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Inherited Rare Platelet Disorder

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Abstract: Hemostasis is just one of many physiological and pathological processes in which platelets are pivotal. Thus, proper survival and functioning, in addition to the daily production of around 1011 platelets, are life-essential occurrences. There is a diverse collection of approximately sixty rare diseases known as inherited platelet disorders (IPDs). These disorders can impact either platelet count or platelet functioning and are caused by molecular defects in numerous genes. Their clinical significance ranges from practically non existent to potentially fatal, depending on the disease and even within the same type. Among the many possible clinical manifestations of IPDs are mucocutaneous bleeding diathesis (epistaxis, gum bleeding, purpura, menorrhagia), . Critically important are prompt and precise diagnoses of IPDs as well as thorough medical follow-up for patients. Because many IPDs have a correlation between genotype and phenotype, a molecular diagnosis is crucial for effective clinical therapy. The widespread use of high throughput sequencing (HTS) methods in the investigation of inherited polymorphisms (IPDs) has substantially simplified genetic diagnosis. On the other hand, generic genetic investigations still have several unanswered ethical questions. Despite improvements in diagnosis, clinical therapy of IPDs has remained stagnant. There are a few therapy options for life-threatening IPDs, including platelet transfusions, thrombopoietin receptor agonists, and allogeneic hematopoietic stem cell transplantation. One potential future approach is gene therapy. A professional hematology service with multidisciplinary support must conduct regular follow-up, particularly for syndromic IPDs.

Keywords:*Inherited Bleeding Disorders, Rare Platelet Disorder*

Introduction

Inherited platelet disorders (IPD) comprise a heterogenous group of rare diseases caused by molecular anomalies in genes that are relevant in platelet formation and/or function. The relevance of clinical complications in patients with these diseases is highly variable, even within the same type, ranging from almost negligible to life-threatening. Consequently, the early and accurate diagnosis of patients and their close medical follow-up is long known to be of great importance [1]. At present, around 60 types of IPD due to molecular defects in about 75 different genes have been recognised [2]. The true prevalence of each is

unknown and, while it is estimated that they affect between $1:10^4$ and $1:10^6$ individual, more moderate disorders are certainly more common, since oftentimes patients go unnoticed for many years and even their entire lives. Noteworthy, a recent survey of the frequency in the general population of molecular variants in genes associated with platelet disorders, has revealed that about 3 in 1000 subjects have a clinically meaningful loss-of-function variant in genes involved in IPDs [3].

The two main groups of IPD are:

i. Inherited thrombocytopenias, in which the most conspicuous defect is the low number of circulating normal-sized, large, or small platelets [4,5,6]

ii. Inherited platelet function disorders, characterized by dysfunctional, typically hypofunctional, platelets resulting from defects of the membrane receptors, granules, elements involved in signal transduction, or other defects of the biochemical platelet machinery [7,8]

