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Review

Diagnosis and treatment of inherited thrombocytopenias

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Knowledge in the field of inherited thrombocytopenias (ITs) has greatly improved over the last 15 years. Several new genes responsible for thrombocytopenia have been identified leading to the definition of novel nosographic entities and to a much better characterization of the phenotypes of these diseases. To date, ITs encompass 22 disorders caused by mutations in 24 genes and characterized by different degrees of complexity and great variability in prognosis. Making a definite diagnosis is important for setting an appropriate follow-up, choosing the best treatments and providing proper counseling. Despite the abovementioned progress, diagnosis of ITs remains difficult and these disorders are still underdiagnosed. The purpose of this review is to provide an updated guide to the diagnosis of ITs based on simple procedures. Moreover, the currently available therapeutic options for these conditions are recapitulated and discussed.

Conflict of interest

The author has declared no conflicting interests.

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Knowledge in the field of inherited thrombocytopenias (ITs) has greatly improved over the last years. At the end of the past century, ITs were poorly characterized diseases. Only a few forms were clearly defined and the genetic defect was known for only two disorders, Bernard–Soulier syndrome (BSS) and Wiskott–Aldrich syndrome (WAS). The known forms were all characterized by severe bleeding since the first years of life due to thrombocytopenia possibly associated with abnormalities of platelet function. During the last 15 years, 20 new genes responsible for ITs have been identified leading to the definition of novel nosographic entities and to a better characterization of the phenotypes of these diseases. These achievements not only have significantly changed our view of ITs, but also indicated that making a molecular diagnosis is important for the correct patients' management. To date, ITs encompass 22 disorders caused by mutations in 24 genes and characterized by different degrees of complexity and great variability in prognosis. The forms identified over the last years were found to be more frequent than those previously known and the analysis of large case series revealed that the majority of patients with recently characterized disorders have mild to moderate thrombocytopenia with mild bleeding tendency or even no bleeding at all. However, better knowledge of ITs revealed that several disorders expose patients to acquire additional clinical manifestations that have a major impact on quality of life or can even be fatal. For instance, *MYH9*-related disease (*MYH9*-RD), the most frequent form of IT, is usually associated with mild bleeding tendency but 30% of patients develop kidney damage leading to end-stage renal failure and 60% develop sensorineural hearing loss that can lead to severe early deafness (1). Bleeding is often absent or mild also among subjects with thrombocytopenias caused by mutations in *RUNX1* or *ANKRD26*, however, both these disorders result in significantly increased risk of acquiring myeloid malignancies (2, 3). Germline mutations in *ETV6* were recently found to be responsible for a third form of autosomal-dominant (AD) thrombocytopenia that predisposes to hematological malignancies (4, 5). Similarly, patients with X-linked thrombocytopenia (XLT), a mild variant of WAS deriving from mutations that do not completely abolish *WAS* expression, often present with mild thrombocytopenia. However, these patients have remarkably increased risk of occurrence of infectious episodes, autoimmunity, and malignancies (6). These observations underscore the importance of

making a definite diagnosis in all patients with ITs, even in individuals with asymptomatic thrombocytopenia, in order to provide proper genetic counseling, set an appropriate follow-up, and choose the best treatments.

Despite the abovementioned progress, diagnosis of ITs remains difficult and these disorders are probably still underdiagnosed. The main reason is that the possibility of a genetic form is often not considered in the evaluation of patients with thrombocytopenia. Whenever a genetic thrombocytopenia is suspected, reaching a definite diagnosis can be complex as the required tools are available only at a few specialized centres. Moreover, diagnosis is still not possible also after a comprehensive diagnostic work-up in about 40–50% of patients with ITs, as they are affected by disorders that have not yet been identified (7–9).

The purpose of this review is to provide an updated guide to the diagnosis of ITs based on simple procedures and recapitulate the currently available treatments for these conditions.

Table 1 classifies ITs according to the presence or absence of other defects associated with the low platelet count (syndromic and non-syndromic forms, respectively) and summarizes the main clinical features of the 22 recognized forms.

Diagnosis of inherited thrombocytopenias

Diagnosis of ITs can be schematically divided into two steps. The first step is the recognition of patients who have a genetic form among individuals with thrombocytopenia. The second phase is the differential diagnosis of ITs in order to diagnose a specific disorder.

Recognition that a patient's thrombocytopenia has a genetic cause

Identification of patients with genetic thrombocytopenia among individuals with low platelet count requires effort by physicians. In fact, many patients are diagnosed with ITs only after a previous wrong diagnosis of immune thrombocytopenia (ITP). Given that diagnosis of ITP is one of exclusion (10), the crucial point is that the possibility of a genetic thrombocytopenia is frequently overlooked. Misdiagnosis of ITP not only prevents ITs patients from a correct management of their diseases, but also exposes them to inappropriate and potentially harmful treatments. A recent multicentric analysis of the outcome of pregnancy in 181 women with different ITs showed that 57 patients were initially misdiagnosed with ITP. Forty-four of them received one or more lines of unnecessary immunosuppressive treatment including splenectomy in 15 patients (11). The key tools to recognize patients affected by ITs among thrombocytopenic individuals are personal and familial medical history, physical examination and evaluation of peripheral blood films.

Medical history

The genetic origin of a thrombocytopenia should be suspected whenever the patient's medical history does not clearly indicate that the low platelet count is an acquired problem, i.e. whenever a previous blood cell count demonstrating a normal platelet concentration is not available or whenever thrombocytopenia is not clearly part of the clinical picture of an acquired condition. The possibility of a genetic form should be considered independently of the patient's age at presentation, as for many IT patients thrombocytopenia comes to medical attention only during adulthood. In fact, patients with ITs causing severe bleeding and/or with syndromic forms associated with defects evident since birth are usually recognized in the pediatric setting. Conversely, in patients with ITs characterized by absent or mild spontaneous bleeding and no associated congenital features thrombocytopenia is often identified incidentally during the adult life. This presentation is common to relatively frequent forms, as *MYH9*-RD, XLT, *ANKRD26*-related thrombocytopenia (*ANKRD26*-RT), *ACTN1*-related thrombocytopenia (*ACTN1*-RT) and familial platelet disorder with propensity to acute myelogenous leukemia (FPD-AML) (6, 8, 12–14).

