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REVIEW

Congenital macrothrombocytopenias

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May-Hegglin anomaly

Summary Congenital macrothrombocytopenias comprise a heterogeneous group of rare disorders, characterized by abnormal giant platelets, thrombocytopenia and bleeding tendency with variable severity. Many of these disorders share common clinical and laboratory features, making accurate diagnosis difficult and patients are often misdiagnosed with and treated for idiopathic thrombocytopenic purpura. Recent progress in the elucidation of underlying defects and further developments of specific diagnostic techniques for several congenital macrothrombocytopenias have renewed our approach to the classification and the diagnosis of the disease. This review summarizes the current knowledge on the clinical and laboratory features of common congenital macrothrombocytopenias and discusses how that knowledge aids in making a proper diagnosis.

Introduction

Abnormal giant platelets are sometimes seen as an incidental finding in routine blood examinations. Many of them are associated with acquired disorders such as idiopathic thrombocytopenic purpura (ITP) and myelodysplasia. In contrast, inherited forms of giant platelet disorders or congenital macrothrombocytopenias are rare. When a bleeding tendency disproportionate to the platelet counts, characteristic morphological findings such as leukocyte inclusions, or associated physical abnormalities are evident, an appropriate diagnosis may be made. However, patients with congenital macrothrombocytopenia are often misdiagnosed with ITP and treated as such. This is partly because congenital macrothrombocytopenias are considered exceedingly rare and limited knowledge is available about them.

In all congenital macrothrombocytopenias, giant platelets and thrombocytopenia are present, but the clinical presentation is widely heterogeneous, ranging from an asymptomatic condition to a severe life-threatening bleeding tendency. In addition, there are syndromic forms associated with physical stigmata. Recent progress in the elucidation of the responsible genes for several congenital macrothrombocytopenias led to advances in our understanding and classification of the disease. However, in approximately half of the patients

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with congenital macrothrombocytopenia the molecular causes remain unknown. This review summarizes the current knowledge on the principal congenital macrothrombocytopenias that are occasionally encountered, especially focusing on the most common macrothrombocytopenia with leukocyte inclusions and Bernard-Soulier syndrome, to facilitate in making a proper diagnosis. More comprehensive reviews on the pathogenesis and pathophysiology of the disease may be found elsewhere.[1–5]

Congenital macrothrombocytopenias

Congenital macrothrombocytopenias are a heterogeneous group of rare disorders and are defined as decreased peripheral blood platelets with large size present from birth. Table 1 lists some principal congenital macrothrombocytopenias according to the underlying cause: abnormalities in the platelet cytoskeleton, GPIb/IX/V, and transcription factors. Clinical and laboratory features as well as responsible genes and chromosomal localizations are also shown.

Macrothrombocytopenia with leukocyte inclusions/*MYH9* disorders

Definition

The autosomal dominant macrothrombocytopenias with leukocyte inclusions are rare disorders characterized by a triad of giant platelets, thrombocytopenia, and Döhle body-like cytoplasmic inclusions in granulocytes (Table 2). Once considered to be extremely rare, a prevalence of not less than 1 in 100,000 may be estimated from intensive studies in Italy and Japan. These disorders are usually transmitted in an autosomal dominant manner, but approximately 20% of cases are considered to be sporadic.[6–8] Mosaicism accounts for some de novo mutations.[9] Although most patients with these disorders do not bleed, a few bleed and need only occasional treatment. The bleeding tendency is related to the measured platelet counts. May-Hegglin anomaly (MHA) is the prototype of these disorders and was first described a century ago.[10,11] Others include Sebastian (SBS),[12] Fechtner (FTNS),[13] and Epstein (EPS) syndromes.[14] All four disorders involve macrothrombocytopenia; however, each of these disorders is distinguished from others by the presence and/or morphology of granulocyte inclusion bodies and the presence of a variable combination of Alport manifestations, including nephritis, deafness and cataracts (Table 2). SBS can be distinguished from MHA by ultrastructural differences in their inclusion bodies. In MHA, inclusions consist of ribosomes aligned along parallel microfilaments, whereas in SBS, the inclusions lack parallel filaments but are full of depolymerized ribosomes. On light microscopic examination, the inclusions can be differentiated by size (MHA > SBS), shape (MHA oval to spindle, SBS round), and stainability (MHA > SBS).[12,15] In the clinical setting, however, it is not always necessary to differentiate MHA and SBS. FTNS is characterized by the same hematologic changes as those in SBS (SBS-type inclusions) but with Alport manifestations.[13] Epstein syndrome has been described as a variant of Alport syndrome associated with macrothrombocytopenia but without leukocyte inclusions.[14] Although these four disorders were previously considered to be separate clinical entities, a recent positional cloning approach disclosed that these disorders are caused by mutations in the same gene, *MYH9*, which encodes the nonmuscle myosin heavy chain-A (NMMHCA).[16–18] Thus, they represent the same entity with different genetic penetrance and variable phenotypic expression. The name ''*MYH9* disorders'' or ''MYHIIA syndrome'' has beenn proposed to encompass all the autosomal dominant macrothrombocytopenias with leukocyte inclusions.[6–8]

Genotype-phenotype relationships

Genetic analysis of *MYH9* disorders showed that there is no clear relationship between clinical phenotypes and the sites of the *MYH9* mutations.[6–8] An *MYH9* mutation is strictly associated with the hematological abnormalities. Although the molecular mechanism of the production of giant platelets has not been elucidated, it is suggested that abnormal NMMHCA, by interfering with the formation of myosin thick-filament, affects proper proplatelet formation in megakaryocytes.[19] An *MYH9* mutation, however, does not predict the clinical course of the affected individuals with respect to the development of Alport manifestations. It has become evident that the *MYH9* mutation alone does not cause associated Alport manifestations and that unknown genetic and/or epigenetic factors might influence the phenotypic consequences of *MYH9* mutations. The expression of Alport manifestation in individuals sharing the same mutation is inconsistent even within the same family.[20,21] Furthermore, careful evaluation of patients with MHA and SBS revealed that most patients had