ECRONICON OPEN ACCESS

EC PAEDIATRICS
Case Report

When the Main Symptom is Missing

Zuzana Podmanická[1]*, Viera Rajčanová[1], Katarína Okáľová[1], Karol Králinský[1,5], Eva Bubanská[2], Helena Fillová[2], Peter Čižnár Csc[3], Júlia Horáková[4], Sabina Šufliarska[6] and Alica Chocholová[7]

[1]II Pediatrics Clinics, Children University Hospital, Banska Bystrica, Slovakia

[2]Pediatrics Hematooncology Clinics, Children University Hospital, Banská Bystrica, Slovakia

[3]Pediatrics Clinics, Faculty of Medicine, Comenius University and National Institute of Childhood Diseases, Bratislava, Slovakia

[4]Bone Marrow Transplant Unit, KDHAO LF UK and NÚDCH Bratislava, Slovakia

[5]Faculty of Health of SZU with its registered office in Banská Bystrica, Slovakia

[6]General Ambulance for Children and Adolescents, Bratislava-Dúbravka, Slovakia

[7]General Doctor for Children and Adolescents, Bratislava 3 - Kramáre, Slovakia

***Corresponding Author:** Zuzana Podmanická, II Pediatrics Clinics, Children University Hospital, Banská Bystrica, Slovakia.

Received: February 21, 2020; **Published:** March 10, 2020

Abstract

The authors would like to show in this paper how is difficult to make a right diagnosis to child with primary immunodeficiency. Most primary immunodeficiencies belong among rare diseases with an incidence of less than 1: 100,000. There are currently no primary screening methods for primary immune deficiencies, and a significant part of the diagnosis consists of basic examination procedures, namely medical history, clinical picture, laboratory and diagnostic imaging examinations. No all of the symptoms may be present in the newborn and early infant. Case report is about patient with early and severe clinical manifestation of Wiskott-Aldrich syndrome without the presence of typical microthrombocytopenia in neonatal age.

Keywords: *Thrombocytopenia; Primary Immunodeficiency; Infections; Juvenile Myelomonocytic Leukemia; Neonatal Alloimmune Thrombocytopenia; Wiskott-Aldrich Syndrome*

Abbreviations

CMV: Cytomegalovirus; CNS: Central Nervous System; HLA: Major Histocompatibility System Antigens; ITP: Idiopathic (Immune) Thrombocytopenic Purpura; JMML: Juvenile Myelomonocytic Leukemia; LAD: Leukocyte Adhesion Deficiency; MPV: Mean Platelet Volume; LAD - Leukocyte adhesion deficiency; MPV- Mean Platelet Volume; NK Cells: Natural Killers - Lymphocyte Subclass; RSV: Respiratory Syncytial Virus; WAS: Wiskott-Aldrich Syndrome; WAPS protein of Wiskott-Aldrich syndrome

Introduction

The authors would like to present the differential diagnosis of thrombocytopenia in neonatal and infant age [1,4,10,12]. Thrombocytopenia with skin and mucosal manifestations of bleeding occurs in children without other co-morbidities, when they suffer from acute respiratory infection. Therefore differential-diagnostic considerations involves diagnosis from the most commonly occurring thrombocytopenias such as: fetal / neonatal thrombocytopenia, or idiopathic (immune) thrombocytopenic purpura of ITP, up to the rarely occurring diagnosis [2,6]. When is present the non-response to initial high-dose intravenous immunoglobulin therapy and the further course is complicated with accumulation of severe infections in organ systems, differential diagnosis has to be extended. There is a gradual failure of the immune system, an we have to look for rare causes of thrombocytopenia in connection with immunodeficiency.

Case Report

The 13-day newborn of the Roma ethnic group was admitted for respiratory insufficiency due to RSV bronchiolitis with petechial manifestations of bleeding into the skin around the navel and the mucosa of the hard palate. On the beginning of him illness he had 3-day cough, which was irritant. The boy has any perinatal and peripartal pathology, he was eutrophic (4050g / 53cm), he was born in term, spontaneous way. He was the third child of his parents, he had two older sisters. The family history was unremarkable, the parents negated consanguinity, but there was a generational difference of 18 years between them.

