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HERITABLE AMEGACARIOCYTIC THROMBOCYTOPENIA: DESCRIPTION OF A CLINICAL CASE

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Annotation. *Features of the clinical course and differential diagnosis of hereditary thrombocytopenia, characterized by the development of pancytopenia in childhood, are described. It was found that the main manifestation of this pathology is hemorrhagic syndrome, accompanied by the presence of polymorphic, polychrome, asymmetric hemorrhagic rashes, frequent bleeding from the mucous membranes. The Mpl gene (1p34) was sequestered to confirm the diagnosis and establish the genomic mutation. Complex diagnosis of this disease requires a comprehensive and interdisciplinary approach involving a coordinated team of hematologists, geneticists, immunologists, neurosurgeons and ophthalmologists.*
Keywords: *children, thrombocytopenia, hemorrhagic syndrome, gen Mpl (1p34).*

Introduction

Congenital amegakaryocyte thrombocytopenia (CAMT) is an isolated constitutional thrombocytopenia characterized by an isolated decrease in the number of platelets and megakaryocytes during the first years of life, which develops into bone marrow failure with pancytopenia later in childhood. Inherited by autosomal recessive type. Prevalence - unknown, less than 100 cases in the world have been reported in the literature. The reason is a mutation in the Mpl gene (1p34). There are: type I - early onset of severe pancytopenia, decreased bone marrow activity and very low platelet count. In this group there is a complete loss of functional c-Mpl. The average platelet count is usually 21 x 10^9 / l or less. Type II is a milder form with a temporary increase in platelet counts to near normal values during the first year of life and the onset of bone marrow failure at 3 to 6 years of age or later. In this group there are partially functional receptors of the c-Mpl gene. The average platelet count is usually from 35 x 10^9 / l to 132 x 10^9 / l, type III - there is an inefficient megakaryopoiesis without defects in the c-Mpl gene [1, 2, 3].

Aim - to study the features of hereditary amegakaryocyte thrombocytopenia type II in child.

Materials and methods

This study was conducted on a case of pediatric practice. Under our supervision was a 7-year-old girl who was admitted for examination to the oncohematology department of VRCCH. Complaints of polymorphic, polychrome, asymmetric hemorrhagic rashes, frequent nosebleeds.

History: lll from birth. In 2013, he was diagnosed with congenital thrombocytopenia. In this regard, an infusion of thromboconcentrate was performed. There were no significant hemorrhagic complications. Once a year the patient was hospitalized in the oncohematology department due to hemorrhagic syndrome, with a diagnosis of idiopathic thrombocytopenic purpura. Upon admission to the hospital, a replacement transfusion was performed human lg G concentrate once a year. During life, the level of platelets between hospitalizations ranged from 5-120 thousand in μl, persistent normochromic anemia; periodic neutropenia (throughout life). Life history: frequent hemorrhagic manifestations due to the disease, pneumonia twice. Molecular genetic studies have shown a decrease in partially functional receptors of the c-Mpl gene. Clinical diagnosis: Hereditary amegacariocytic thrombocytopenia (CAMT-II).

At the age of 6, an allogeneic transplant was performed from a non-family donor in Israel. Currently +180 days after transplantation, minor manifestations of GVHD, receiving immunosuppressive therapy.

Results

Clinical case (description of a pediatric case from practice). A 3-day-old girl was transferred from the maternity hospital to the neonatal pathology department due to the appearance of hemorrhagic rashes on the skin of the extremities and torso. In the general analysis of blood: Hb 114 g / l Er 3,3x10^{12} / l, L-10x10^9 / l, Tr single in sample). In the myelogram from 16.09.2013 - hematopoiesis of the normoblastic type, blasts 1.6%; 4 megakaryocytes of I-II degree of maturity. Advised by a hematologist, geneticist, immunologist. Diagnosis: Congenital thrombocytopenia. Thromboconcentrate B (III) 50 ml was transfused in the neonatal pathology department. There were no significant hemorrhagic complications. Once a year the patient was hospitalized in the Department of Oncohematology of the children's clinical hospital in Vinnytsia due to hemorrhagic syndrome with a diagnosis of Idiopathic thrombocytopenic purpura. Replacement transfusion therapy with human lgG concentrate (Octagam 10%) was performed once a year. During life, the level of platelets between hospitalizations

ranged from 5-120 thousand in μl., persistent normochromic anemia; periodic neutropenia (throughout life). At the age of 6 years, she entered the oncohematology department of the Vinnytsia children's clinical hospital. Bone marrow puncture and trepan biopsy of the iliac bone were performed.

- General blood test from 17.09.2019: PLT - $75x10^9$ / l, Hb - 125 g / l, Er $3.68x10^{12}$/l, WBC $8.06x10^9$ / l, ret. - 1%.