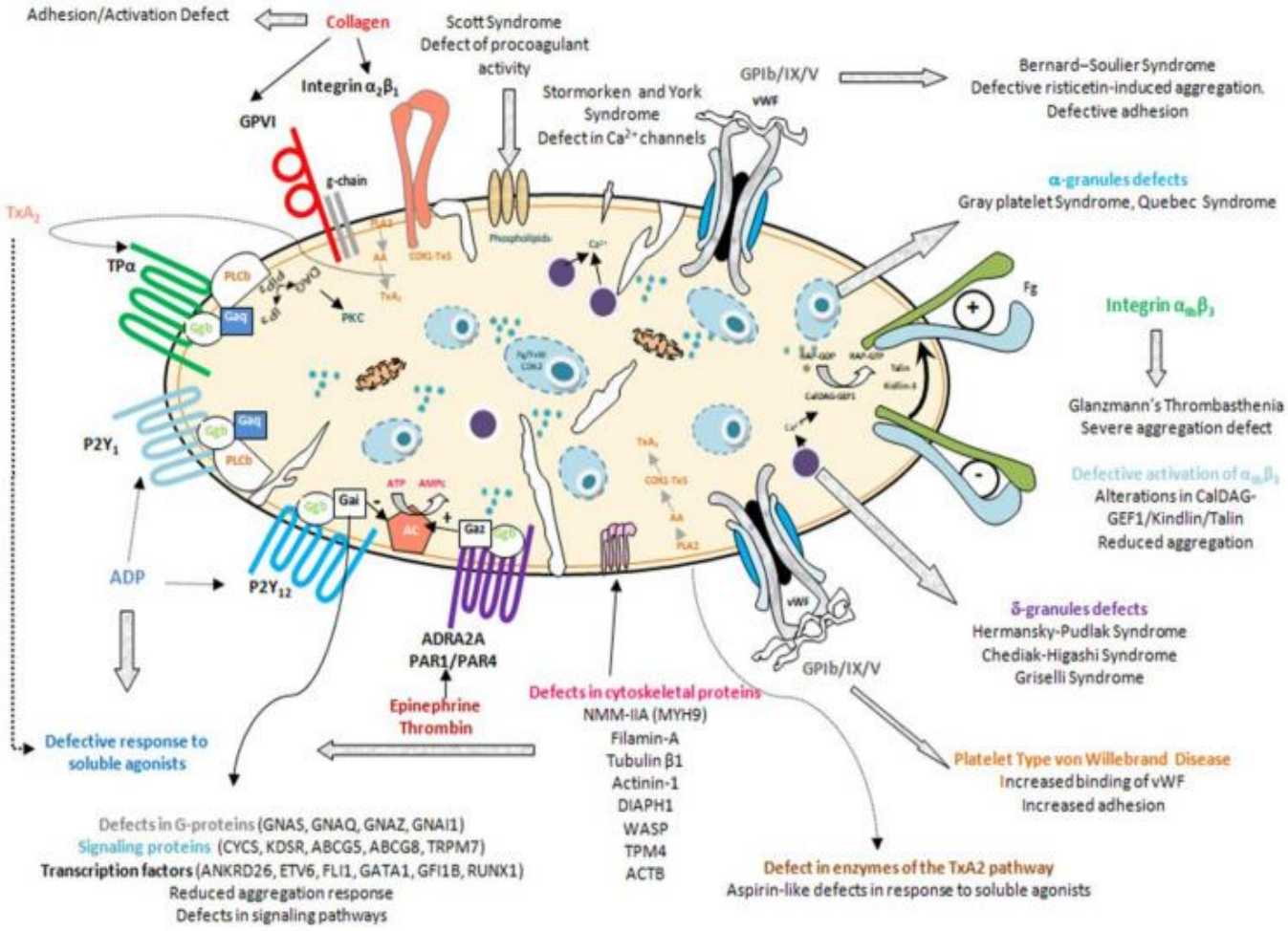

Figure 1 Inherited Platelet Disorders. The image shows the myriad of IPDs according to the protein and/or platelet function element which is affected by the genetic anomaly.

Thrombocytopenia and thrombocytopathy are typically associated.

The common feature of IPD is a predisposition toward spontaneous mucocutaneous bleeding (epistaxis, gum bleeding, purpura, menorrhagia) beginning in childhood, which is usually moderate although it can worsen in situations of hemostatic compromise, such as trauma, drug treatments, surgeries, or childbirth. Less frequently, deep, severe bleeding can also occur (central nervous system hemorrhage, digestive bleeding) [1,9,10]. Likewise, many of these IPD comprise part of multisystemic disorders known as syndromic IPD. In

some, bleeding may be clinically irrelevant, but patients display or are at high risk of presenting relevant disorders of other organs or tissues, or even neoplasms [1,5,7,11,12] . A relationship between genotype (the gene and type of molecular defect) and prognosis and/or clinical severity has been established in some IPD, making a molecular diagnosis especially imperative to guide clinical management [2,13]. Genetic diagnosis of IPD has been greatly facilitated by the introduction of high throughput sequencing (HTS) techniques into mainstream investigation practice in these diseases [14,15,16]. However, there still are unsolved ethical concerns on general genetic investigations as variants of unknown significance (VUS) and unexpected genetic defects can be found. Thus, patients should be informed in advance and comprehend the potential implications of such genetic findings [17,18].

2. Inherited Platelet Disorder Diagnosis

The diagnosis of IPD has traditionally been limited by their considerable clinical and laboratory heterogeneity, as well as by the scant reproducibility and specificity of platelet function tests [19,20]. This has led to many patients reaching adulthood undiagnosed or misdiagnosed, thereby exposing themselves to a high risk of suboptimal clinical management or even harmful and unnecessarily invasive treatment. One clear example of this is the misdiagnosis of immune thrombocytopenia (ITP) in many individuals with Bernard-Soulier syndrome (BSS) and improper treatment with steroids or even splenectomy [9].

According to expert recommendations, the first-line diagnostic evaluation of IPD calls for: (i) comprehensive clinical investigation (including a physical examination paying special attention to signs of bleeding, the presence of extra-hemorrhagic syndromic alterations, and family history); (ii) laboratory analyses with general biochemical and coagulation testing, and (iii) complete blood count (CBC) and blood smear, focusing especially on platelet numbers and morphology. Analysis of the functional phenotype of the platelets, begin with the use of relatively basic, widespread, and largely nonspecific tests. Later, more definitive, complex methods are used that are generally only available in laboratories that are specialized in IPDs diagnosis [2,21]. outline the diagnostic approach for inherited thrombocytopenias and inherited platelet function disorders, respectively, on the basis of the presence or absence of extra-hematological alterations and platelet size and function.

