Thromkid – a Competence Network for Functional Platelet Abnormalities

Results of a Population Based Survey Carried Out by the Pediatric Group of the German Society of Thrombosis and Hemostasis Research (GTH)

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Key Words

Platelets · Platelet function tests · Platelet disorders ·
Data collection

Summary

Background: Hereditary disorders of platelet function are often complex. Bleeding due to defective platelet function may be intermittent and unpredictable. Only few guidelines concerning testing for platelet function and treatment of affected patients have been developed so far. These experiences prompted the authors to initiate a collaborative patterns-of-practice survey and to establish a competence network in order to improve diagnosis and treatment of affected patients in German speaking countries (Thromkid quality project). **Materials and Methods:** Data were obtained by using standardized survey protocols between May 2005 and August 2006. **Results:** A total of 50 centers were identified. 88% agreed to participate in Thromkid. The laboratories offered a median of 4 tests. All laboratories offered platelet aggregometry. 28 laboratories used the PFA-100® closure time. Further widely used tests were the in vivo bleeding time and flow cytometry. 215 affected patients were identified 123 of whom fulfilled the authors' set of criteria, 43% were considered poorly characterized. Morbus Glanzmann, aspirin-like defects, and receptor defects were the most common diagnoses. **Discussion:** Future activities include i) to establish a web-based register of all centers, ii) to establish a patient registry, and iii) to prepare the basis for well-designed clinical studies resulting in rational and clinically useful guidelines for diagnosis and treatment of affected patients.

Schlüsselwörter

Blutplättchen · Thrombozytenfunktion ·
Thrombozytenfunktionsstörung · Datensammlung

Zusammenfassung

Hintergrund: Angeborene Störungen der Thrombozytenfunktion sind häufig komplexe Erkrankungen mit unterschiedlich stark ausgeprägter Blutungsneigung. Bis heute gibt es kaum Richtlinien für die Durchführung von Thrombozytenfunktionstests und die Behandlung von betroffenen Patienten. Diese Erfahrung veranlasste die Autoren zur Durchführung einer Umfrage in spezialisierten Zentren und zur Gründung eines Qualitätsnetzwerkes (Thromkid-Qualitätsprojekt), mit dem Ziel die Diagnosestellung und Behandlung betroffener Patienten im deutschen Sprachraum zu verbessern. **Material und Methoden:** Die Daten wurden mit Hilfe standardisierter Fragebögen zwischen Mai 2005 und August 2006 erhoben. **Ergebnisse:** Insgesamt konnten 50 Zentren identifiziert werden, von denen 88% zur Teilnahme an der Studie bereit waren. Alle Labors boten die Aggregometrie als wichtigste Methode an. 28 Labors verwendeten den PFA-100®. Weitere wichtige Methoden waren die In-vivo-Blutungszeit und die Durchflusszytometrie. 215 betroffene Patienten konnten identifiziert werden, von denen 123 eine eindeutige Diagnose aufwiesen, bei 43% war die Diagnose unklar. Morbus Glanzmann, Aspirin-ähnliche Defekte und Rezeptordefekte waren die häufigsten Diagnosen. **Diskussion:** In Planung ist 1) die Anlage eines internetbasierten Registers aller Diagnose- und Behandlungszentren, 2) ein Patientenregister und 3) die Vorbereitung für die Durchführung von gut konzipierten klinischen Studien, die die Entwicklung von rationalen und sinnvollen Leitlinien zur Diagnose und Behandlung betroffener Patienten erlauben.

Introduction

Platelets are essential for normal hemostasis. They contain many structural, metabolic and signaling components, resulting in four interconnected mechanisms all of which promote hemostasis: i) adhesion to sites of vascular injury and to artificial surfaces, ii) release of compounds by granules, iii) aggregation in order to form a platelet plug, and iv) presentation of a procoagulant surface for activation of protein complexes of the coagulation cascade [1].

Hereditary disorders of platelet function are often complex, and some are not completely understood [2]. The hallmarks are mucocutaneous and gastrointestinal bleeding, menorrhagia, epistaxis, easy bruising and bleeding from the oral cavity. Defective platelet function must be severe for clinically important spontaneous bleeding to occur, and even with severe abnormalities, bleeding may be intermittent and unpredictable. However, blood loss after trauma and surgery may be severe and life threatening in these patients [3].