Family history often leads to the identification of relatives with thrombocytopenia and therefore clearly indicates a genetic disorder. However, a negative family history does not exclude this possibility, as some ITs are inherited in a recessive manner or characterized by high incidence of *de novo* mutations. For instance, about 40% of probands diagnosed with *MYH9*-RD were affected by sporadic forms arising from *de novo* mutational events (12). In cases where family history is negative or unclear, investigation of proband's history of bleeding may provide useful elements. If an adult subject with severe thrombocytopenia has new bleeding symptoms, the probability of a genetic form is low. In fact, in patients with ITs, platelet count usually remains stable over time: thus, subjects without spontaneous bleeding during childhood are not expected to bleed spontaneously in adulthood and bleeding can occur only after exposure to additional risk factors, as major or minor surgery, menses, or antiplatelet drugs. The likelihood of an IT is instead much higher in the case of an asymptomatic subject with mild or moderate thrombocytopenia who has not been subjected to prior hemostatic challenges. On the other hand, a history of bleeding disproportionate to the degree of thrombocytopenia should raise the suspicion of one of the ITs that can associate with clinically relevant defects of platelet function, as biallelic BSS, XLT, FPD-AML, or thrombocytopenias deriving from *ITGA2B*/*ITGB3* or *FLNA* mutations (2, 15–18).

As nine forms of ITs are syndromic disorders, the search for the defects associated with the low platelet count is crucial to recognize these diseases in the evaluation of a thrombocytopenic individual (Table 1 and Fig. 1). Associated manifestations should be sought not only in the proband but also in the relatives. In fact, in some syndromic ITs the associated defects have variable expressivity within the same families and/or can occur late in life; in the latter case, they can be absent in young individuals and investigation of older relatives is more informative. For instance, patients with *MYH9*-RD often develop deafness, kidney damage and/or cataract

Table 1. Main clinical features of inherited thrombocytopenias.

Disease (abbreviation, OMIM entry) (ref.)	Inh.	Gene (locus)	Bleeding[a]	Main clinical features
Syndromic forms				
MYH9-related disease (*MYH9*-RD, na) (1, 12, 80)	AD	*MYH9* (22q12)	A to Mi	Sensorineural deafness, nephropathy, cataract, and/or elevated liver enzymes. Giant platelets. Döhle-like inclusions in granulocytes. Also non-syndromic.[b]
Wiskott–Aldrich syndrome (WAS, 301000) (6, 25)	XL	*WAS* (Xp11)	S	Severe immunodeficiency leading to early death. Eczema. Increased risk of malignancies and autoimmunity. Reduced platelet size.
X-linked thrombocytopenia (XLT, 313900) (6, 16, 25)	XL	*WAS* (Xp11)	A to Mo	Mild immunodeficiency. Mild transient eczema. Increased risk of malignancies and autoimmunity. Reduced platelet size. Also non-syndromic.[b]
Paris–Trousseau thrombocytopenia (TCPT, 188025), Jacobsen syndrome (JBS, 147791) (81, 82)	AD	Deletions in 11q23	Mo to S	Physical growth delay, mental retardation, facial and skull dysmorphisms, malformations of the cardiovascular system, CNS, gastrointestinal apparatus, kidney, and/or urinary tract; other malformations.
Thrombocytopenia-absent radius syndrome (TAR, 274000) (22, 83, 84)	AR	*RBM8A* (1q21)	S	Bilateral radial aplasia +/– other upper and lower limb bone abnormalities. Kidney, cardiac, and/or CNS malformations. Reduced/absent megakaryocytes in BM. Platelet count tends to raise over time and often normalizes.
Thrombocytopenia associated with sitosterolaemia (STSL, 210250) (19, 35)	AR	*ABCG5*, *ABCG8* (2p21)	A to Mi	Tendon and tuberous xanthomas. Premature atherosclerosis. Hemolytic anemia with stomatocytosis. Large platelets. Also non-syndromic.[b]
Radioulnar synostosis with amegakaryocytic thrombocytopenia (RUSAT, 605432) (23, 85)	AD	*HOXA11* (7p15)	S	Bilateral radio-ulnar synostosis +/– other malformations. Reduced/absent megakaryocytes in BM. Possible evolution to bone marrow aplasia.
GATA1-related disease: X-linked thrombocytopenia with thalassemia (XLTT, 314050), X-linked thrombocytopenia with dyserythropoietic anemia (XLTDA, 300367) (20)	XL	*GATA1* (Xp11)	Mi to S	Hemolytic anemia with laboratory abnormalities resembling beta-thalassemia, splenomegaly, or dyserythropoietic anemia. Congenital erythropoietic porphyria.
FLNA-related thrombocytopenia (*FLNA*-RT, na) (17)	XL	*FLNA* (Xq28)	Mi to Mo	Periventricular nodular heterotopia (OMIM 300049). Large platelets. Also non-syndromic.[b]