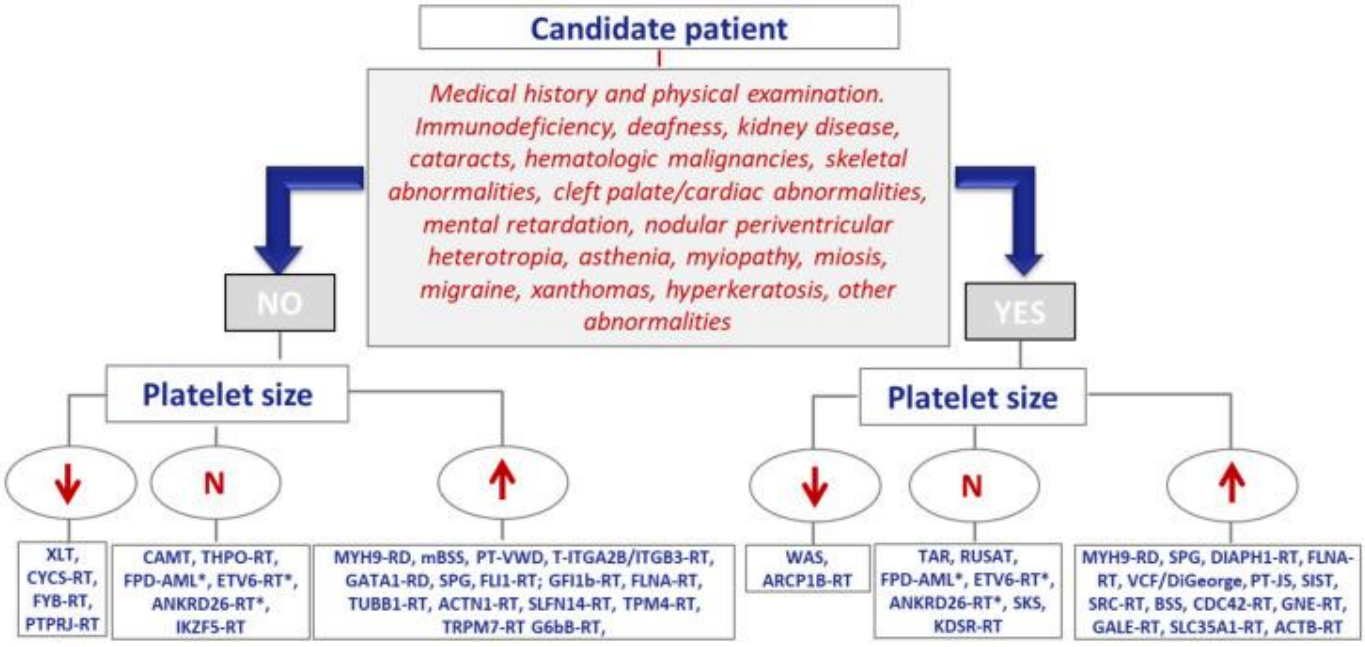

Figure 2

Diagnostic approach for inherited thrombocytopenias. N: Normal; XLT: X-Linked thrombocytopenia; CYCS-RT: CYCS-related thrombocytopenia (thrombocytopenia type 4); FYB-RT: FYB-related thrombocytopenia (adap-related thrombocytopenia); PTPRJ-RT: Thrombocytopenia due to variants affecting the phosphatase CD148; CAMT: Congenital amegakaryocytic thrombocytopenia (associated to a severe bone marrow aplasia); THPO-RT: thrombocytopenia due to mutations in *THPO* encoding thrombopoietin; FPD-AML: Familial platelet disorder with propensity to acute myelogenous leukemia; ANKRD26-RT: Thrombocytopenia due to variants affecting ankyrin repeat domain 26; ETV6-RT: Thrombocytopenia due to variants in the transcription factor ETV6; IKZF5-RT: Thrombocytopenia due to variants in the transcription factor IKZF5; MYH9-RD: Disorders related to variants in MYH9 (neutrophil inclusions, deafness, kidney disease, cataracts); mSBS: monoalellic Bernard-Soulier syndrome (Mediterranean macrothrombocytopenia); PT-VWD: Platelet type von Willebrand disease; ITGA2B/ITGB3-RT: Thrombocytopenia due to variants in *ITGA2B/ITGB3*; GATA1-RD:GATA1–related disorders (commonly associated to red cells anomalies); GPS: Gray platelet syndrome (myelofibrosis); FLI1-RT: Thrombocytopenia due to variants in the transcription factor FLI1; GFI1-RT: Thrombocytopenia due to variants in *GFI1B* (abnormal CD34 expression in platelets); FLNA-RT: Thrombocytopenia with filaminopathy (syndromic or only thrombocytopenia); TUBB1-RT; Thrombocytopenia due to variants affecting tubulin b1; ACTN1-RT: Thrombocytopenia due to variants affecting Actinin-1; SLFN14-RT: SLFN14-Related thrombocytopenia; TPM4-RT: Thrombocytopenia due to variants in tropomyosin 4; TRPM7-RT: Thrombocytopenia related with the ionic channel TRPM7; G6b-B: Thrombocytopenia due to variants affecting the immunoreceptor G6b-B (myelofibrosis); WAS: Wiskott-Aldrich syndrome (eczema and severe infections; ARCP1B-RT: Mycrothrombocytopenia linked to a ARCPB; TAR: Thrombocytopenia with absent radii; RUSAT: Radioulnar synostosis with amegakaryocytic thrombocytopenia; SKS: Stormorken syndrome; KDSR-RT: Thrombocytopenia with variable hyperkeratosis due to variants affecting 3-dehydrosphinganine reductase; DIAPH1-RT: Thrombocytopenia associated to dominant deafness and variants in DIAPH1; PT-JS: Paris-Trousseau/Jacobsen syndrome; VCF-DiGeorge syndromes: velocardiofacial/DiGeorge syndrome; SIST: sistosterolemia (elevated plasma levels of plant sterols); SRC: Thrombocytopenia associated to gain-of-function variant in tyrosine kinase SRC; BSS: Bernard-Soulier syndrome; CDC42-RT: CDC42-related thrombocytopenia (Takenouchi-Kosaki syndrome); GNE-RT: GNE-related thrombocytopenia; GALE-RT: GALE-related thrombocytopenia (galactosemia); SLC35A1-RT: Syndromic thrombocytopenia due to variants affecting the CMP-sialic acid transporter; ACTB-RT: Thrombocytopenia due to variants affecting actin beta .