Only few guidelines concerning testing for platelet function and treatment of patients with hereditary disorders of platelet function have been developed and published so far [4, 5]. To our knowledge, until now none of these efforts has resulted in widely accepted and clinical useful recommendations for the

Table 1. Questionnaire about laboratories and platelet function tests

General information about processing laboratory
General information about used tests
Detailed information on various aspects of test procedure and validation and interpretation of test results
Turbidimetric aggregometry, impedance aggregometry and luminometry
PFA-100® CT
In vivo bleeding time
Thrombelastography including ROTEM®
Flow cytometry
Electron microscopy
Molecular genetic tests
Other rare tests of platelet function

Table 2. Diagnostic criteria for patients with hereditary disorders of platelet function

Disease	Diagnostic criteria		
	primary	secondary	Tertiary
<i>Defects of adhesion proteins</i>			
Morbus Glanzmann	flow cytometry molecular genetics	aggregometry blood smear	PFA-100® CT in vivo bleeding time thrombelastography platelet count
Bernard Soulier syndrome	flow cytometry molecular genetics	aggregometry blood smear	PFA-100® CT in vivo bleeding time thrombelastography platelet count
<i>Secretion- and signal transduction defects</i>			
α - and/or δ -Storage pool defects*	electron microscopy	mepakrin test luminometry serotonin releasing assay flow cytometry	PFA-100® CT in vivo bleeding time platelet count aggregometry blood smear thrombelastography
Aspirin-like defects	enzymatic defect assay	aggregometry PFA-100® -CT malondialdehyde assay	platelet count in vivo bleeding time flow cytometry
<i>Receptor defects</i>			
Collagen, α 2-adrenergic, TXA2 receptor defects	flow cytometry	aggregometry blood smear / microscopy	PFA-100® CT in vivo bleeding time thrombelastography platelet count
<i>MYH9 macrothrombopenia</i>			
Fechtner syndrome, May-Hegglin anomaly	molecular genetics	blood smear / microscopy immuno histochemistry	platelet count in vivo bleeding time
*Including Hermansky-Pudlak syndrome.			

Table 3. Platelet function tests performed by participating laboratories

	Number of laboratories
Aggregation and adhesion	
Turbidimetric aggregometry	34
Impedance aggregometry	9
Platelet adhesion assays*	4
Platelet secretion	
Luminometry	5
Serotonin secretion assay	3
Global platelet function	
PFA-100® CT	28
Flow cytometry-based platelet function tests	26
In vivo bleeding time	19
Platelet metabolism	
Malondialdehyde assay	1
Clot formation	
Thrombelastography including ROTEM®	7
Clot retraction test	2
Morphology of platelets	
Electron microscopy	4
Molecular genetic methods	3

* DiaMed Impact-R test, Adeplat, adhesion measurement on various surfaces.

diagnosis and treatment of these patients. In addition, personal communications with clinical experts in the field revealed a considerable number of patients with bleeding symptoms, which are highly suggestive for disorders of primary hemostasis that are not sufficiently characterized up to now.

These experiences prompted the authors together with other members of the pediatric group of the GTH to initiate a collaborative patterns-of-practice survey and to establish a competence network in order to improve diagnosis and treatment of patients with functional platelet abnormalities.

The goals of Thromkid are i) to obtain information on the evaluation of hereditary disorders of platelet function in clinical laboratories, ii) to collect information on patients diagnosed with or suffering from symptoms highly suggestive for hereditary disorders of platelet function, iii) to establish a web-based register of all centers offering diagnostic tests and/or expert patient care for patients with hereditary disorders of platelet function, iv) to establish a registry for patients with hereditary disorders of platelet function, and v) to prepare the basis for well-designed clinical studies resulting in rational and clinical useful guidelines for diagnosis and treatment of these patients.

We report on the first results of Thromkid, based on the sur-

vey carried out between May 2005 and August 2006. A general overview and an outlook on future perspectives and activities of the Thromkid study group are presented.

Materials and Methods

Thromkid data acquisition was carried out between May 2005 and August 2006. All senior investigators of the Thromkid study group are members of the pediatric group of the GTH. All investigators are specialized in clinical hemostasis. They aim to improve diagnosis and treatment of coagulation disorders preferentially in German speaking countries.