In addition to finding a small number of platelets of appropriate size, monocytosis appears in the peripheral blood count, along with various stages of development of granulocytes - leftward shift to the blasts.

	Patient value	Reference values
WBC	14	[5-19.5]x 10^{*9}/l
Neu %	28.2	[20-46] %
Neu abs.	3.94	[1.0-9.0] x10^{*9}/l
Lym %	37.3 ↓	[50-85] %
Lym abs.	5.21	[2.5-16.5] x10^{*9}/l
Mono %	30.7 ↑	[3.0-10.3] %
Mono abs.	4.29 ↑	[0.15-2.0]
Eos %	1.9	[1.4-4.6] %
Eos abs.	0.26	[0.07-0.9] x10^{*9}/l
Baso %	1.9 ↑	[0-1.0] %
Baso abs.	0.27 ↑	[0-0.2] x10^{*9}/l
RBC	4.35	[3.6-6.2] x10^{*12}/l
HGB	145	[125-20.5] g/l
HCT	41.5	[39-63]%
MCV	95.4	[86-124] fl
PLT	22 ↓	[150-666] x10^{*9}/l
PCT	0.02 ↓	[0.12-0.36] %
MPV	7.9	[7.2-11.1] fl
PDW	9.5 ↓	[25-65]

Microscopic blood smear

Segment. Neu	25%
Band Neu	14%
Lymphocytes	32%
Monocytes	15%
Eosinophils	2%
Myelocytes	1%
Metamyelocytes	9%
Promyelocytes	1%
Blast cells	1%

Figure 1: *Initial blood count and differential blood count with microscopic coating.*

The child didn´t respond to ITP treatment, even not to blocking treatment of fetal / neonatal alloimmune thrombocytopenia. (IVIG: 2g / kg) [2]. To avoid bleeding in mucous membranes and bleeding in the CNS, he required repeated substitutions with platelets.

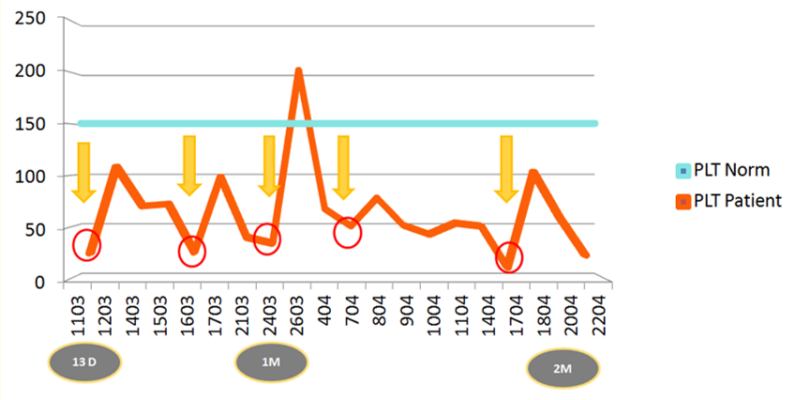

Figure 2: *Persistence of thrombocytopenia and repeated substitution of thrombocyte concentrate like a therapy in clinical manifestations of bleeding.*

For persistent abnormal findings in peripheral blood counts typical of juvenile myelomonocytic leukemia: leukocytosis 14x10 * 9 / l, monocytosis 4.29x10 * 9 / l, thrombocytopenia 22x10 * 9 / l, presence of erythroblasts, we repeated bone marrow examination. Morphological examinations of bone marrow, ancillary examinations (without fetal hemoglobin elevation) and genetic examinations (monosomy 7 was not considered) do not confirm the diagnosis of juvenile myelomonocytic leukemia [3,7,11].