Table 1. continued

Disease (abbreviation, OMIM entry) (ref.)	Inh.	Gene (locus)	Bleeding[a]	Main clinical features
Non-syndromic forms				
Bernard–Soulier syndrome (BSS, 231200/153670) (38, 43, 44, 86)		*GP1BA* (17p13) *GPIBB* (22q11) *GP9* (3q21)		
Biallelic	AR		S	Giant platelets.
Monoallelic	AD		A to Mi	Large platelets.
Congenital amegakaryocytic thrombocytopenia (CAMT, 604498) (21)	AR	*MPL* (1p34.2)	S	Reduced/absent megakaryocytes in BM. Evolution to fatal bone marrow aplasia in infancy in all patients.
Familial platelet disorder with propensity to acute myelogenous leukemia (FPD-AML, 601399) (2)	AD	*RUNX1* (21q22)	A to Mo	Over 40% of patients acquire acute myelogenous leukemia or myelodysplastic syndromes. Increased risk of T acute lymphoblastic leukemia.
ANKRD26-related thrombocytopenia (*ANKRD26*-RT or THC2, 188000) (13)	AD	*ANKRD26* (10p12)	A to Mi	About 8% of patients acquire myeloid malignancies. Some patients have increased hemoglobin levels and/or leukocytosis.
Gray platelet syndrome (GPS, 139090) (34, 87)	AR	*NBEAL2* (3p21)	Mi to S	Platelet count decreases over time. Development of progressive myelofibrosis and splenomegaly. Elevated serum vitamin B12 levels. Pale platelets due to severe alpha-granule deficiency. Large platelets.
ACTN1-related thrombocytopenia (*ACTN1*-RT, 615193) (8, 9)	AD	*ACTN1* (14q24)	A to Mi	Large platelets.
Platelet-type von Willebrand disease (PTvWD, 177820) (39)	AD	*GP1BA* (17p13)	A to Mi	Platelet count can decrease under stress.
ITGA2B/*ITGB3*-related thrombocytopenia (*ITGA2B*/*ITGB3*-RT, 187800) (18)	AD	*ITGA2B* (17q21), *ITGB3* (17q21)	Mi to Mo	Large platelets.
ETV6-related thrombocytopenia (*ETV6*-RT, na) (4, 5)	AD	*ETV6* (12p13)	A to Mo	Increased risk of myeloid and lymphoid malignancies.
TUBB1-related thrombocytopenia (*TUBB1*-RT, 613112) (46)	AD	*TUBB1* (20q13)	A to Mi	Large platelets.
CYCS-related thrombocytopenia (*CYCS*-RT or THC4, 612004) (33)	AD	*CYCS* (7p15)	A	Normal/reduced platelet size.
GFI1b-related thrombocytopenia (*GFI1b*-RT, 187900) (36, 37)	AD	*GFI1B* (9q34)	Mo to S	Some pale platelets reflecting a variable alpha-granule deficiency. Large platelets.
PRKACG-related thrombocytopenia (*PRKACG*-RT, na) (47)	AR	*PRKACG* (9q21)	S	Large platelets.

AD, autosomal-dominant; AR, autosomal recessive; BM, bone marrow; CNS, central nervous system; Inh., inheritance; na, not available; Ref., references; XL, X-linked.

[a]Bleeding, severity of bleeding tendency in the majority of patients reported for each form: A, absent; Mi, mild; Mo, moderate; S, severe.

[b]'Also non-syndromic' indicates syndromic forms for which some patients having only thrombocytopenia (without the associated defects) have been reported.

only in the adult life (1); moreover, variability for the occurrence of these defects among members of the same *MYH9*-RD pedigrees has been reported (12). Similarly, in patients with sitosterolemia tendon xanthomas or signs of atherosclerosis become apparent over time (19). It is recommended to search for a family history of myeloid leukemias or myelodysplastic syndromes, which occur in more than 40% of individuals with FPD-AML and in almost 10% of *ANKRD26*-RT patients (2, 3). The recently discovered *ETV6*-related thrombocytopenia (*ETV6*-RT) is characterized by high incidence of both lymphoid and myeloid neoplasms (4, 5).

As regards the examination of routine blood cell counts, most patients with ITs present with the alteration of only platelet parameters unless they have developed iron deficiency anemia because of chronic bleeding. However, the finding of a concurrent hemolytic anemia should raise the suspicion of thrombocytopenia caused by *GATA1* mutations or sitosterolemia (19, 20), whereas a persistent increase in hemoglobin level and/or leukocytosis is found in some patients with *ANKRD26*-RT (13). Children with congenital amegakaryocytic thrombocytopenia (CAMT) may present with signs of pancytopenia due to generalized bone marrow aplasia (21) and children with WAS often have a reduced lymphocyte count (6).

Physical examination

Physical examination aims at identifying the defects associated with thrombocytopenia in syndromic ITs. Figure 1 summarizes these features and suggests that examination should be as complete as possible. Some abnormalities are obvious and the general examination is sufficient to identify them, while in other cases the defects are less evident and their identification requires a targeted search. For instance, bilateral radial aplasia and the associated upper limbs bone defects of thrombocytopenia-absent radius syndrome (TAR) (hypoplasia of the thumbs, ulna and/or humerus, underdevelopment of shoulder girdle and/or phocomelia) are easily recognized (22). Conversely, in patients with radioulnar synostosis with amegakaryocytic thrombocytopenia (RUSAT) the bone defect has to be sought by the demonstration of the limited pronation and supination of the upper extremities (23).

Examination of peripheral blood slides

Examination of peripheral blood slide is mandatory in the initial evaluation of all patients with thrombocytopenia (10) and can reveal several findings that raise the suspicion of a genetic form. These findings include abnormalities of platelets, red blood cells, or leukocytes (Table 2). Figure 2 shows some representative examples.

Evaluation of platelet size is unanimously considered a key tool for both distinguishing inherited from acquired thrombocytopenia and driving the differential diagnosis of ITs. Some ITs are characterized by marked platelet macrocytosis with notable presence of platelets larger than erythrocytes (giant platelets), whereas platelet microcytosis is recognized as the hallmark of WAS/XLT (24, 25). However, knowledge on abnormalities of platelet size in ITs mainly derives from observations on case reports or series of patients affected by one form of IT. A recent study investigated platelet diameters in a systematic manner on blood slides of 376 patients with most forms of genetic thrombocytopenia and provided data for a classification of ITs on the basis of platelet size (Table 3) (26). The authors demonstrated that two parameters, the mean platelet diameter and the percentage of large platelets (platelets larger than the upper limit of normal range, 3.9 μm), were effective for distinguishing the ITs with giant platelets or those with normal/reduced platelet size (Table 3) not only from ITP, but also from the other ITs. Cut-off values with good diagnostic accuracy have been calculated. The image analysis technique used in this study is time-consuming and this is a strong limit for its application in clinical practice. However, by coincidence, the cut-off value for identifying large platelets, i.e. 3.9 μm, is about half the diameter of normal erythrocytes on blood films. Thus, by comparing platelets with erythrocytes, the percentage of large platelets can be easily estimated without using software-assisted image analysis. In summary, the finding of more than 40% or less than 10% of platelets larger than half an erythrocyte strongly supports the diagnosis of IT with giant platelets or IT with normal/reduced platelet size, respectively, and makes the diagnosis of ITP unlikely (26).

