CHILD CONGENITAL PLATELET PATHOLOGY

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Abstract: *Congenital platelet pathology refers to disorders of platelet function, the red cells being essential for the coagulation of blood. Congenital platelet disorders are important causes of bleeding that can quantitatively and qualitatively alter platelets, impairing their function. The purpose of this study is to summarize current knowledge on the different types of inherited platelet disorders, their clinical and laboratory data, molecular genetic causes, and the therapies used in clinical practice.*

Keywords: *platelet function pathology, children.*

Rezumat: *Patologia trombocitară congenitală face referire la defectele de funcţie trombocitară înăscute, trombocitele având rol esenţial în coagulare. Anomaliile trombocitare congenitale sunt cauze importante de sângerare ca rezultat al unor alterări cantitative şi calitative. Referatul aduce în atenţie date recente de genetică moleculară, date de laborator, terapie şi practică clinică.*

Cuvinte cheie: *defecte de funcţie trombocitară, copil*

Congenital platelet anomalies are the result of certain qualitative and quantitative disorders. The majority of the anomalies involve both qualitative and quantitative disorders, their classification being according of the dominant deficiency.

QUALITATIVE DEFICIENCIES

A. Platelet membrane. Membrane receptors.

1. Glanzmann's thrombasthenia (GT). In 1918, the Swedish pediatrist Glanzmann described a heterogeneous group of anomalies called "thrombasthenia", which define a normal number of platelets and an abnormal retraction of the thrombus. A very rare recessive autosomal hemorrhagic disease, Glanzmann's thrombasthenia is characterized by the platelets incapacity of binding fibrinogen and of aggregating after the stimulation with physiologic agonists, such as adenosine-diphosphate (ADP), epinephrine or collagen. Ristocetin stimulation aggregation is normal. The cause is represented by an anomaly of the genes that encode chains of the αIIb-β3 integrin from the receptors for fibrinogen placed on the platelet membrane. (1,5,7). The increased incidence of this affection may be encountered in isolated communities or in case of consanguinities. Particularly, the carrier status is encountered in a quite increased percentage in the population of the Arabian Peninsula, south India, in the Jewish population, in which 50% of the αIIb-β3 receptors are normal, without platelet disorders or significant bleedings.

The modern methods of biological exploration (electrophoresis, flow-cytometry, immunoblot-type analyses) allowed a new method of platelet classification, according to the normal percentage of the αIIb-β3 receptors from the surface of the platelet membrane: type I – receptors cannot be detected; type II – moderate levels of the αIIb-β3 receptors can be detected, about 15-20%; type III – a normal or cvasi-normal number of dysfunctional αIIb-β3 receptors. No correlation between the type of GT and symptomathology severity were proved. The patients belonging to GT type I may present a discrete or moderate clinical picture. There are patients with GT type III, who needed multiple platelet transfusions due to recurrent bleedings. The diagnosis is supported by the detection of the receptors on the platelet surface and genetic tests that prove the mutation responsible for the occurrence of the dysfunctional receptors. (1,8)

Clinically, Glanzmann's thrombasthenia (GT) is characterized by recurrent cutaneous-mucous bleedings starting at low age. The most common symptoms are expistasis and digestive bleeding. Metrorrhagia is commonly encountered in adolescence. The bleedings that accompany the surgical interventions, dental extractions, traumatisms or pregnancy are exacerbated in the case of GT patients. An important cause of death is the intracranial or gastrointestinal bleeding. Some of the patients were recorded with a symptomathology resembling to hemophilia: intra-articular bleeding or visceral hematomas. The therapeutic protocol comprises transfusion of platelets 1U/5-10kg; as a temporary measure, all patients develop αIIb-β3 anti receptors antibodies. Recent studies recommend the recombined factor VII. Regarding the easy and moderate bleeding episodes, Desmopresin iv. 0,3μg/kg. is recommended (1,5,7). The specialized literature describes two cases of recurrent bleedings with the lack or low density of another receptor of platelet membrane, α2-β1, receptor for collagen, Mg^{2+}depending. The low density of this type of

receptors, which was also detected in the patients with hemophilia, supports the role of this deficiency in causing bleedings. (1,2,3).