Centers for diagnosis and treatment of patients with hereditary disorders of platelet function were identified by personal communication with members of the GTH and by contacting local staff members of these identified centers and asking for further coagulation laboratories and treatment centers in their area.

Diagnostic centers were defined as facilities providing various platelet function tests. Laboratories offering exclusively the PFA-100® closure time (CT) (Dade-Behring, Marburg, Germany) and/or in vivo bleeding time were not considered as centers. *Treatment centers* were defined as facilities that provide continuous medical care for patients with well established diagnosis of hereditary disorders of platelet function.

Study survey protocols included a variety of questions addressing diagnosis and treatment and other disease-related aspects of patients suffering from hereditary disorders of platelet function, or of patients presenting with symptoms highly suggestive for a diagnosis of hereditary disorders of platelet function (table 1). Table 2 summarizes diagnostic criteria that were applied by the authors. Depending on the suspected diagnosis, a set of primary, secondary and tertiary criteria was obligatory for acceptance of diagnosis.

Data were obtained by using standardized protocols. Interviews were carried out by personnel previously trained by senior investigators. All identified centers were visited and underwent an audit procedure. All data were critically appraised by senior investigators. Conflicts were solved by re-contacting local members of each center.

The study was approved by the institutional research ethics board requirements (MUI UN2436, 235/4.3).

Results

A total of 50 centers in Austria, Germany, Switzerland and Alto Adige (German-speaking part of former Tyrol, Italy) were identified. 44 centers (88%) agreed to participate in Thromkid. Figures 1 and 2 specify the centers. 22% of the centers were certified according to various commonly accepted quality requirements.

The laboratories offered a variety of tests with a median of 4 tests per laboratory. All laboratories offered platelet aggregometry and its variants. 28 laboratories assessed platelet function using the PFA-100 CT. The PFA-100 CT was frequently used as screening method in combination with aggregometry. Another widely used test was the in vivo bleeding time (n = 19). Morbus Glanzmann and Bernard Soulier syndrome were preferentially diagnosed or ruled out by flow cytometry. Aggregometry, PFA-100 CT, in vivo bleeding time, and flow cytometry turned out to be the most trusted methods in diagnosis of patients with hereditary platelet disorders.

Fig. 1. Characterization of centers offering platelet function tests 1.

Fig. 2. Characterization of centers offering platelet function tests 2.

215 patients with suspected hereditary disorders of platelet function were identified. 123 patients fulfilled the authors' set of criteria outlined in table 2. M. Glanzmann, aspirin-like defects, receptor defects, storage pool defects, and Bernard Soulier syndrome were the most common diagnoses (fig. 3). In collaboration with the members of GTH, the authors developed information sheets for each center (fig. 4). These will be published on the official webpage of the GTH.

Discussion

Hereditary disorders of platelet function are a heterogeneous group of diseases with a predominantly mild or moderate bleeding tendency [3, 6]. Bleeding may be severe and difficult to control in case of trauma, surgery, and other situations which challenge the hemostatic system. Due to technical difficulties, time-consuming test procedures and the short survival time of platelets after venipuncture, most platelet function tests are restricted to highly specialized laboratories, resulting in potential under-diagnosis of these diseases.

Personal experience of the authors and communication with other colleagues in the field, who have had similar experiences, prompted the authors to initiate a collaborative survey and to establish a competence network in order to improve diagnosis and treatment of patients with functional platelet abnormalities.

Thromkid is a quality project of the pediatric group of the GTH. The core of this study is a collaborative patterns-of-practice survey intended to overview diagnosis and treatment of patients with functional platelet abnormalities in German-speaking countries. These data will form the cornerstone of a new competence network that will address various diagnosis- and treatment-related questions. The overall goal is to improve diagnosis and treatment of these patients.