An obvious question is if routine measurement of mean platelet volume (MPV) by electronic cell counters can be used to screen for patients with ITs instead of platelet diameter on blood films. Unfortunately, the use of MPV for this purpose is strongly limited by the fact that automated counters often fail to recognize the very large platelets of patients with ITs with giant platelets and therefore underestimate MPV as well as platelet count of these subjects (27). Moreover, different electronic counters have different ability to identify large platelets, thus making it difficult to compare findings obtained at different centres; in general, impedentiometric counters proved less reliable than optical ones (28, 29). In summary, the finding of a very high MPV in a thrombocytopenic subject suggests a genetic thrombocytopenia: studies on small case series showed that a MPV value 50% higher than the average value of healthy subjects (obtained by the same instrument) has good diagnostic accuracy in this respect (27, 28). Conversely, the finding of a normal MPV does not exclude at all the presence of giant platelets and examination of blood films is always required.

Differential diagnosis of inherited thrombocytopenias

Figure 3 shows a flow-chart for the differential diagnosis of ITs. In 2003, the Italian Platelet Study Group proposed a diagnostic algorithm for ITs (30). In 2004, the application of that algorithm to 46 consecutive IT probands demonstrated its effectiveness (7) and thereafter this tool has been used by different centres with good results (31). The flow-chart in Fig. 3 represents a version of that algorithm updated according to the recent advances in the field of ITs. The rationale of the

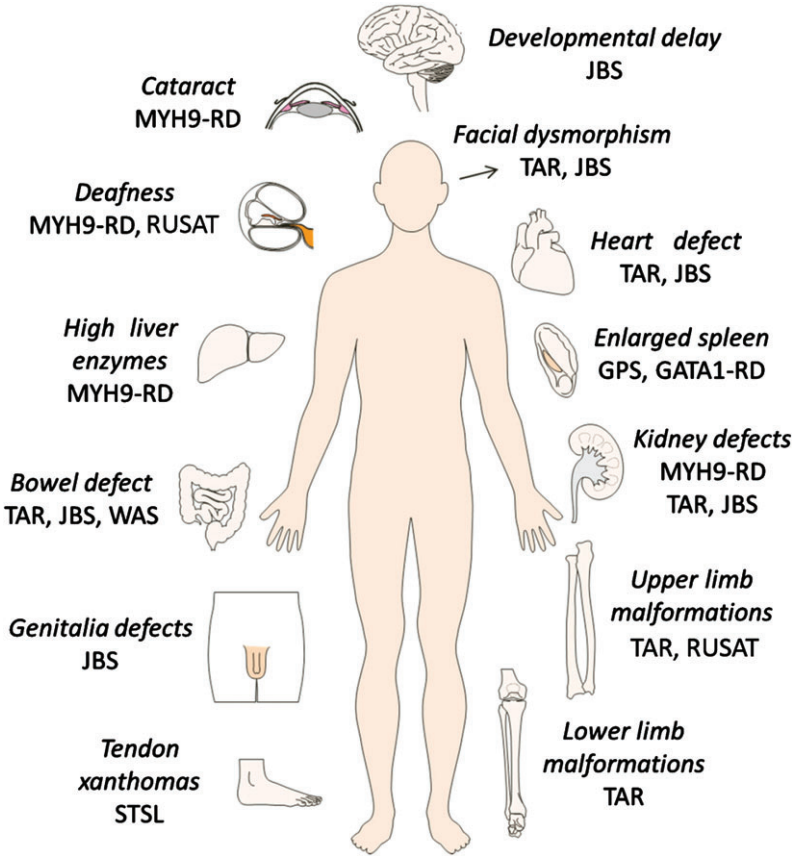

Fig. 1. Schematic representation of the defects associated with reduced platelet count in syndromic forms of inherited thrombocytopenia (IT). For abbreviations of disorders, see Table 1. Reproduced with permission from Thieme Medical Publishers (79).

Table 2. Morphological abnormalities of blood cells at examination of peripheral blood slides that raise the suspicion that thrombocytopenia has a genetic cause[a]

Blood cell abnormality	Inherited thrombocytopenia	References
Platelets		
Giant platelets and >40% of platelets larger than half a red blood cell	*MYH9*-RD, biallelic BSS	(1, 15, 24, 26)
Small platelets and/or <10% of platelets larger than half a red blood cell	WAS, XLT, CAMT, *CYCS*-RT	(6, 25, 26)
Agranular ('pale') platelets (with large platelets)	GPS, *GFI1b*-RT	(34, 36, 37)
Hypo-granular platelets (with normal-sized platelets)	*ANKRD26*-RT	(13)
Some platelets have one single giant granule	TCPT, JBS	(81, 82)
Vacuolated platelets	XLTT	(88)
Leukocytes		
Basophilic 'Döhle-like' inclusions in neutrophils	*MYH9*-RD	(12)
Red blood cells		
Anisopoikilocytosis or anisocytosis	*GATA1*-RD, *GFI1b*-RT	(20, 36, 37, 88)
Stomatocytosis	Sitosterolemia	(35)
Anisopoikilocytosis with dacryocytosis	GPS	(34)

[a]For abbreviations of disorders, see Table 1.

proposed diagnostic process is the use of a few, simple tests that are offered in many institutions to drive the genetic analysis ideally required for a definite diagnosis. Once identified and prioritized the gene(s) to be screened, molecular analyses can be carried out at specialized institutions on shipped DNA samples. This approach limits the use of complex pre-genetic laboratory tests and requires sample shipments rather than patients' travels to specialized institutions, which could make the diagnosis of ITs simpler and less expensive.