Standardized scales or questionnaires, such as the International Society of Thrombosis and Haemostasis' Bleeding Assessment Tool (ISTH-BAT) are recommended. The ISTH-BAT is a relatively straightforward tool that can be completed in 5 min [22]. Its usefulness in distinguishing IPD from von Willebrand disease (VWD) and from healthy controls has recently been assessed in a large cohort of 1098 subjects, 482 of whom were affected with an IPD (286 inherited thrombocytopenias and 196 inherited platelet dysfunction). The ISTH-BAT appears to be helpful when defining which patients require further functional studies to identify their disorder [10]. Broadly put, a ISTH-BAT >3 points in children, 4 in men, and 6 in women, is established to select cases with abnormal hemorrhagic diathesis who would be eligible for a more in-depth platelet function work-up for suspicion of thrombocytopathy. The ISTH-BAT was inaccurate in discriminating inherited thrombocytopenias from controls [10].

Many inherited thrombocytopenias display a moderately low platelet count and platelet dysfunction; clinical bleeding is very mild or absent. It is therefore not uncommon for thrombocytopenia to be an incidental finding in adulthood. Moreover, its genetic origin may not be suspected if there is no family history, either because it is recessively-inherited, or because, as documented in up to 40% of individuals with MYH9-RD (MYH9-related disease) it is due to molecular defects with incomplete penetrance or that appear *"de novo"* in the patient Fundamentals that inform the diagnosis of inherited thrombocytopenias include platelet size evaluation on the peripheral blood smear and a proper physical examination that points toward a syndrome. Platelet size (small, normal, large) tends to be characteristic of the different types, but it is worth remembering that exceptions do exist [23]. All of this increases the risk that ITP can be misdiagnosed,

thereby exposing the patient to the risk of unnecessary treatments for years. Consequently, just as ITP is considered a diagnosis of exclusion, so too should inherited thrombocytopenias.

The definitive diagnosis of IPD is reached by identifying the underlying molecular pathology. Until a decade ago, molecular study was deemed the last, non-essential step in the process of diagnosing IPD [20] and was performed almost solely by Sanger sequencing of the candidate genes identified according to patients' clinical and laboratory phenotype [2,21]. This strategy, while being useful, is tedious and not applicable to cases with a non-specific phenotype [9], which is why it is being relegated to confirming molecular defects and family studies. After 2010, the molecular study of IPD begun to be undertaken by means of high throughput sequencing (HTS) of pre-selected gene panels (between 10 and 300 genes) or even the entire exome or genome. In just a few years, the use of this powerful technology has substantially broadened our knowledge of IPD, and HTS has identified the molecular base in almost two thirds of the approximately 60 known types of IPD [14,15,16,24,25,]. In fact, the growing availability of this methodology at lower cost is changing the traditional IPD diagnostic process and many experts propose that molecular study be incorporated much earlier, even after the most basic initial testing [2,26].

Nowadays, early, accurate molecular diagnosis of IPD undoubtedly facilitates clinical management, particularly in the serious, potentially fatal types, in which genotype is related to prognosis and severity of hematological and/or extra-hematological disease, such as congenital amegakaryocytic thrombocytopenia (CAMT), familial platelet disorder with predisposition to hematological malignancies (FPD/AML), MYH9-RD, Wiskott-Aldrich syndrome (WAS), Hermansky-Pudlak syndrome (HPS) or Chediak-Higashi Syndrome (CHS) [8,26]. Nevertheless, HTS also has its limitations, such as managing the vast amount of molecular data obtained, which can only be addressed with the help of bioinformatics experts, and the accurate interpretation of the pathogenicity of the candidate variants [2,24,26].

