurrent epistaxis(46 episods)	menorrhagia	menorrhagia	Menorrhagia of great abundance	Gastro-intestinal bleeding
Follow up duration	13 years	10 years	14 years	7 years	27 years
Allo immunization	yes	No	No	No	No

F: female, M: male, ND: not done, rFVIIa: recombinant activated factor VII

Discussion

This is the first and largest cohort study of congenital thrombopathies in our country. The haemophilia center at the Aziza Othmana hospital (Northern Tunisia) reported 35 cases of GT in 2017 (9). The World Federation of Haemophilia documented a total of 80 cases of congenital thrombopathies in Tunisia in its 2022 annual global survey (10) (GT: 71 cases, BSS: 9 cases, unkown platelet disorders: 13 cases). In this report, GT emerges as the most prevalent inherited platelet disorder, accounting for 71 out of 93 cases.

However, the precise prevalence of inherited thrombopathies in our country remains undetermined due to the absence of a national registry.

Our cohort includes 54 cases of GT, which is the most common inherited thrombopathy. As with other autosomal recessive disorders, the prevalence of GT is higher in communities with a high frequence of consanguinity, such as Pakistanis and Iranians (3,11). The highest prevalence of the disease was reported by Toogeh et al. in a large Iranian cohort of 382 patients with GT (1 in 200000) (3).

The number of GT cases in our cohort is higher than that reported in the north of the country; this can be attributed to the higher frequency of consanguinity in southern Tunisia. In fact, Mahmoudi H et al. reported a rate of consanguinity of 68% in a cohort of 35 patients with GT (9), whereas Ben Arbia et al. reported an even higher rate of 82% of consanguinity among patients in the southern region (12). This frequency of GT in our population is undoubtedly underestimated due to the lack of family studies that detect asymptomatic carriers. In fact, only 7 families consented to undergo platelet aggregation testing in our study.

As an autosomal recessive disorder, GT affects both sexes equally. This has been demonstrated in some studies, which have shown a sex ratio close to 1 (9, 13). In our study and that of Toogeh et al (3), GT was observed predominantly in males.

GT is usually diagnosed before the age of 5 years. In our cohort, the mean age at diagnosis was 5.1 years. In line with the literature, the most common presenting symptoms were epistaxis, gingival bleeding and easy bruising (3). One male patient was diagnosed at the age of 70 years following an episode of upper gastrointestinal bleeding. In the cohort of Mahmoudi et al. in northern Tunisia, easy bruising was the main cause of the diagnosis circumstances (9). During the course of the disease, ten women (45.4%) presented with menorrhagia. The prevalence of menorrhagia in women with GT exceeds 9 in 10 cases and can severely affect their quality of life, leading to recurrent hospitalizations and the need for multiple blood transfusions (14).

In our region, the diagnosis of GT is based on platelet aggregation testing and/or flow cytometry analysis. Unfortunately, genetic testing remains unavailable in our country, limiting comprehensive molecular characterization.

As these two diagnostic analyses are conducted exclusively in a specialized laboratory, their availability is restricted to the Sfax region. This geographic limitation significantly hinders the early and accurate diagnosis of hereditary platelet disorders, particularly for patients residing in other regions with limited access to specialized hematological testing.

Consequently, the lack of widespread diagnostic facilities not only delays appropriate clinical management but also contributes to an underestimation of the true prevalence of these conditions at the national level.

In our cohort, the management of GT primarily involves local hemostatic measures (nasal packing, prolonged local compression), in addition to antifibrinolytics and leukocyte-depleted platelet transfusion. The use of recombinant activated factor VII (rFVIIa) is restricted, it has only been reserved for cases where the above modalities fail to achieve hemostasis or in patients with alloimmunization.

The French reference center for inherited platelet disorders recommends the use of rFVII in cases of refractoriness to platelet transfusion or when platelets consentrates are not readily available in certain emergency situations (15).

In our study, we identified 5 cases of BSS. The World federation of hemophilia reported 9 cases of BSS in Tunisia in their 2022 annual report (10). The largest cohort reported in the literature to date was described in Iran (16). BSS is a rare inherited disorder, typically transmitted in an autosomal recessive manner, characterized by thrombocytopenia associated with thrombopathy and large platelets (17).

BSS is clinically characterized by a history of recurrent epistaxis, gingival and cutaneous bleeding and prolonged bleeding after trauma. In affected women, it may also be associated with heavy menstrual bleeding (17). Due to its association with thrombocytopenia, BSS is often misdiagnosed as immune thrombocytopenia (ITP), particularly in cases of chronic ITP that do not respond to standard therapies. Further investigations are required, especially in chronic ITP, such as a blood smear showing typical large or giant platelets, aggregometry tests and flow cytometry analyses to assess glycoprotein Ib-IX-V complex expression and function. Despite the importance of genetic testing for definitive confirmation of BSS, this diagnostic modality remains unavailable in our country.

WAS is a rare X-linked primary immunodeficiency disease characterized by recurrent infections, eczema and microthrombocytopenia. The estimated incidence is approximately 1 case per 100000 live births (18). The Tunisian Primary Immunodeficiency Registry reported 6 cases over a 25-year period (1988-2012) corresponding to an incidence of 0.54 cases per million people (19). The largest recent cohort in the literature was reported by Gueerero and al. in Spain, they collected 97 cases over a 21-year period (1997-2017), with a mean annual incidence of 1.1 cases per 10 million inhabitants (20).

The presenting symptoms in our patient were easy bruising within the first 48 hours of life, associated with neonatal thrombocytopenia. The diagnosis was suspected at the age of 7 months when eczema appeared and was confirmed through genetic testing. During follow-up, the patient didn't have any hemorrhagic accidents, however, he developed recurrent and severe infections and autoimmune complications (autoimmune hemolytic anemia). Given the severity of the phenotype according to the WAS score (21), our patient has been proposed for HLA haploidentical stem cell transplantation in the absence of a geno-identical donor.

Our study had several limitations. Firstly, the lack of family study due to parental refusal hindered the identification of asymptomatic carriers; Secondly, the bleeding severity of all patients was not systematically assessed using the ISTH-BAT score, limiting the comparability of clinical manifestations. Finally, the unavailability of molecular diagnostic testing for patients with GT and BSS precluded genetic confirmation, which is essential for precise diagnosis, genetic counseling, and family screening. We emphasize the importance of creating a national registry for CT in order to accurately determine the exact prevalence of CT in our country and to standardize diagnosis and management's strategies for patients suffering from CT.

A key strength of our study is that case identification was conducted as part of the establishment of a registry for congenital bleeding disorders in southern Tunisia. This initiative aims to improve epidemiological surveillance, facilitate early diagnosis, and optimize patient management in this region.

Additionally, our study is multicentric, involving multiple healthcare institutions, which enhances the representativeness of the data and provides a more comprehensive assessment of the burden of inherited platelet disorders in our population. This collaborative approach strengthens the reliability of our findings and underscores the need for continued efforts to improve diagnostic and therapeutic strategies for these rare conditions.

Conclusion

This is the largest multicenter study of CT in our country. We demonstrate that CT in general and GT in particular are more common in southern Tunisia because of the high consanguinity rate, but this frequency is certainly underestimated.

The establishment of a registry for bleeding disorders in southern Tunisia is a crucial step in systematically collecting all cases of affected patients, allowing for a comprehensive characterization of these conditions and improve patient care.

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