As discussed, medical history and physical examination aimed at identifying the associated defects in syndromic ITs can directly raise the suspicion of a specific disease and indicate the gene to be analyzed. Specific instrumental or laboratory tests may be required to identify and/or characterize certain phenotypes. For

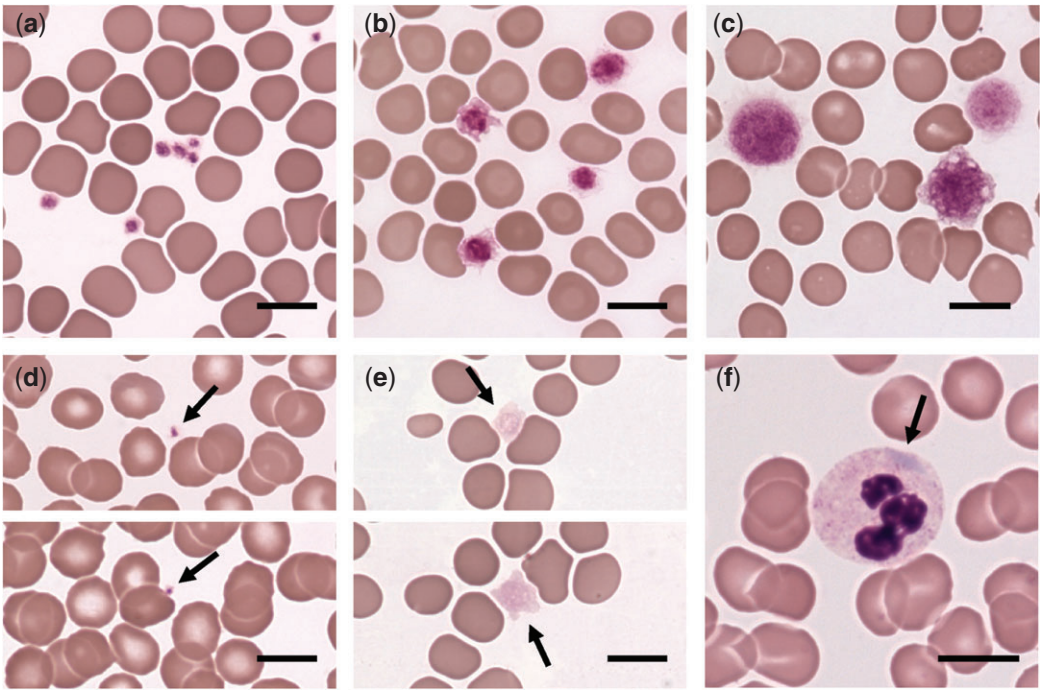

Fig. 2. Examples of morphological abnormalities of blood cells at examination of peripheral blood slides of patients with ITs. May–Grünwald–Giemsa staining. (**b**) Large platelets. (**c**) Giant platelets (platelets larger than erythrocytes). (**d**) Small platelets (arrows). In (**a**) platelets of a healthy subject with normal size are shown for comparison. (**e**) 'Pale' platelets due to the absence of azurrophilic granules of a patient with gray platelet syndrome (arrows). (**f**) Basophilic Döhle-like inclusion (arrow) in a granulocyte of a patient with *MYH9*-related disease. Scale bars correspond to 10 µm.

Table 3. Classification of inherited thrombocytopenias (ITs) based on platelet size according to the findings of Noris et al. (reference 26)[a].

ITs with giant platelets	*MYH9*-RD
	Biallelic BSS
ITs with large platelets	*TUBB1*-RT
	GPS
	FLNA-RT
	GFI1b-RT
	Monoallelic BSS
	ITGA2B/*ITGB3*-RT
	ACTN1-RT
ITs with normal/slightly increased platelet size	FDP-AML
	TCPT
	ANKRD26-RT
ITs with normal/reduced platelet size	CAMT
	CYCS-RT
	WAS
	XLT

[a]Modified from the research originally published in ref. (26). ©The American Society of Hematology. For abbreviations of disorders, see Table 1.

instance, radiographic studies are needed to characterize the bone defects of some ITs (22, 23). If *MYH9*-RD is suspected, audiometric examination and ophthalmological evaluation confirm the presence of sensorineural deafness and cataracts, respectively, while urinanalysis is recommended to search for proteinuria, which is the first sign of kidney damage (32).

Once syndromic forms of IT are excluded, the platelet size evaluated by examination of blood films provides key information to drive the diagnostic process. Infants or children with isolated thrombocytopenia and normal or reduced platelet size should undergo bone marrow examination to exclude CAMT, a non-syndromic, recessive thrombocytopenia that always evolves into fatal bone marrow aplasia during childhood (21). CAMT is suspected by the absence or severe reduction of megakaryocytes in the bone marrow, which indicates the need for the analysis of the *MPL* gene. Inconspicuous forms of Fanconi anemia or dyskeratosis congenita should be considered in patients without *MPL* mutations. Diagnosis of CAMT requires the immediate search of a stem cell donor (21). In pediatric patients excluded of having CAMT, or in adult patients with non-syndromic IT and normal or reduced platelet size, the alternative diagnoses are *ANKRD26*-RT, FPD-AML, *ETV6*-RT, or *CYCS*-related thrombocytopenia (*CYCS*-RT) (from the less rare to the most rare, at least in the Italian population). All these disorders are transmitted in an AD manner even if penetrance of mutations for thrombocytopenia can be incomplete: in fact, mutation carriers with platelet counts within the normal range have been reported in *ANKRD26*-RT, FPD-AML, or *CYCS*-RT pedigrees (2, 13, 33). In male individuals, whenever an X-linked transmission cannot be excluded, XLT must also be considered (Fig. 3).