I. Clinical and hematological features (all three features mandatory)
Peripheral blood monocyte count > $1x10^9$/L
Blast percentage in PB and BM < 20%
Splenomegaly
II. Oncogenetic studies (1 parameter sufficient)
Somatic mutation in PTPN11* or RAS
NF1 mutation or clinical diagnosis of NF1
Monosomy 7
III. In the absence of one parameter listed under II, the following criteria have to be fulfilled:
Absence of Philadelphia chromosome (BCR/ABL rearrangement) (mandatory)
And at least two of the following criteria
Spontaneous growth or GM-CSF hypersensitivity in colony assay
Hemoglobin F increased for age
Myeloid precursors on peripheral blood smear
White blood count > $10x10^9$/L
Clonal abnormality besides monosomy 7

Figure 3: *Diagnostic criteria for juvenile myelomonocytic leukemia (JMML), according to Clinical Trial Protocol, EWOG-MDS 2006.*

Explanatory notes: PB- peripheral blood count, BM –bone marrow, NF1- neurofibromatosis 1, GM-CSF- granulocyte and macrophage colony-stimulating factor.

In addition, the boy starts to suffer from serious infections (bacterial and viral), and we notice also failure to thrive. Several systems are affected - initially from respiratory insufficiency due to RSV, a week later occur enteritis with enterorrhage caused by enteropathogenic *E. coli*. When he was 1.5 months old, he was still fighting with severe skin affections on the head and face. Findings were similar to seborrheic dermatitis, they were caused by Klebsiella pneumoniae. In 2 months was patient status complicated with medial otitis caused by Streptococcus pneumoniae. In 3 months added CMV pneumonitis also.

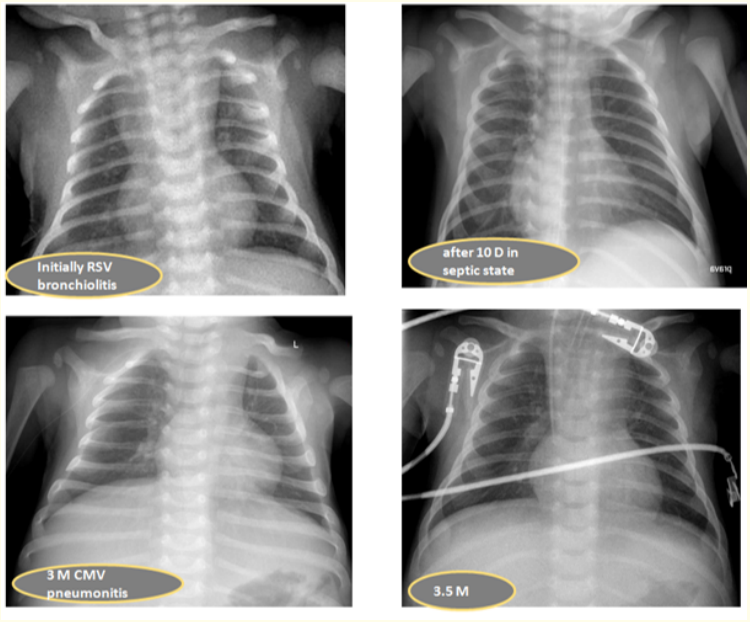

Figure 4: *Patient X-ray documentation.*

.

Its immune profile, which is largely influenced by treatment and infections, shows signs of lack of function. There is a gradual increase in gamaglobulinemia A, after repeated supportive treatment with intravenous immunoglobulins, hypergammaglobulinaemia G is also found. Skin finding on the head slowly resolved on combination of antibiotic therapy and local treatment, but at 3.5 months occur again new manifestations of dermatitis similar to the atopic dermatitis on the flexor sides of the limbs. There was hypergammaglobulinaemia E in laboratory tests.