Recognizing the potential value of identifying molecular defects, it must be remembered that incorrectly assigning molecular pathogenicity can also undermine clinical management. Therefore, expert recommendations must be followed when filtering and interpreting the pathogenicity of variants identified by HTS. Currently, the most widely used guideline is the American College of Medical Genetics and Genomics [27]. Likewise, despite the greater availability of HTS, the importance of the clinical evaluation and detailed analysis of the patients' platelet phenotype cannot be ignored. Ethical issues also surround the use of HTS and shouldn't be overlooked, such as properly informing patient before their molecular study or managing incidental molecular findings [17,18,28].

Given that IPD are rare diseases, collaboration between clinicians and researchers, both nationally and internationally, is indispensable to facilitate accessibility to early, accurate IPD diagnosis, enhance the definition of clinical phenotypes, establish clear-cut pathogenicity of new molecular variants, and to comprehend genotype-phenotype relationships better [24,26].

3. Inherited Platelet Disorders of Particular Clinical Relevance

Inherited platelet disorders with special clinical importance are discussed below, such as syndromic disorders caused by congenital defects and platelet disorders with a high degree of bleeding.

3.1. Syndromic Platelet Diseases

Approximately half of all inherited thrombocytopenias, as well as some inherited platelet function disorders, are syndromes in which the congenital platelet defect is associated with a high probability of clinically relevant alterations in other cell types, organs, or tissues, or with developing neoplastic disease [5,8, 19,26]. In light of their considerable clinical relevance, we will highlight the following:

3.1.1. Congenital Amegakaryocytic Thrombocytopenia (CAMT)

This is a rare bone marrow failure that presents at birth as hypomegakaryocytic thrombocytopenia without any other physical characteristics. Most affected individuals develop additional cytopenias during childhood until finally progressing to bone marrow aplasia.

This autosomal recessive disorder is caused by mutations in the *c-MPL* gene that provoke the expression of a dysfunctional thrombopoietin (TPO) receptor. There is a correlation between genotype and phenotype, such that the nonsense mutations display a more aggressive pattern with progression to hypocellular bone marrow within the first decade of life, whereas patients with amino acid substitution mutations can exhibit moderate decrease in platelet counts and later go on to develop anemia or pancytopenia. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only curative option for these patients [9].

3.1.2. MYH9-Related Disease (MYH9-RD)

These diseases are the leading cause of inherited thrombocytopenia worldwide, with more than 300 families identified. This category includes anomalies previously known as May-Hegglin, Fechtner, Sebastian, and Epstein syndromes. This autosomal dominant syndrome is caused by monoallelic mutations (some 100 different mutations) in the *MYH9* gene, which encodes for the non-muscle myosin heavy chain IIA chain (NMM-IIA protein) involved in platelet cytoskeletal contractility [29,30,31]. Noteworthy, *de novo* mutations are common in this disease and somatic germinal mosaicism has been reported [32].

Patients with MYH9-RD exhibit varying degrees of thrombocytopenia from birth; exceptional cases display normal numbers, but all clearly exhibit giant platelets. Often, albeit not always, neutrophilic inclusions similar toDöhle bodies are visible on the blood smear. These inclusions are more evident on immunofluorescence staining for NMM-IIA aggregates, a test currently used to diagnose this disease in specialized laboratories [31].

Although bleeding episodes tend to be rare and mild, and even absent, this is not a trivial disorder because 25% of the patients develop nephropathy with proteinuria that, in most cases, evolves into end-stage kidney failure and require dialysis or a kidney transplant. Furthermore, almost 50% of the patients will suffer neurosensorial deafness and 18%, presenile cataracts. Therefore, the clinical course of MYH9-RD is quite heterogeneous and ranges from asymptomatic, isolated thrombocytopenia to a complex disorder that severely affects quality of life. Should the need for preoperative increase in platelets arise, TPO-RA can be an acceptable option [33].

Research with large patient populations has identified genotype-phenotype correlations that aid in predicting how the disease will evolve in approximately 85% of the cases and, possibly strategies or treatments to prevent or delay kidney disease can be adopted.

3.1.3. Wiskott-Aldrich Syndrome (WAS)

WAS is an X-linked disease that affects males almost exclusively, with clinical manifestations that include bleeding, eczema, and combined immunodeficiency (many patients have infections caused by opportunistic germs). Autoimmune syndromes have been observed in some 40% of the cases and patients have and increased risk of developing tumors, especially lymphoma, at any age. With the exception of extremely rare instances, one clinical hallmark of WAS is microthrombocytopenia, with counts of between 5 and 50 $\times 10^9$/L and small dysfunctional platelet (mean platelet volume [MPV]: 3.5-7 fL; normal: 7-11 fL) [34].