If IT is associated with large platelets (inherited macrothrombocytopenia) the diagnostic possibilities are more numerous. The examination of blood smears can

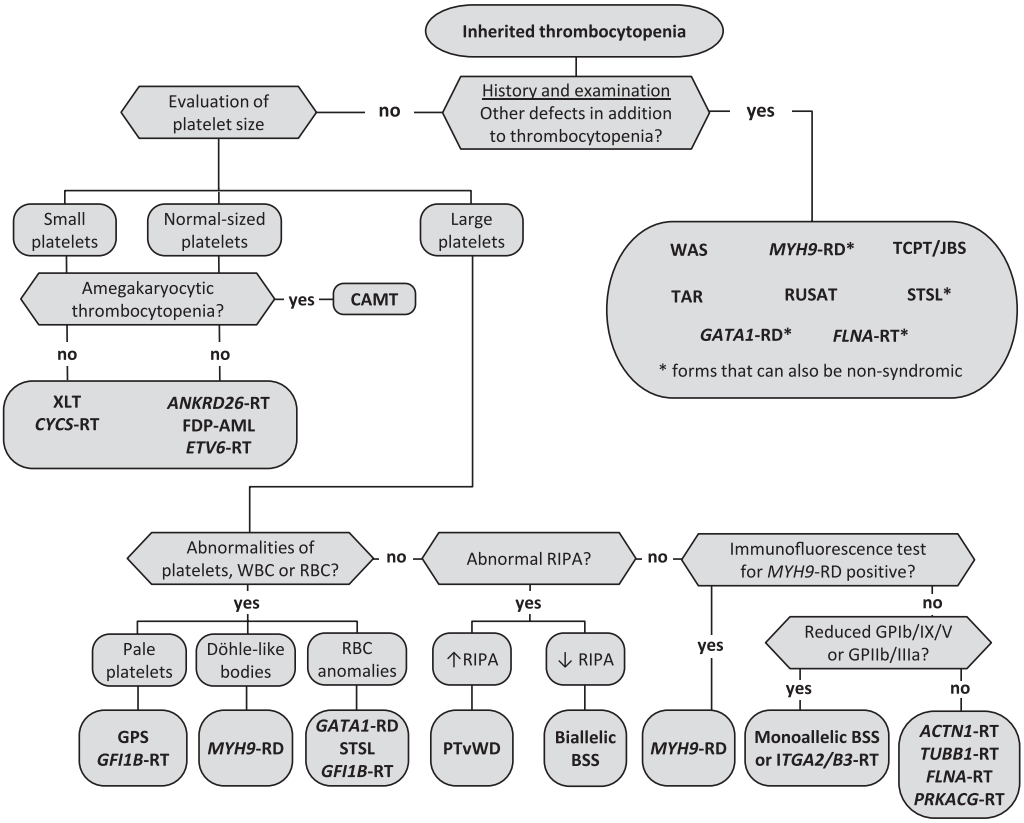

Fig. 3. Flow-chart for differential diagnosis of inherited thrombocytopenias (ITs). The rationale of the proposed diagnostic process is the use of a few, simple tests offered in many institutions to drive the genetic analysis required for a definite diagnosis. For abbreviations of disorders, see Table 1. RBC, red blood cells; RIPA, ristocetin-induced platelet aggregation; WBC, white blood cells.

indicate specific disorders. The finding of 'pale', 'gray' platelets due to severe reduction in azurrophilic granules is the hallmark of gray platelet syndrome (GPS) and should induce the search for *NBEAL2* mutations (Fig. 2e). The demonstration of elevated serum vitamin B12, signs of myelofibrosis, and/or splenomegaly corroborates this diagnostic suspicion (34). The finding of basophilic Döhle-like inclusions in neutrophils of a subject with giant platelets is pathognomonic for the *MYH9*-RD (Fig. 2f) (12). The demonstration of erythrocyte anisopoikilocytosis, often associated with anemia, suggests thrombocytopenia deriving from *GATA1* mutations. Familial history consistent with X-linked inheritance, the finding of hemolysis, dyserythropoiesis or abnormalities resembling minor thalassemia (elevated A2 or fetal hemoglobin, unbalanced globin chain synthesis) strengthen this diagnostic hypothesis (20). Stomatocytosis, sometime associated with hemolytic anemia, suggests sitosterolemia (35). A variable deficiency of platelet granules (with a variable proportion of 'pale' platelets) and erythrocyte anisopoikilocytosis have been described in the two recently reported families with *GFI1b*-related thrombocytopenia (36, 37). If these blood cell abnormalities are not present, three rather simple and cheap laboratory tests are recommended to further drive the diagnostic process (Fig. 3). *In vitro* platelet aggregation after stimulation with ristocetin is greatly reduced or absent in patients with biallelic BSS: this diagnosis is confirmed by flow cytometry (see below) (15, 38). Conversely, an abnormally increased response to ristocetin, sometime associated with spontaneous platelet aggregation upon stirring, suggests platelet-type or type 2 von Willebrand disease (39, 40). Some patients with *MYH9*-RD do not present Döhle-like bodies at examination of conventionally stained blood films or these inclusions may escape detection because they are faint and/or small (12). Immunofluorescence assay for the MYH9 protein on blood slides allows the easy recognition of the typical protein aggregates in neutrophils that are present in all *MYH9*-RD patients. In fact, this assay showed a 100% sensitivity and a 95% specificity for the diagnosis of *MYH9*-RD (41, 42). Finally, flow cytometry for platelet surface glycoproteins indicates the absence or severe reduction of the GPIb/IX/V complex, which is diagnostic for biallelic BSS (38), whereas an about 50% reduction of this complex suggests monoallelic BSS (43, 44). Monoallelic BSS deriving from the Ala156Val substitution of GPIbα is relatively frequent among subjects of Italian origin, as this mutation probably arose from a unique event that occurred on an ancestral Italian chromosome (43). Although other heterozygous *GPIBA* mutations causing macrothrombocytopenia have been identified in different populations (44), monoallelic BSS may be rare in populations other than the Italian. Flow cytometry can show a reduced expression of the GPIIb/IIIa complex on platelet surface, which suggests