After repeated transfusions, started creation alloantibodies against both platelets and leukocytes, and the efficacy of platelets concentrates decreases. Commonly available treatment options are exhausted. Efforts to restore the loss of haemopoietic organ functions to provide immune homeostasis lead to stem cell transplantation. Pre-transplant examinations of parents brought surprising finding of HLA identity of mother with child (finding in common population found among siblings) and HLA haploidentity between father and mother (finding in common population found between parent and child) which suggests the presence of consanguinity in the family. From the point of view of donation and graft acceptance, a relative HLA identity is ideal.

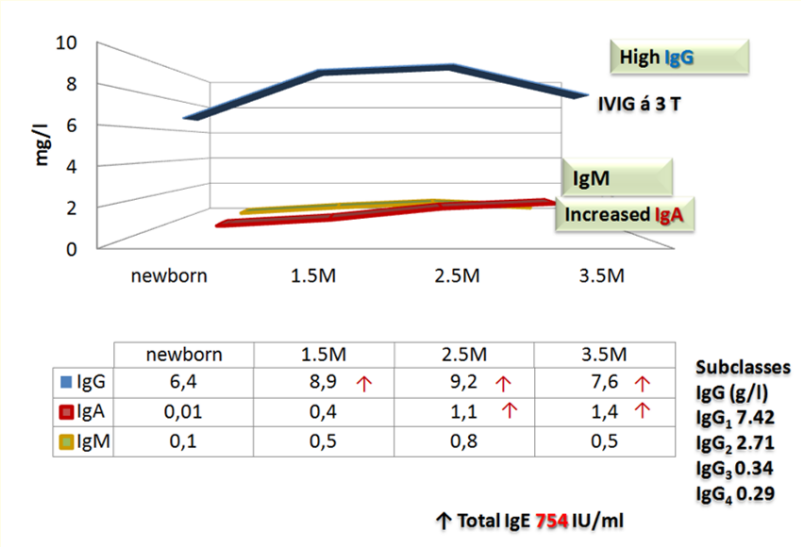

Figure 5: *Immunoglobulin profile in a patient.*

It would be properly to send the patient to a stem cell transplantation with right diagnosis. It is based on the normal platelet size (reference mean SVTr / MPV 7.2-11.1 fl platelet volume).

Fetal / neonatal alloimmune thrombocytopenia or idiopathic thrombocytopenic purpura would respond to treatment with high dose intravenous immunoglobulins [2,6]. The diagnosis of Wiskott-Aldrich syndrome lacks the main symptom – microtrombocytopenia. It is characterized by small platelets with SVTr / MPV <7fl, most commonly SVTr / MPV (3.8-5fl) [5,6,8,9,10]. For phagocytosis disorder with impaired leukocyte adhesion (LAD syndrome) miss the signs of extreme leukocytosis and significantly low oxidative burst of neutrophils - (the patient had marginally lower values) [1,4]. In the beginning was Di-George's syndrome considered, because of hypocalcaemia in laboratory findings, but later was confirmed vitamin D deficiency. Also calcium was normal after substitution. (1.4) Typical skeletal changes were lacking for infantile osteopetrosis. Because of increased destruction of platelets in the spleen with presence of free and bound antithrombocyte antibodies - their absence at the beginning was not indicative. Congenital CMV infection would make a increase amount of platelets like response after causal ganciclovir treatment. For juvenile myelomonocytic leukemia lacked the positivity of morphological examinations from bone marrow and genetic examinations [3,7,11].

The diagnosis was made only after complete clinical manifestation of Wiskott-Aldrich syndrome (microtrombocytopenia, eczema, hyper IgA, hyper IgE, immunodeficiency) with unmasking of microtombocytopenia. After a secondary review of all blood count findings, 7.0 fl platelets appeared for the first time at 1.5 months of age [14,15]. Then they appear intermittently (after platelet survival from platelet concentrates) with a minimum platelet size of MPV 6.6fl. Molecular genetic examination confirmed the X-linked recessive form of inheritance- WASp mutation, Xp11.22-23, mother was a carrier.

