Wiskott-Aldrich Syndrome with Macrothrombocytopenia

*#DEJAN SKORIC, *ALEKSANDAR DIMITRIJEVIC, *#GORAN CUTURILO AND *#PETAR IVANOVSKI
*From *University Children's Hospital and #Faculty of Medicine, University of Belgrade, Belgrade, Serbia.*

Correspondence to:
Dr Aleksandar Dimitrijevic,
Department of Neurology,
University Children's Hospital, Belgrade, Serbia.
aleksandar.dimitrijevic@udk.bg.ac.rs
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Background: Wiskott-Aldrich syndrome is a rare X-linked immunodeficiency disorder with a variable phenotype. **Case Characteristics**: 3.5-year-old boy diagnosed with Wiskott-Aldrich syndrome. **Observation**: Unusual and persistent thrombocytopenia with increased platelet volume (>10fL). He did not exhibit characteristic clinical and laboratory finding for the syndrome. **Outcome**: Maternally inherited causative mutation in the exon 2 of the *WAS* gene was disclosed. **Message**: This is a need for multidisciplinary assessment of patients with congenital or early infantile thrombocytopenia, including testing for mutations of the *WAS* gene in all unexplained cases even in the absence of characteristic microthrombocytopenia.

Keywords: *Immunodeficiency, Platelet abnormalities, Thrombocytopenia*.

Wiskott-Aldrich syndrome (WAS) is a rare X-linked disorder characterized by microtrombocytopenia, eczema and reccurent infections [1]. WAS gene has been linked to the region Xp11.23, encoding a 502-amino acids intracellular protein expressed exclusively in the cytoplasm of hematopoetic cells [2]. So far, a wide spectrum of the WAS gene mutations have been identified causing a wide variety of clinical phenotypes, ranging from isolated thrombocytopenia to severe WAS [3-5].

CASE-REPORT

A 4-month-old patient was admitted to our hospital together with his twin brother due to a persistent thrombocytopenia complicated with muosal bleeding and skin petechiae. Both twins presented with thrombocytopenia on 1st day of life with normal findings on the initial physical examination.

Comprehensive clinical and laboratory evaluation was performed aimed to exclude other possible diagnosis. Neonatal alloimune thrombocytopenia was ruled out based on their age (5 months). The bone marrow examination ruled out a myelodisplastic syndrome and malignant infiltration as the cause of thrombocytopenia. Immunophenotyping of lymphocytes from peripheral blood showed no "double negative" $CD3^+CD4^-CD8^-$ T-lymphocytes with normal range of absolute and relative B-and T-lymphocyte count for the age as well as CD4 to CD8 ratio. This finding and abscence of lymphadenopathy and splenomegaly ruled out auto-immune lymphoproliferative syndrome. Presence of persistent macrothrombocytopenia and no skin changes initially ruled out WAS. Abdominal ultrasound was normal. Comprehensive metabolic analysis ruled out common metabolic conditions. Serology tests for viruses *viz*. Epstein–Barr virus (EBV), Parvovirus B19, Herpes simplex virus 1 and Human Immunodeficiency Virus (HIV) screening were all negative. Initial assessment of humoral and cellular immunity of both twin brothers at the age of 5 months were normal. Our patient's twin brother died suddenly at the age of 6 months due to acute and progressive respiratory failure. Post-mortem examination confirmed that the cause of the death was massive interstitial pneumonia.

At the age of 10 months, our patient developed a severe neurological deterioration, characterized by pronounced hypotonia, high-pitch cry, rapid visual and hearing decline and decreased level of consciousness. MRI of the brain revealed confluent symetrical signal changes of demyelinization and dysmyelination in the subcortical and deep white mater of both hemispheres. These findings were suggested the possibility of acute disseminated encephalomyelitis (ADEM) and further investigation was performed. Blood analysis proved CMV infection, with confirmed seroconversion at later time. During the following few months, his neurological status gradually improved, with regaining of the head and posture control. However, the right sided hemiparesis continued to persist.

Analysis of serum immunoglobulins revealed increase of IgE. Cellular imunodefficiency was found since our patient had decreased lymphocyte proliferation on phytohaemaglutinine (PHA) while proliferative response of cell cultures stimulated with concavaline A (conA) remained negative. Further investigation showed Coombs positive tests in several episodes of hemolytic anemia, with positive antinuclear antibodies (ANA) and antineutrophil cytoplasmic antibodies (ANCA). He also developed a chronic generalised molluscum contagiosum infection starting from the age of 18 months.

Due to a cellular immuno-defficiency, increase of the IgE antibodies, opportunistic infections as well as male gender and autoimmune disease manifestations, we suspected WAS. Genetic analysis for the detection of a mutation of *WAS* gene was performed in the patient at the age of 2 years, and subsequently in the patient's mother, by polymerase chain reaction-single strand conformational polymorphism analysis (PCR-SSCP) and direct sequencing of the PCR products. PCR-SSCP analysis in the exon 2 of the *WAS* gene disclosed aberrantly migrating bands in the patient and his mother. In the direct sequencing analysis of the PCR products for SSCP, a nucleotide substitution 190 T>C in the exon 2 was observed in the patient. Direct sequencing performed in the patient's mother confirmed that she is a heterozygous carrier of the same mutation; thus, X-linked recessive inheritance was shown. Genetic status of mother's parents and relatives is unknown.

Our patient was referred for hematopoetic cell transplantation.

DISCUSSION

Wiskott-Aldrich syndrome is an X-linked recessive condition that exhibits a wide spectrum of clinical severity [6]. Patients may develop mild thrombocytopenia or suffer more severe disorders from the spectrum. Autoimmune disorders are frequent, being present in 40% of large cohort of families [7]. In addition, malignant tumors can occur during childhood, but are more frequent in adolescents and young adults with the classic form of disorder [8]. Thus, the clinical diagnosis can be difficult and is usually supported by the detection of *WAS* gene mutations [9]. Our patient with mutation of *WAS* gene did not exhibit characteristic microthrombocytopenia, but increased platelet volume. Presence of macrothrombocytopenia in our patient could be due to the presence of autoimmune disorder. Causes of macrothrombocytopenia could also be immune trombocytopenic purpura (ITP) usually due to infection, drugs, vaccination and other causes. Rare hereditary causes of macrotrombocytopenia such as Bernard–Soulier syndrome, DiGeorge/Velocardiofacial syndrome or Platelet-type von Willebrand disease were ruled out based on clinical and laboratory findings**.**

In addition, he did not develop eczema or malignancies. Such clinical course was pointing out other possible diagnoses, such as congenital CMV infection resulting in delayed diagnosis. We stress the need for multidisciplinary assessment of patients with congenital or early infantile thrombocytopenia, including testing for mutations of the *WAS* gene in all unexplained cases even in the absence of characteristic microthrombocytopenia.

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