thrombocytopenia deriving from *ITGA2B*/*ITGB3* mutations (18, 45). If all the above disorders are excluded, four other inherited macrothrombocytopenias should be considered. The less rare form is *ACTN1*-RT, which was found to account for 5.5% and 6.6% of IT with large platelets in two case series (8, 9). The remaining disorders have been described in very few families and are the AD thrombocytopenia caused by *TUBB1* mutations, the X-linked form deriving from *FLNA* mutations, and the recessive IT caused by *PRKACG* defect recently reported in one West Indian pedigree (17, 46, 47). In patients with non-syndromic familial thrombocytopenia with large platelets, whenever morphological examination of blood slides, ristocetin-induced platelet aggregation and immunofluorescence for MYH9 exclude the forms indicated in Fig. 3, the search for a definite diagnosis may be limited to selected cases. In fact, the remaining known forms of inherited macrothrombocytopenia are often mild disorders that are not associated with the risk of developing other manifestations in addition to thrombocytopenia.

The development of next generation sequencing for parallel screening of several genes could provide an alternative approach for the differential diagnosis of ITs in the near future. In fact, these techniques are becoming more effective and less expensive. Therefore, the single-step sequencing of all known IT genes as the first diagnostic approach for patients with ITs may prove more cost-effective than the application of diagnostic algorithms to identify and prioritize a series of genes to be analyzed. Future studies for the validation of this kind of approach in differential diagnosis of ITs are therefore needed.

Treatment of inherited thrombocytopenias

The majority of patients with ITs have no or mild spontaneous bleedings and require medical surveillance and sometimes prophylactic intervention for bleeding only on the occasion of hemostatic challenges, such as surgery, other invasive procedures or deliveries. The treatment of hemorrhages is mainly based on local measures and platelet transfusions; the efficacy of other hemostatic agents remains uncertain. The recent availability of thrombopoietin receptor agonists (TPO-RA) opened new prospects in treatment of ITs. Allogeneic hematopoietic stem cell transplantation (HSCT) is the treatment of choice for the most severe forms of IT.

General measures

General measures are aimed at preventing bleeding. Patients and their family physicians must be instructed to avoid drugs that impair platelet function. These medications (salicylates and other non-steroidal anti-inflammatory drugs, some antidepressants, antibiotics, and anaesthetics) should be administered only after a careful assessment of the ratio between the risks and the benefits (48). Subjects with severe forms should avoid activities at high risk of traumas such as contact sports. Regular dental care and oral hygiene prevent gum bleeding and limit the requirement for invasive dental procedures. Administration of oral contraceptives is usually effective in preventing or controlling menorrhagia.

Even patients with ITs, mostly those with mild or moderate thrombocytopenia and normal platelet function, develop thromboembolic events (49). The use of antithrombotic prophylaxis or treatment (such as heparins) must be carefully balanced against the risks according to the overall clinical picture of each patient.

Local measures

Local measures should be the first-line treatment for mucocutaneous bleeding and often are sufficient to control mild or moderate bleedings. Nasal packing or endoscopic identification and cauterization of the bleeding site are recommended for treatment of epistaxis. Compression and application of gelatin sponges or gauzes soaked in tranexamic acid can control bleeding from superficial wounds. Suturing can stop hemorrhages from accidental or surgical wounds (for instance, bleeding after tooth extraction). Mouthwash with tranexamic acid may be useful to control gingival bleeding.

Platelet transfusions

Transfusion of platelet concentrates is highly effective in stopping hemorrhages of IT patients, but exposes them to the risk of infectious diseases transmission, acute reactions, and alloimmunization that can lead to refractoriness to subsequent transfusions. The use of platelet concentrates should therefore be limited to treatment of bleedings that are not controlled by local measures and antifibrinolytic agents, life-threatening bleedings, and/or hemorrhages at critical sites.

The indication for prophylactic platelet transfusion before surgery or other invasive procedures should be assessed according to the type of procedure and the patient's features (platelet count and function, past history of bleeding, overall evaluation of hemostasis) in order to avoid unnecessary transfusions. If the patient has an IT with normal platelet function, the threshold platelet count required for 'safe' surgery can be deduced from general guidelines for platelet transfusions (50, 51). For instance, a platelet count of at least 50×10^9/L is recommended for major surgery at non-critical sites, while a threshold of 100×10^9/L is recommended for eye surgery or neurosurgery. Patients with ITs and defective platelet function may require prophylactic transfusions even if their platelet counts are above these levels. Platelets from human leukocyte antigen (HLA)-matched donors should be used whenever possible to prevent or overcome alloimmunization. Patients with biallelic BSS, whose platelets may completely lack the GPIb/IX/V complex, can develop isoimmunization against components of this complex of donor platelets. In this case, the efficacy of platelet transfusion can be restored only by immunosuppression and/or plasmapheresis to clear isoantibodies (52). ITs patients who frequently need transfusions

should be immunized against hepatitis A and B and monitored for liver enzymes (53).

Other hemostatic agents

Antifibrinolytic drugs

Several expert authors recommend the systemic administration of antifibrinolytic agents, such as tranexamic or epsilon-aminocaproic acid, to treat mild or moderate mucocutaneous bleedings or cover minor surgery in patients with ITs (53–55). Tranexamic acid has been also successfully used to prepare for major surgery one patient with *MYH9*-RD and moderate thrombocytopenia (56). However, data supporting the actual effectiveness of antifibrinolytic drugs in ITs are still lacking.

Desmopressin

Desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP) has a role in treatment of hemophilia A, type 1 von Willebrand disease and mild platelet function disorders. Hemostatic activity of DDAVP was associated to release of von Willebrand factor from endothelium and enhancement of the procoagulant activity of platelets (57). Studies on small series of ITs patients showed that DDAVP reduces bleeding time in a significant proportion of cases (58). Successful surgery in ITs subjects after prophylaxis with DDAVP has been reported (59) and some authors routinely use DDVAP to cover surgery in ITs patients considered at low bleeding risk, as those with *MYH9*-RD (55). However, no evidences on the actual clinical efficacy of DDAVP in ITs are presently available.