Discussion

Wiskott-Alrich syndrome is a primary immunodeficiency with a rare incidence of 2-8.8%, with an incidence of 4.1 per 1,000,000 live births. It is diagnosed by newborns or later in childhood [1,4,10,12]. Inheritance is most often X-linked recessive (boys affected), but can also be autosomal dominant, autosomal recessive, or unspecified. WAS is caused by a mutation of the WAS gene for the WAS protein. (WASp Xp11,22-23). The WAS gene is expressed exclusively in hemopoietic cells. Its exact function is not yet fully understood [4].

The product of the WAS gene is the WASP protein, which is required for many functions in lymphoid and myeloid immune cells [9]. It is part of the cytoskeleton of cells, affecting the polymerization of new branched actin microfilaments. Deficiency or lack can lead to immune deficiency at all levels. From impaired antigen recognition by the receptor, through impaired migration and chemotaxis of neutrophils and T-lymphocytes. In addition, a disorder of phagocytic function of dendritic cells and macrophages is present. Impaired formation of podosomes, phagosome, cytokine secretion, intergrin function, impaired cell polarization. In neutrophils, integrin-mediated adhesion and migration fail, granule release from neutrophils is impaired, oxidative enzymatic reactions are reduced. Lymphocytes are incapable of generating an immune synapse for impaired signaling functions and cytokine production. Immune sympathetic disorders also affect NK cells, T cells and B cells. These changes lead to the development of an immunodeficient state with insufficient cooperation between immunocompetent cells [9].

WAS is clinically characterized by a triad of symptoms: microtrombocytopenia (∂1.8 µm, SVTr / MVP 3.8-5fl), primary immunodeficiency and eczema. In laboratory tests, heterogeneity may be: decreased IgM, hyper IgA, hyper IgE, decreased concentrations of isohemagglutinins, or complete lack thereof. The disorder is also in cellular immunity - decreased number and function of T lymphocytes, decreased oxidative burst of neutrophils [1]. In 70% of cases, autoimmune disease may develop, in 10-20% of cases haematological malignancies occur [4].

WAS requires consistent and comprehensive care. Patients may be asymptomatic, others have recurrent infections (where prophylactic antibiotic and immunoglobulin replacement therapy is indicated), or severe course. They are suitable preventive measures - vaccination against pneumococcal and polysaccharide antigens. In bleeding manifestations, they require platelet concentrate replacement therapy. In patients with severe course of treatment, curative treatment is important as soon as possible after diagnosis. Treatment consists of stem cell transplantation. [4,10]. In some European centers (Great Ormond Street Hospital –London, Necker Children's Hospital-Paris), have started prospective studies using gene therapy with the implantation of recombinant WAS gene transmitted by Lentiviruses into stem cells [4,5,13].