- Platelet morphology from 19.09.19: macroforms - 5-6%, mesoforms - 68%, microforms - 26%.

Additional examination methods were performed: bone marrow puncture from three points from 09/19/2019 (anterior crest of the left iliac bone, anterior crest of the right iliac bone, posterior crest of the left iliac bone).

Pathohistological, immunohistochemical study of trepan biopsy of the iliac bone, description of histological preparations - bone marrow architecture is disturbed due to mosaic hypocellularity, cell brain is 10-14% of the surface of structural units of bone marrow. Erythroid islets are shallow with blurred edges. Granulocyte sprout is represented by separate clusters. At differentiation of a granulocytic sprout existence of transitional forms is noted. Progenitor cells are solitary. Megakaryocytes were not detected. Immunohistochemical study: Ab-Clone OBEnd / 10- (- / +), Ab-1 Clone JC / 70A - (+), Peroxidase Clone 2c7- (- / +) focal in the form of individual clusters. Pathoanatomical diagnosis: histological picture corresponds to severe hypoplasia of bone marrow tissue, which is characteristic of both congenital bone marrow failure and acquired aplastic anemia.

The child was also examined for a group of herpes viruses - no herpes infection was found.

Advised by related specialists: ENT: d-z: vasomotor rhinitis. Ophthalmologist: no pathology detected.

Also consulted by a geneticist (from 24.09.2019), the child has no dysmorphic changes and stigmas. In a child with thrombocytopenia, data on the syndromic diagnosis were not detected. Additional examination by a hematologist is recommended.

- Ro-graphy of the forearms (from 20.09.2019): no pathology was detected.

- Molecular cytogenetic study of oral epithelial cells for the presence of mutations in the MPL gene (September 27, 2019) - mutation detected (conclusion attached). Detection of thrombopoietin levels in the blood (09/27/2019). Material in the work.

According to the results of HLA-typing (from 09/26/2019): no fully compatible donor was found. The patient is partially compatible (haploidentical) with her parents.

Conclusions: on the basis of the clinical picture, medical history, cytomorphological examination of the bone marrow; histopathological and immunohistological studies of trepan biopsy of the iliac bone and molecular cytogenetic examination of saliva for the presence of mutations in the MPL gene can establish a preliminary diagnosis: Hereditary amegacariocytic thrombocytopenia (CAMT-II). Blood group: B (III) Rh positive.

Transfusion support during the stay in the ICT department was performed with the available drug - Thromboconcentrate - №3. After transfusion of thromboconcentrate to the child, we received positive hematological changes in blood parameters, namely General blood test from 01.10.2019: Ltitz-3,5x10^9 / l, Hb-10^8g / l, Tr-161 thousand / μl. We got a stable condition of the child.

Discussion

Thrombocytopenia is a condition in which the peripheral blood platelet count is less than 150 x 10^9 / L. At birth, 1-5% of newborns have thrombocytopenia [1, 2].

The etiology and pathogenesis of thrombocytopenia in children is determined by the nature of the disease: hereditary or acquired. In hereditary thrombocytopenia, there is increased platelet destruction (95%) due to antibodies, mechanical factors, or intravascular coagulation. Less often (5%), congenital thrombocytopenias are caused by a decrease in platelet production or have a mixed origin [1, 2, 6, 8].

The development of hemorrhagic syndrome in thrombocytopenia is mainly due to a violation of the angiotrophic function of platelets. The vascular endothelium in this situation becomes more permeable and fragile, which leads to the occurrence of spontaneous hemorrhages and bleeding from the microvasculature. The causes of thrombocytopenia in newborns are variable [3, 4, 8, 10].

These are primary thrombocytopenias, which are usually caused by immunopathological processes. Secondary (symptomatic) thrombocytopenia occurs against the background of various conditions, among which are more often viral or bacterial infections, severe hypoxic conditions, immunodeficiencies, intravascular coagulation syndrome and others thrombohemorrhagic syndromes [4, 5]

In addition, acquired thrombocytopenia in newborns is divided into immune and non-immune.

Accordingly, to existing concepts, thrombocytopenia (TP) is divided into 2 large groups depending on the origin (central and peripheral) [6].

Thrombocytopenias of central origin develops due to impaired platelet production in the bone marrow (a-hypomegakaryocytosis). There are exclusively amegakaryocytic thrombocytopenias that do not involve any pathology [7, 9].