WAS is attributable to a molecular defect on the *WAS* gene (Xp11.22) that encodes the WASP protein that is involved in actin cytoskeletal remodeling. Four hundred different mutations have been reported in WAS patients, one third of which are located in nine gene hotspots. A relationship between clinical course and genotype has been reported, such that the mutations having the greatest effect on WASP expression/ functionality are associated with a more severe phenotype [34]. Hypomorphic mutations of the WAS gene can lead to an attenuated form of WAS called chronic or intermittent X-linked thrombocytopenia (XLT), which is correlated with a lower risk of the infections and malignancy, which otherwise are the leading cause of early death in the classical form of WAS.

The only curative treatment to date is allo-HSCT, with an 80% survival rate. Gene therapy comprises a promising approach for patients without a suitable donor. Immunoglobulin replacement therapy and oral

antibiotics prevent infections and TPO-RA can be used to temporarily boost platelet counts in cases of severe refractory thrombocytopenia [34,35].

3.1.4. Sitosterolemia (STSL)

Sitosterolemia, also known as phytosterolemia, is a rare autosomal recessive sterol storage disorder characterized by increased plant sterol levels in plasma. This disease results from recessive pathogenic variants in the *ABCG5* and *ABCG8* genes. The clinical characteristics of STSL include cutaneous and tendon xanthomas, xanthelasmas, premature coronary atherosclerosis and associated complications, arthritis, and/or arthralgias.

Hematologic abnormalities, such as hemolytic anemia (with a negative direct antiglobulin test and stomatocytosis) and macrothrombocytopenia are present in 80-90% of the cases, and/or splenomegaly may also be present with other clinical attributes. Ezetimib (EZE) improves the distribution of VLDL and HDL, thereby lowering the atherogenic lipid profile, yielding a potential clinical benefit in STSL and increasing platelet count. A delay in diagnosis is not without consequences, as it can lead to inadequate clinical management with its incumbent risk of advanced atherosclerotic cardiovascular disease [36,37].

3.1.5. DIAPH1-Related Thrombocytopenia (DIAPH1-RT)

DIAPH1-related thrombocytopenia is an autosomal dominant defect with macrothrombocytopenia and variable neutropenia, as well as hearing loss beginning in the first decade of life (at much younger ages than in MYH9-RD). DIAPH1, encoded by the homonymous gene *DIAPH1*, is a formin involved in the organization of the cytoskeleton of megakaryocytes and platelets, also present in the organ of Corti.

In a recent multicenter study, we have reported a 16-case series that reveals that patients exhibit megakaryocyte clustering in bone marrow, with deficient proplatelet formation. In in vitro cultures of megakaryocytes, these defects can be overcome, at least partially, with eltrombopag. This drug can enable DIAPH1-related thrombocytopenia to be temporarily corrected prior to surgery, thereby obviating platelet transfusion [38].

3.2. Inherited Platelet Disorders with Predisposition to Hematological Neoplasms

The WHO's 2016 revision of the classification of myeloid neoplasms and acute leukemias [39] introduced a new category of diseases defined as myeloid neoplasms with germline predisposition and pre-existing platelet disorders, that includes those that evolve with molecular variants on ankyrin repeat domain 26 gene (*ANKRD26*) or on transcription factors *ETV6* and *RUNX1* [12,18,19,20,22,40,41].

These three autosomal dominant inherited disorders justify 18%, 3%, and 5%, of the inherited thrombocytopenias, respectively, and, together, account for almost one quarter of the cases. Individuals affected by these diseases typically present with mild, isolated, non-syndromic thrombocytopenia with normal-sized platelets. In all three conditions, bone marrow examination reveals a normal or increased number of megakaryocytes, typically with dysplastic characteristics, such as small hypolobulated nuclei. In patients with *ANKRD26*-RT (thrombocytopenia type-2) or *ETV6*-related disease (thrombocytopenia type-5), bleeding, when present, is generally mild, consistent with normal platelet function. In contrast, individuals with congenital *RUNX1*-related thrombocytopenia, known as familial platelet disorder with propensity to acute myelogenous leukemia (FPD/AML) typically exhibit platelet function abnormalities, primarily alpha/dense granules deficiency, that can associate a propensity toward bleeding of varying severity.

3.3. Syndromic Disorders Due to Congenital Defects of Platelet Granules

Several congenital defects cause a quantitative or qualitative deficiency of platelet granules α, δ, or both. Although patients with these conditions usually display a tendency toward moderate bleeding, some develop other highly relevant clinical complications [1,42,43].

Gray platelet syndrome (GPS) is a serious congenital deficit of α granules (number and/or content) ordinarily due to mutations in the *NBEAL2* gene [44,45]. People suffering from this autosomal recessive disorder usually present moderate thrombocytopenia, with large, pale platelets and moderate mucocutaneous hemorrhagic diathesis. This is a progressive syndrome, such that usually evolves towards severe thrombocytopenia during

adolescence and adulthood, accompanied by a gradual degree of myelofibrosis and, in some cases, splenomegaly. Very recently, these patients have been reported to exhibit leukopenia, predisposition to autoimmune diseases, defective NETosis and to developing autoantibodies [44,46,47,48].