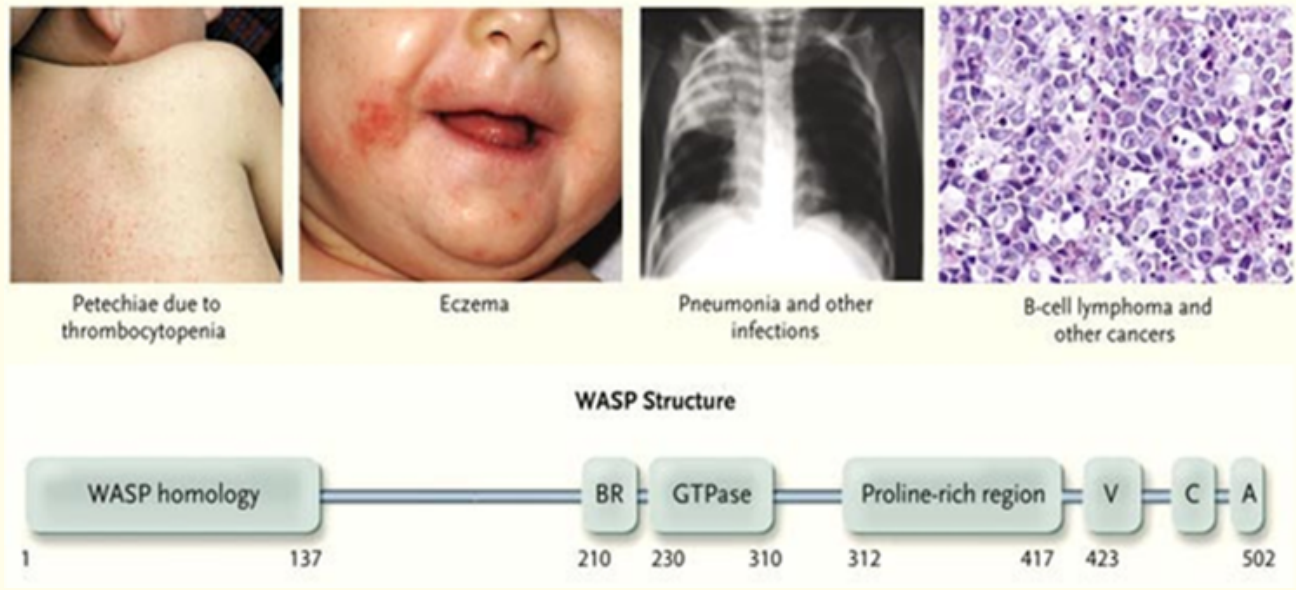

Figure 6: *Typical clinical manifestation of Wiskott-Aldrich syndrome (adapted to Focosi D. Inherited monogenic immune disorders, Copyright © 2001-2014).*