Activated recombinant Factor VIIa (rFVIIa)

rFVIIa enhances thrombin generation by both tissue factor-dependent and -independent mechanisms and is used in Glanzmann thrombasthenia and other platelet function disorders. In the setting of ITs, rFVIIa has been successfully used for management of bleeding episodes or for covering surgery in a few patients with biallelic BSS and one girl with TAR (60, 61).

Thrombopoietin receptor agonists

The TPO-RA eltrombopag and romiplostim, which are in use in some forms of acquired thrombocytopenia (62), have been tested also in patients with some ITs to increase platelet count. Eltrombopag was given for 3–6 weeks to 12 patients with *MYH9*-RD and platelet counts lower than 50×10^9/L. Eleven patients responded and eight of them obtained platelet counts higher than 100×10^9/L or three times the baseline value. Remission of spontaneous bleeding was achieved by 8 of 10 patients and treatment was well tolerated in all the cases (63). On the basis of these findings, short-term eltrombopag courses have been used for preparing for major surgery two patients with *MYH9*-RD and less than 20×10^9 platelets/L. Surgery was carried out without complications in both subjects after their platelet counts rose over 155 and 70×10^9/L, respectively (64, 65). It remains unclear whether *MYH9*-RD patients who suffer from spontaneous bleedings because of severe thrombocytopenia may benefit from long-term administration of TPO-RA. One *MYH9*-RD patient with severe bleeding symptoms has been treated with romiplostim because of an initial misdiagnosis of ITP. He achieved increase in platelet count and remission of bleeding that were maintained for 20 months; thereafter, his platelet count returned to baseline levels despite continuous romiplostim administration (66).

Whether TPO-RA could increase platelet counts also in ITs other than *MYH9*-RD is presently unknown. Clinical experience is limited to one report on four patients with WAS/XLT published in abstract form (67). Romiplostim was given to two infants with WAS, whereas eltrombopag was administered to one adult with XLT and one boy with WAS. The XLT patient obtained increase in platelet count and amelioration of bleeding tendency. One WAS infant had transient responses, but platelet count was maintained over 30×10^9/L only in intervals between infectious episodes. The other two WAS patients did not respond. The effect of TPO-RA in WAS/XLT clearly requires further investigation.

Administration of TPO-RA to patients with acquired thrombocytopenias was associated with increased risk of thromboembolism, reversible bone marrow fibrosis and increased liver enzymes (62). Romiplostim was also suspected to increase the risk of progression to leukemia in patients with myelodysplastic syndromes (68). These safety issues must be carefully considered before using these drugs also in patients with ITs.

Allogeneic hematopoietic stem cell transplantation

Allogeneic HSCT is the treatment of choice for WAS and can lead to correction of all the disease features. The outcome of HSCT in WAS patients depends on donor source and age and disease severity at transplantation (69). A recent multicentre retrospective study of 194 patients reported that 5-year overall survival of patients who underwent HSCT since the year 2000 was 100% for children transplanted from HLA-matched siblings and 90% for HLA-matched unrelated or mismatched related donor transplantations. This study underscored the improvements in the outcome of mismatched family donor HSCT obtained during the last years (70). Age at transplantation older than 5 years correlated with lower overall survival in patients transplanted from unrelated donors. However, a marked improvement of outcome during the last decade has been reported also for patients transplanted at age older than 5 years. Thus, even if early HSCT is still desirable, the effect of age on outcome has become less prominent over time (70, 71). Another retrospective study reported 24 patients with XLT treated by HSCT. Engraftment was successful in all cases. Four patients died for infections 8 to 24 months after HSCT; the remaining 20 patients were alive without serious complications after a median follow-up of 50 months (72).

Allogeneic HSCT is the only effective therapy for CAMT. A total of 59 CAMT children treated by HSCT have been reported, even if detailed clinical data are

not available for all of these cases (21, 73, 74). About 55% of them received transplant from HLA-identical or haplo-identical related donors, whereas the remaining patients underwent matched unrelated donor HSCT. A recent literature review reported an overall long-term survival rate of 80%, with 72% of patients having normal donor hematopoiesis and good quality of life (21). The reported HSCT-related mortality was 8% in children transplanted from related donors and around 23% in patients transplanted from unrelated donors (73).

Three patients with biallelic BSS and repeated, life-threatening hemorrhages were successfully treated by HSCT from HLA-identical siblings (75).

Gene therapy

Autologous gene-modified HSCT is an experimental option for WAS children without a suitable donor for allogeneic transplantation. A first gene therapy trial enrolled 10 patients and used a long term repeats (LTR)-intact γ-retroviral vector to transduce cells. Treatment resulted in a significant expression of WAS protein in patients' hematopoietic cells and clinical improvement was obtained by nine subjects. However, seven patients subsequently developed leukemias, most probably because of activation of proto-oncogenes by the strong LTR enhancer (76, 77). A second trial enrolled three patients and used a self-inactivating lentiviral vector encoding an endogenous *WAS* promoter. All patients showed robust multilineage engraftment of transduced cells in bone marrow and progressive increase in WAS protein expression in blood cells. All patients achieved good immune system reconstitution, increase in platelet counts with abolition of the need for transfusions and resolution of eczema. Clinical improvement was persistent after 20–32 months without major adverse events (78). Further trials of gene therapy in WAS are currently ongoing.

Splenectomy

Splenectomy is a therapeutic option for patients with XLT. In these subjects, splenectomy increases platelet count up to normal, but also results in higher incidence of severe infections. Therefore, the risks and benefits of splenectomy should be carefully weighted in each XLT patient. Vaccination against gram-positive bacteria and lifelong antibacterial prophylaxis are recommended (16). Splenectomy increases platelet count also in patients with WAS, however, because of the associated severe immunodeficiency, HSCT is the treatment of choice for this disease (25). In all the other ITs, splenectomy has no therapeutic role. As discussed, several patients with ITs other than WAS/XLT have been splenectomized because of misdiagnosis of ITP, without any substantial benefit.

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