2. Bernard-Soulier syndrome (BSS), rare affection, recessive autosomal, described in 1948, in an infant of 5 months years old, who presented an increase bleeding time and giant platelets in the peripheral blood smear. The biological sublevel is represented by the defective formation of the receptor complex GPIb-IX. The platelet membrane presents two sites of binding the vW factor:

- αIIb-β3 (dysfunctional in the case of GT), receptor that initially requires platelet activation.
- GPIb-IX membrane platelet with a key part in the initial attachment and normal adhesion to the extracelullar matrix of the injured vessel. It is assumed that the GPIb-IX receptor also binds P selectin and thrombin. The binding of the vW factor to the GPIb-IX receptor complex activates the platelets by the activation of the C phospholipasis and C protein kinase, which together with the increased level of Ca^{2+}, launch the secretion and intensify the platelet aggregation. The GPIb-IX complex plays a part in the platelet activation and by the binding of the 14-3-3 cytoskeleton protein, thus interacting with the platelet receptors FcγRIIA.

Clinical manifestations: cutaneous-mucous bleeding, purple, epistasis, gastrointestinal bleeding, metrorrhagia. (1,7). Laboratory diagnosis is supported by: *increased bleeding time, *presence of the representative anomaly for this affection, that is the lack of platelet agglutination in the presence of ristocetin, anomaly that cannot be adjusted by the combination with normal plasma; *normal aggregation to the ADP stimulation, collagen and epinephrine, variable levels of thrombocytopenia; *average platelet diameter 3 up to 20 times higher than normally; *platelet average weight may be normal, in this situation, thrombocytopenia is a compensatory response; *vacuolar megakaryocytes, detectable characteristics through electronic microscopy.

The detection of the genetic mutation responsible for the GPIb-IX complex deficiency represents a modern method of diagnosing the Bernard-Soulier syndrome. (1,2,8).

GT resembling therapeutic protocol involves the administration of platelet mass, the VIII recombined factor. There is a synthetic homologue of the 1-deamino-8-D-arginin vasopressin (DDAVP) in this study.

3. **Platelet-type, von Willebrand disease:** dominant autosomal affection characterized by easy or severe bleeding episodes, increased bleeding time, mild thrombocytopenia and low levels of circulating multimers with large molecular weight of the vW factor. In contrast with the vW disease, type 2B, where the mutation of the vW factor results in the increase of its affinity towards the GPIb-IX normal platelet complex, platelet-type vW disease is brought about by a change (especially by a mutation of the GPIbα area) at the level of the GPIb-IX complex, which results in the increased affinity towards the circulating multimers of the vW factors.

Other congenital disorders of the platelet membrane receptors.

G-protein-Coupled Receptors. Two cases of recurrent bleeding episodes were described in the patients with low response to the ADP stimulation and reduced sites of binding the ADP analogues. The specialized literature mentions certain cases of bleeding episodes in the patients with congenital absence of the receptors for thromboxan A2.

Scot syndrome is defined by: rare selective deficiency of the platelet coagulant activity, number of sites for the Xa factor 75% less than normally, defective response to the thrombin and collagen stimulation, normal bleeding time, normal platelet aggregation and secretion, normal prothrombin time, normal partial thromboplastin time, reduced time of the prothrombin serum due to the reduced consumption of prothrombin by the platelet incapacity for generating normal procoagulant activity. The therapy consists in the administration of platelet mass. (1,9).

B. Platelet intracytoplasmic granules.

1. Dense granules deficiency (δ). Characteristic for this group of deficiencies is the lack of granules containing ADP, ATP, Ca^{2+} and serotonin. Clinically, episodes of moderate bleeding diathesis could be observed, associated to anomalies of platelet aggregation, frequently, increased bleeding time. The electronic microscopy establishes the diagnosis by the observation of the lack of the intracytoplasmic and platelet granules.

There are affections having the pathologic element associated with the dense granules deficit, out of which the most frequent are:

- **Hermansky-Pudlak syndrome,** characterized by: recessive autosomal transmission, severe albinism, photophobia, nystagmus, diminishing of the visual acuity, excessive accumulation of ceroid-like material in the reticuloensotelial cells, bleeding diathesis on medium or severe intensity.
- **Chediak-Higashi syndrome,** characterized by albinism, wick, intracytoplasmic accumulation of huge granules in leucocytes, lymphocytes, monocytes and thrombocytes, associated with immune deficiencies, deficient medullar leukocytary mobilization, deficient chemotaxia, diminished bacterial activity; intracytoplasmatic granule may be encountered in other tissues, too.(1,2).