In addition to *NBEAL2*, other genes (*GATA1*, *VPS33B*, *VIPAS39, GFI1B, PLAU*) have been implicated in congenital α-granule deficiency [26]. Phenotypic differences among patients with mutations in these genes pose the controversy of whether hereditary disorders of α granule biogenesis should be characterized as GPS [49].

α-granule deficiencies may appear as a single phenomenon of unknown genetic cause or as one component of multisystemic diseases that affect all lysosome-like organelles. Among these deficiencies are Hermansky-Pudlak (HPS), Chediak-Higashi (CHS), and Griscelli (GS) syndromes, in which platelet numbers are typically normal and platelet function is moderately impaired. Consequently, moderate hemorrhagic diathesis is also common. Nevertheless, individuals with these diseases can present other complications that are clinically highly relevant [43].

HPS is a serious deficiency of dense granules, characterized by oculocutaneous albinism, accumulation of ceroid material in cells of the mononuclear phagocytic system, variable pulmonary fibrosis, inflammatory intestinal disease, and hemorrhagic diathesis. Its molecular basis is heterogenous, with mutations in up to 11 different genes, all of which participate directly or indirectly in intracellular vesicular traffic. A relation between the affected gene and clinical severity has been proven (particularly in HPS subtypes 1 and 4), making early molecular diagnosis particularly important [50,51,52].

CHS is caused by mutations in the *LYST* gene, which encodes the lysosomal trafficking regulating protein CHS1 (or LYST). It manifests with partial oculocutaneous albinism, silver hair, giant lysosomal granules, inclusion bodies in neutrophils and other cells, frequent pyogenic infections, peripheral neuropathy, and accelerated phase in up to 85% of the cases. Allo-HSCT is the only curative option in severe cases [53].

GS presents with partial albinism, silver hair, central neurological defects, and/or lymphohistiocytosis. It arises from mutations in genes encoding the proteins MYO5A, RAB27A, or melanophilin, involved in organelle traffic. Platelet counts are usually normal, but platelet function is moderately altered [42,43].

3.4. Platelet Disorders with High Risk of Severe Bleeding

In a small number of IPD, there is severe platelet dysfunction, sometimes combined with thrombocytopenia, which conditions a high risk of clinically serious, even life-threatening, bleeding, particularly in situations of high hemostatic compromise (trauma, surgeries, childbirth). We will focus here on the most widely characterized disorders, Bernard-Soulier syndrome (BSS) and Glanzmann thrombasthenia (GT).

3.4.1. Defects of the GPIb/IX/V Complex

Bernard-Soulier syndrome (BSS) is an autosomal recessive hemorrhagic diathesis characterized by moderate or severe thrombocytopenia and giant, dysfunctional platelets. It is due to mutations (more than 100 different mutations reported) in *GP1BA*, *GP1BB*, and *GP9* genes, leading to the absence of the Ib/IX/V complex in platelets (classical BSS) or, in exceptional cases, the expression of a non-functional receptor (variant BSS) [31]. The most unique laboratory anomaly of BSS is the absence of platelet agglutination with ristocetin, which is not corrected with normal plasma, unlike severe von Willebrand disease (VWD). In contrast, aggregation with other agonists (adenosine diphosphate [ADP], collagen, adrenaline, thrombin, etc.) is normal. Flow cytometry enables rapid detection of the selective deficit of the Ib/IX/V receptor and increased MPV.

BSS must be, early in life, differentiated from other macrothrombocytopenias and from ITP to avoid inappropriate therapies or splenectomy [9]. Ordinarily, only homozygous patients display relevant mucocutaneous bleeding beginning in childhood, whereas heterozygous individuals (monoallelic BSS) tend to be asymptomatic with mild thrombocytopenia [1,31,35].

3.4.2. Glanzmann Thrombasthenia

In the hemostatic response, platelets adhered to the vascular wound recruit other circulating platelets to form the thrombus [54 ,55]. This platelet aggregation is achieved by means of fibrinogen bridges between αIIbβ3 integrins of nearby platelets. Molecular defects of the *ITGA2B* and *ITGB3* genes, that encode for the αIIbβ3 complex, cause GT. Some 200 different mutations (deletions, insertions, point mutations, etc.) have been reported in approximately 200 families, and these numbers are growing constantly [56,57,58].

Individuals with GT display normal platelet count and morphology, as well as strikingly defective aggregation to multiple agonists (ADP, collagen, arachidonic acid, and thrombin), whereas agglutination with ristocetin is normal or moderately decreased in its second wave. Flow cytometry reveals the deficit of the αIIbβ3 receptor. According to the platelet expression level of the integrin, there are three types of GT: i) Type I, with a total absence (<5%) of αIIbβ3; ii) Type II, with 10–20% of residual αIIbβ3; iii) variant GT, with non-functional expression (>50%) of αIIbβ3.