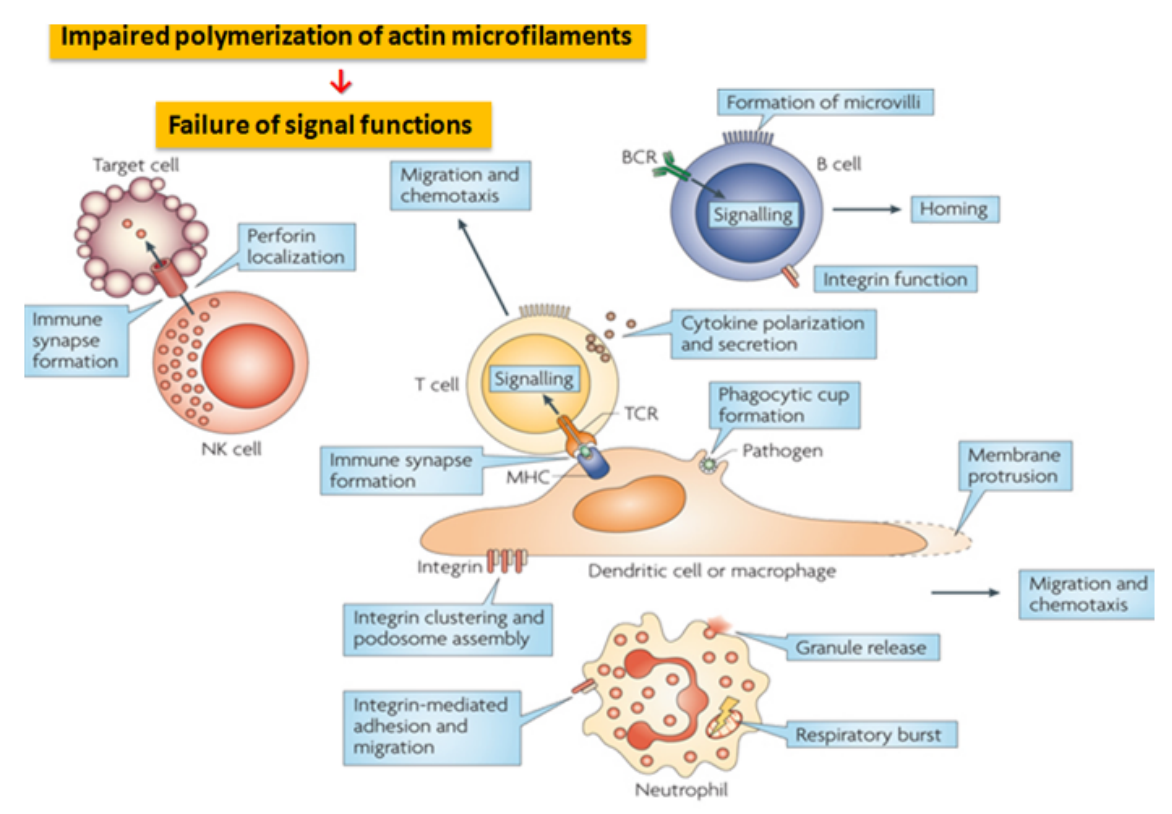

Figure 7: *Effects of WAS protein (modified according to Thrasher 2010).*

Conclusion

As the case study suggests, not all symptoms are fully expressed at the same time. Microtrombocytopenia, a symptom considered to be a pathognomic sign, may be masked at infant age by infection and leaching of younger (larger) forms of platelets from the bone marrow, which may lead to diagnostic delay [14,15].

The patient underwent a stem cell transplantation at the Bone Marrow Transplant Unit, Pediatrics Hematooncology Clinics Faculty of Medicine, Comenius University and National Institute of Childhood Diseases, Bratislava, Slovakia, where a definitive diagnosis was established. The first transplantation was performed from an HLA identical mother to minimize antigen loading. For graft rejection, he underwent retransplantation from an HLA identical unrelated donor. He developed full chimerism, is regularly monitored for TJKD : Bone Marrow Transplant Unit and he enjoys good health.

Bibliography

1. Šašinka M., *et al*. "Pediatria". 2nd edition. Bratislava, Slovakia: Herba (2007).

2. Bertrand G., *et al*. "Prediction of IVIG treatment efficiency in fetal/neonatal alloimmune thrombocytopenia". *Blood* 124.4 (2014): 654-655.

3. Niemeyer Ch. Clinical Trial Protocol, EWOG-MDS 2006 (2006): 97s, 24-34.

4. Jeseňák M., *et al*. "Vrodené poruchy imunity". Bratislava, Slovakia: A-medi management (2014).

5. "Wiskott-Aldrich Syndrome". In: IDF Patient and Family Handbook or Primary Immunodeficiency Diseases. 5th edition, USA, Chapter 10. Copyright by Immune Deficiency Foundation (2013).

6. Drachman JG. "Inherited thrombocytopenia: when a low platelet count does not mean ITP". *Blood* 103.2 (2004): 390-398.

7. Lazarchick J. "Marrow findings in JMML-1". American society of haematology. Copyright by American society of haematology (2017).

8. Focosi D. "Inherited monogenic immune disorders (see also diseases of the immune system and diseases with intrinsic aetiology)". Copyright © 2001-2014.

9. Thrasher AJ and Burns SO. "WASP: a key immunological multitasker". *Nature Reviews Immunology* 10.3 (2010): 182-192.

10. Orphanet: Wiskott Aldrich syndrome.

11. Watanabe N., *et al*. "Wiskott-Aldrich syndrome is an important differential diagnosis in male infants with juvenile myelomonocytic leukemia like features". *Journal of Pediatric Hematology/Oncology* 29.12 (2007): 836-838.

12. Schwartz RA. "Pediatric Wiskott-Aldrich Syndrome". Medscape (2017).

13. Hickman RJ. "Gene Therapy Effective in Wiskott-Aldrich Syndrome". Rare Disease Report (2015).

14. Canpolat FE., *et al*. "Mean platelet volume in neonatal respiratory distress syndrome". *Pediatrics International* 51.2 (2009): 314-316.

Volume 9 Issue 4 April 2020