Among them are congenital amegakaryocytosis and hypomegakaryocytosis in combination with malformations (TAR syndrome: thrombocytopenia + aplasia of the radius + deficiency of factors VII and X), chromosomal aberrations (trisomy of 13 and 18 chromosomes), thrombocytopenia with ineffective thrombocytopoiesis (thrombocytopoiesis) Bernard-Soulier and May-Hegglin syndromes, a combination of thrombocytopenia and thrombocytopathy - "gray platelet" syndrome, Wiskott-Aldrich and Murphy

syndromes [1, 6].

TP of peripheral origin is the result of:

1. increased destruction of platelets by antiplatelet antibodies (immune TP), abnormal distribution (sequestration), as well as after exchange or other blood transfusion;

2. excessive consumption (DIC syndrome, bleeding, massive thrombosis, mechanical ventilation, syndromes - Kasabach-Merritt, Wiskott-Aldrich, Bernard-Soulier, May-Hegglin, Gaucher and others):

a) Kasabach-Merritt syndrome - solitary hemangiomas with TP and general coagulation disorders in the form of hemorrhages of the microcirculatory type (hemorrhages into the skin, bleeding from mucous membranes, melena, hemorrhages into the brain). In this syndrome, there is a mechanical destruction of platelets due to their increased consumption in cavernous vascular formations (hemangiomas) with the development of thrombocytopenia.

b) Wiskott-Aldrich syndrome - there is a congenital defect of platelets (abnormal, small), which contributes to their increased destruction. Diagnostic value is a large number of small platelets in the blood, low IgM levels, elevated levels of IgA and IgE, normal or elevated IgG levels, impaired platelet aggregation, lymphopenia.

c) May-Hegglin syndrome (giant, unnatural platelets with Doehle bodies, abnormal platelet survival and impaired production).

e) Gaucher syndrome - an inherited disorder of accumulation (deficiency of lysosomal enzyme that breaks down ceramide glucose, leading to the formation of Gaucher cells). There are three types of Gaucher disease. The clinical picture of Gaucher disease is characterized by enlargement of parenchymal organs, especially the spleen. Splenomegaly is accompanied by hyposplenism with thrombocytopenia, anemia and leukopenia. The most severe complication of the first and third types are changes in the bones [2, 8].

Congenital amegakaryocytic thrombocytopenia (CAMT) - thrombocytopenia in children due to amegakaryocytosis. The etiology of the disease is not precisely established, it is inherited in an autosomal recessive manner, with impaired embryogenesis at 7-9 weeks of gestation. Hemorrhagic syndrome usually manifests itself in the first days of a child's life and is characterized by microcirculatory bleeding. In the analysis of blood, severe thrombocytopenia, often anemia, and impaired platelet aggregation are determined. Bone marrow puncture reveals hypoplasia or aplasia of the megakaryocytic apparatus. The prognosis of the disease is unfavorable.

The most common cause of death is cerebral hemorrhage. CAMT is subdivided into:

1) type I is characterized by an early onset of the disease with severe pancytopenia, including thrombocytopenia, and decreased bone marrow activity;

2) type II proceeds more mildly and is characterized by a transient increase in the number of platelets almost to normal values during the first year of life, a decrease in megakaryocytes in the bone marrow appears at the age of 3 years and later [8, 10].

Conclusions and prospects for further development

1. Hereditary amegacariocytic thrombocytopenia is a genetic pathology caused by amegakaryocytosis, which is complicated by severe anemic, hemorrhagic and subarachnoid syndromes in children. Complex diagnosis of this disease requires a comprehensive and interdisciplinary approach involving a coordinated team of hematologists, geneticists, immunologists, neurosurgeons and ophthalmologists.

Prospects for further development in the study of the "mask" of the manifestation of hemorrhagic syndrome of neonatal age due to thrombocytopenia, which will be accompanied by the manifestation of the underlying oncohematological disease in children.

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СПАДКОВА АМЕГАКАРІОЦИТАРНА ТРОМБОЦИТОПЕНІЯ: КЛІНІЧНИЙ КЕЙС

Дудник В.М., Фурман В.Г., Куцак О.В., Ізюмець О.І.

Анотація. *Описані особливості клінічного перебігу та диференційної діагностики спадкової тромбоцитопенії, що характеризується розвитком тромбоцитопенії в ранньому дитячому віці. Було встановлено, що основним проявом даної патології є геморагічний синдром, що супроводжувався наявністю поліморфних, поліхромних, асиметричних геморагічних висипань, частими кровотечами зі слизових оболонок. Для підтвердження діагнозу та встановлення геномної мутації було проведено секвенування гена Mpl (1p34). Складна діагностика даного захворювання потребує комплексного та міждисциплінарного підходу з залученням координованої робочої команди зі складом гематолога, генетика, імунолога, нейрохірурга та офтальмолога.*

Ключові слова: *діти, тромбоцитопенія, геморагічний синдром, ген Mpl(1p34).*