A total of 50 centers were identified by the investigators. 88% agreed to cooperate. Not unexpected, most centers were em-

bedded in universities and medical schools. 36 clinical laboratories offered a wide variety of tests. In accordance with practical considerations, laboratories offered a set of tests (median 4 tests). Platelet counts and assessment of blood smears were standard procedures in all laboratories. Detailed descriptions of these, without any doubt, very useful tests are beyond the scope of this paper. Aggregometry, PFA-100 CT, in vivo bleeding time, and flow cytometry were the most frequently applied platelet function tests. Although introduced more than 40 years ago, aggregometry was by far the most commonly performed platelet function test. The Moffat et al. [7] survey of the North American Specialized Coagulation Laboratory Association (NASCOLA) revealed similar results. The in vivo bleeding time is still the only routine test that may assess most aspects of hemostasis, including platelet function, coagulation and vessel wall function [8]. In vivo bleeding time played an important role in screening for defects of primary hemostasis in clinical laboratories participating in our study. This may be explained at least in part by the fact that the majority of centers combined in vivo bleeding time with careful physical examination of the patient and clinical assessment of bleeding symptoms. Many specialists in hemostasis, especially those practicing in the UK and USA, consider in vivo bleeding time a cumbersome test with poor reproducibility [9]. Over the last years, the PFA-100 CT, also often addressed as in vitro bleeding time, has replaced in vivo bleeding time in many laboratories. Restricted to screening investigations, the PFA-100 CT may facilitate fast identification of patients with von Willebrand disease and some platelet function disorders in clinical settings [4]. Flow cytometry allows testing for membrane glycoprotein deficiencies, such as M. Glanzmann (CD41/61) and Bernard Soulier syndrome (CD42b/42a/42d) with very small sample sizes [10]. Since these important hereditary disorders of platelet function disorders (which frequently present with severe bleeding symptoms) can safely be diagnosed by flow cytometry, 26 centers have adopted this method. Due to the time-consuming

Fig. 3. Diagnoses of 215 patients with suspected hereditary disorders of platelet function.

and difficult method, in our study flow cytometry was only used as second line test in order to confirm or exclude suspected defects of platelet membrane glycoproteins.

However, most routinely applied test sets were likely to miss various hereditary platelet disorders, especially those with mild and moderate bleeding tendency. In addition, mild and moderate bleeding tendency often puts little pressure on responsible physicians. Compared to other diseases, diagnostic assessment of patients with hereditary platelet defects is sometimes difficult and time-consuming or even impossible. In our study, 57% of patients were sufficiently characterized following the criteria proposed by the authors (table 2). M. Glanzmann that is associated with moderate to severe bleeding tendency, was the most frequent diagnosis. The local frequency of rarer diagnoses often appeared to be dependent on the availability of testing methods resulting in potential underdiagnosis of many platelet disorders. In the light of these findings, it is not surprising that 43% of patients had an unclear diagnosis even though bleeding symptoms and some laboratory findings were highly suggestive for platelet disorders (fig. 3). Diagnosis of inherited disorders of platelet function will always need careful history and clinical examination of the patients in question. Laboratory results can only confirm or rule out clinical suspicion.

At least some of these undiagnosed or poorly characterized patients may directly profit from a competence network reducing the effort necessary for responsible physicians to find and contact highly specialized centers. Publication of data

sheets addressing all frequently asked questions concerning diagnostic and treatment centers (fig. 4) will be published soon on the official society webpage of the GTH (www.gth-online.org).

Only recently registries for hemophilia, the classic bleeding disorder, have been started in Germany and Austria. The relatively high number of hemophiliacs, the clear therapeutic concept with coagulation factor administration together with the burden of high treatment costs for the communities certainly have contributed to the early establishment of these registries. Although some registries, including www.orpha.net in France and www.med.mssm.edu/glanzmannfdb in the USA, collect data on M. Glanzmann, no general non-profit registry for patients with hereditary disorders for platelet function exists. The European organization of rare diseases (www.eurordis.org) including www.orpha.net may play a role in collection and distribution of information from and for these patients in the future. A registry may be the cornerstone to allow for developing of evidence-based criteria for diagnosis and treatment of patients with hereditary platelet function disorders. Although many questions have not yet been answered, Thromkid has collected enough data to initiate a patient registry. Well designed multicenter trials are urgently needed to develop treatment options for these patients.

The data from the Thromkid survey demonstrate the difficulties for clinical laboratories to diagnose patients with hereditary platelet disorders. Moreover, platelet test sets varied

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Fig. 4. Example of future information sheet accessible through webpage of the GTH www.gth-online.org.

widely between laboratories. Consequently, under-diagnosis may jeopardize patients' lives in the case of emergency bleeding. Further research should focus on the development of con-

sensus guidelines for diagnostic tests and treatment options for these patients. The Thromkid competence network has the potential to fulfill these needs.

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Appendix

Participating centers in alphabetical order:

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