Because it is a recessive autosomal disorder, only homozygote subjects exhibit moderate-severe mucocutaneous bleeding starting in childhood, whereas heterozygote individuals tend to be asymptomatic [1,8,58]. On the other hand, some *ITGA2B* and *ITGB3* heterozygous variants can cause autosomal dominant inherited thrombocytopenia [39].

4. Management of Patients with Inherited Platelet Disorders

In the last few years, there have been no major changes in the clinical management of IPD patients and the recommendations issued years ago are still valid [1]. These include educational and preventive measures, first and foremost to minimize their risk of bleeding (avoiding activities with risk of trauma, good dental hygiene, no antiplatelet drugs), inclusion in registries, and regular follow-up by a specialized hematology service with multidisciplinary support especially for syndromic IPD.

Depending on their severity or level of risk, hemorrhagic complications and situations that entail bleeding risk are managed with hemostatic drugs, such as anti-fibrinolytics or desmopressin (DDAVP), and, when necessary with recombinant factor VII (rFVIIa) or with platelet transfusions.

rFVIIa acts by increasing thrombin generation. It is licensed and mainly used in GT, particularly in patients refractory to treatment with platelet concentrates [60,61]. There is scant evidence for the remaining platelet syndromes, but it has been successfully used to treat or prevent bleeding in few patients with BSS and a patient with thrombocytopenia-absent radii (TAR) [5,62,63].

Given the high risk of alloimmunization, platelet transfusion should be restricted to severe bleeds in which antifibrinolytics and local measures fail, or in patients with very severe thrombocytopenias who are to undergo major surgery or during childbirth. Leukodepleted single donor and/or HLA-identical platelet products are preferable for IPD patients. Overall, platelet transfusion should be indicated on a case-by-case basis, assessing risk-benefit and bearing in mind personal history and platelet count [1,64]. In a recent international study, surgical hemorrhage was shown to be common in patients with IPD (19.7%), with a significantly higher incidence of bleeding in individuals with inherited platelet disorders (24.8%) than in people with inherited thrombocytopenias (13.4%) [61]. It is paradoxical that, although the most commonly used prophylaxis was platelet transfusion, DDAVP, alone or with antifibrinolytics, was the preventive treatment associated with the lowest bleeding rates. Moreover, platelet transfusions in these patients were only effective when more than 6 units of platelets were transfused [61]. In this regard, recent studies suggest that in diseases with significantly dysfunctional platelets (such as GT), a critical proportion of approximately 2:1 of endogenous (dysfunctional) to transfused (healthy) platelets is essential to prevent prolonged bleeding induced by hemostatic lesions [65].

When deemed necessary to improve thrombocytopenia, such as in high bleeding risk surgery, treatment can involve platelet transfusion or, in some cases, TPO-RA (eltrombopag, romiplostin) [1,7,60,61] (reviewed in Bastida el al in this special issue).

Insofar as inherited syndromic thrombocytopenias are concerned, a multidisciplinary clinical approach is essential. MYH9-RD patients may benefit from regular urine analysis, since appearance of proteinuria may support the use of therapies such as angiotensin II receptor blockers (ARB-II) and/or angiotensin-converting

enzyme inhibitors (ACEI), aiming to prevent or delay kidney failure. MYH9-RD patients also benefit from routine hearing and eye examinations to avoid treatment delays; both cochlear implant and standard cataract surgery generally restore the function of both organs [29,11,66,67].

Insofar management for thrombocytopenias associated with *RUNX1*, *ANKRD26*, or *ETV6* mutations are concerned, a cytogenetic bone marrow examination is recommende at the time of diagnosis, particularly if the mutations have already been reported and have proven pathogenicity. If no significant finding are identified, annual CBC, blood smear, and clinical evaluation are suggested, so as to identify early signs of malignant disorders. In this case, if allo-HSCT is under consideration potential family stem cells donors must be tested and ruled out for the molecular alteration of the patient [11,18,20,22].

Gene correction is long expected to become a curative treatment for severe IPD. To date, it has been an experimental clinical option only for some cases of WAS, treated with autologous hematopoietic stem cells transduced with self-inactivating lentiviral vector encoding WAS protein. In these cases, all but one in pediatric age, sustained cell engraftment was achieved and platelet counts and function, bleeding and immunity improved significantly with no relevant vector-related toxicity [70,71,72,73]. For other IPD, however, gene therapy still is at pre-clinical research level [74].

Conclusions

To date, around 60 types of IPD due to molecular disease in about 75 different genes are known. The true prevalence of each type is unknown, but the overall frequency in the general population can reach up to 3 in 1000 subjects. While some IPD may remain asymptomatic for years, even during the lifetime, complications can arise upon hemostatic challenges. In others cases, IPD present relevant bleeding complications since birth, are syndromic diseases or predispose to malignancy. Therefore, early and accurate diagnosis, including genetics, and close medical, follow-up, including multidisciplinary approaches in syndromic IPD, are of great importance for preventive and therapeutic managements of IPD patients. Further basic and clinical research, including development of safe and potentially curative treatments, will benefit IPD patient' quality of life and life expectancy.

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