Evaluation of platelet function in rare or undiagnosed bleeding disorders

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BACKGROUND / OBJECTIVES

Qualitative and/or quantitative platelet defects promote bleeding and its identification requires a careful clinical evaluation and a rational use of diagnostic laboratory assays.

The objectives were to study platelet function by different methods in patients with hemorrhagic symptoms who are suspected of thrombopathy to compare results obtained with each system and validate usefulness of methods employed.

MATERIALS & METHODS

We included 72 patients with bleeding suspected of thrombopathy, which in some cases were confirmed by genetic study (Table 1). Patients with coagulation disorders were excluded. The following methods to test platelet function were used:

- Light aggregometry in platelet-rich plasma (PRP) using ADP, collagen, epinephrine and arachidonic acid as stimulating agonists.
- Flow cytometry in PRP using TRAP and ADP to induce platelet activation, and PAC1 monoclonal antibody (mAb) to recognize activated fibrinogen receptor, and anti P-selectin and anti-CD63 mAbs to test, respectively, release from alpha and dense granules.
- PFA-100® in whole citrated blood with collagen+ADP and collagen+Epinephrine cartridges.
- Total Thrombus-formation Analysis System (T-TAS® 01, Zacros, Japan) with T-TAS® PL- chip (capillaries covered with collagen / under flow) in blood samples drawn in BAPA, a potent synthetic anticoagulant which inhibits Factor Xa and thrombin.

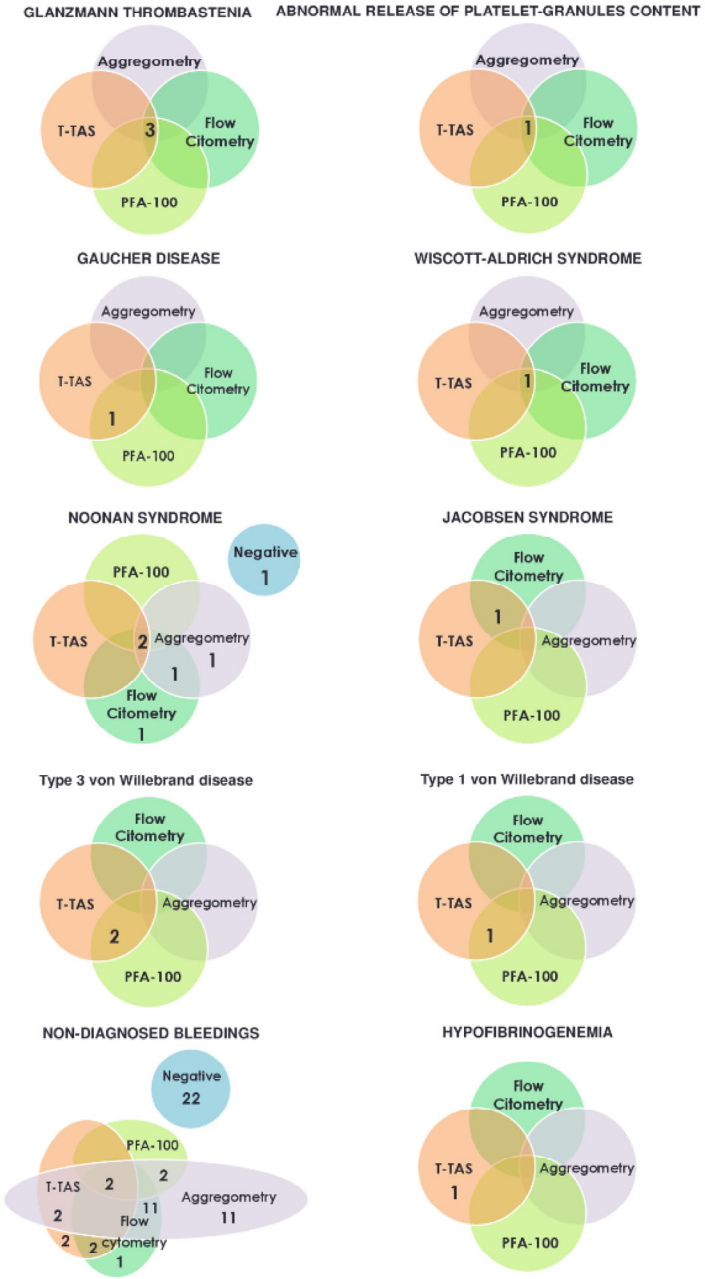
RESULTS

Some bleedings due to platelet dysfunction were diagnosed by any of the methods used, but others can only be detected with some of the techniques tested (Figure 1). This difference in the sensitivity of the methods may be due to the different experimental conditions used in each of them: type of sample used, platelets' activators, and flow vs static conditions. Forty % of undiagnosed bleedings did not seem to be related to platelet dysfunction.

Table 1.Characteristics of patients included

Glazmann thrombastenia	Lack/disminution of fibrinogen receptor. Diagnosed by flow cytometry.
Release defect	Lack of release of P-selectin after agonist stimulation. Diagnosed by flow cytometry.
Wiscott Aldrich Syndrome	Characterized by immune deficiency and microthrombocytopenia. Diagnosed by genetic study of WAS gene. Mutation leads to a lack of functional WASP and consequently, disruption of the function of the actin cytoskeleton in developing blood cells.
Gaucher disease	Characterized by accumulation of harmful quantities of certain fats (lipids), specifically the glycolipid glucocerebroside, throughout the body especially within the bone marrow, spleen and liver, with defects in platelets adhesion. Diagnosed by genetic study.
Noonan Syndrome	Characterized by mildly unusual facial features, short stature, heart defects, bleeding problems, skeletal malformations, and many other signs and symptoms. Diagnosed by genetic study.
Jacobsen Syndrome	Characterized by intellectual disability, behavioural problems including autism and attention deficit, hyperactivity disorder, congenital heart defects, structural kidney defects, genitourinary problems, immunodeficiency, and bleeding disorder due to impaired platelet production and function. Diagnosed by genetic study.
Hypofibrinogenemia	Characterized by abnormal low levels of fibrinogen in plasma. Diagnosed by genetic study.
vWD-type 1	Characterized by partial deficiency of von Willebrand factor (VWF). Diagnosed by laboratory test.
vWD-type 3	Characterized by absence of von Willebrand factor (VWF). Diagnosed by laboratory test.
Undiagnosed bleedings	Bleedings of unknown origin.

Figure 1. Number of cases diagnosed with assays employed



CONCLUSION

All methods are complementary and their sensitivity depends on the pathway evaluated by the technique used and the mechanism involved in platelet dysfunction.

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