2. α granules deficiency. It is characterized by bleeding episodes similar with those of (δ) dense granules deficiency, mild thrombocytopenia and increased bleeding time. It is called the syndrome of the grey platelets due to the microscopic aspect of thrombocytes. Regarding the electronic microscopy, thrombocytes are increased by volume and are lacking in α granules. Thrombocytes contain deficient quantities of proteins specific to α granulations: PF4, vWF, fibronectin V factor. The vacuolar aspect is given by the empty α granulations that present P selectin and αIIb-β3 receptors.

The agglutination capacity with physiologic stimuli, especially thrombin is much reduced and the response to the Ca^{2+} mobilization is delayed and incomplete. Thrombocytes with α granules deficit contain important quantities of proteins intracytoplasmically, including

immunoglobulins and albumins, proteins that were contained in α granulations, and the proteins that normally are contained in α granulations are released from thrombocytes. One of these proteins is PF4, responsible for myelofibrosis or cystic fibrosis associated to this platelet deficiency.(1,7)

Other granular deficiencies.

- The specialized literature describes cases of patients that presented **both granular deficiencies** at the same time - δ and α. granulations deficiencies. δ granulations deficiency is usually more expressed than α granulations deficiency. Characteristic for these cases are the easy or mild bleeding episodes, reduced levels of serotonin and ADP-ATP low relation.
- **Quebec syndrome** is a rare affection, initially associated to a deficiency of V platelet factor. Recent data identified the generalized autolysis of a large number of α granules resulting in the ectopic expression of urokinase at the level of α granulations. (1,6)

C. Deficiencies of the transduction signal. A small group of patients was described as having phenotypes that express an abnormal platelet aggregation, similar to that of the patients with platelet intracytoplasmic granulations disorders. The described anomaly is the lack of arahydonic acid releasing capacity, probably due to the A2 phospholipase deficiency. Other patients presented disorders of cyclooxygenase activity and abnormal platelet aggregation as a response to ADP stimulation, epinephrine, collagen and arahydonic acid, but with normal response to the stimulation with G2 prostaglandin. (2,4,9)

QUANTITATIVE DEFICIENCIES

Thrombocytopenia associated to megacariocytary deficiencies including:

Congenital amegacariocytary thrombocytopenia. It is a rare affection that associated a very low number of thrombocytes, megacariocytes lack and increased risk of aplastic anemia.

Thrombocytopenia absent radii with hipomegacriocytary thrombocytopenia and radius absence. The major skeletal anomaly is the radius absence and is associated to the cardiac malformations: Fallot's tetralogy, atrial septum defect.

Deficiencies of the hematopoietic transcription factors:

- **Deficiency of the GATA-1 gene from the X chromosome,** encountered in a rare form of X-linked anemia, that associates the severe thrombocytopenia; large number and sizes of magariocytes, its nucleus pushed towards the exterior and abnormal intracytoplasmic contents.

CBFA2 gene deficiency (AML-1) transcription factor involved in the translocations from the acute myeloid leukaemia. (1,6,7)

B. Thrombocytopenia associated to microthrombocytes. Wiskott-Aldrich syndrome. X-linked platelet anomaly associated to eczema, sever immune deficiency, thrombocytopenia, microthrombocyte; the responsible gene is placed on the short arm of the X chromosome, the affected protein being WASP.

C. Thrombocytopenia associated to macrothrombocytes. Maz-Hegglin syndrome is characterised by macrothrombocytes associated to thrombocytopenia and normal coagulant tests. The leukocytes present spindle-shaped cytoplasmic inclusions, called Dohle bodies. The association with the neuro-sensorial deafness and ocular anomalies is called Fechtner syndrome. Recent chromosomal studies suggest the involvement of the long arm of chromosome 22, the gene that encodes the heavy chain A of the nonmuscular myosin (NMMHC-A).

Montreal syndrome is characterised by the presence of macrothrombocytes, increased coagulation time and spontaneous platelet aggregation to pH values of 7,4. The biologic sublevel and the mechanism of this anomaly are not known but a defect of a neuter protein kinase, calcium activated is assumed.

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