Wiskott-Aldrich syndrome

Abstract
The Wiskott-Aldrich syndrome (WAS) is a rare hereditary immune deficiency with recessive inheritance linked to the X chromosome (Xp11.22-p11.23). This syndrome is characterized by the association of thrombocytopenia with small-sized platelets, eczema and repeated infections. The deficiency occurs early in childhood, during the first decade and usually before the age of 3 years. Several clinical signs can orientate this diagnosis. The subject is a young boy with hemorrhagic signs (purpura, petechiae, ecchymoses, epistaxis, bloody diarrhoea or others), recurrent infections (bronchial, pulmonary, ENT (ear, nose, throat), eczema and, sometimes, signs of autoimmunity. Children with WAS should be followed in paediatric centres specialized in immunology and haematology. Management consists of treating and preventing infections. When the thrombocytopenia is very severe, splenectomy may be beneficial. Only a bone-marrow transplantation can cure this pathology.

Keywords
Immune deficiency, X linked inheritance, thrombocytopenia, small sized platelets, eczema, repeated infections, bone-marrow transplantation.

Name of the disease and synonyms
Wiskott-Aldrich syndrome

Diagnostic criteria/definition
The Wiskott-Aldrich syndrome (WAS) (OMIM 301000) is a rare hereditary immune deficiency with recessive inheritance linked to the X chromosome. This syndrome is characterized by the association of thrombocytopenia with small-sized platelets, eczema and repeated infections.

Differential diagnosis
WAS differs from isolated thrombocytopenia linked to the X chromosome and other idiopathic thrombocytopenias that do not have an immune deficiency. Isolated thrombocytopenia linked to the X chromosome presents the same hematological characteristics as WAS but the thrombocytopenia in the former is the sole symptom, with no particular susceptibility to infections. This isolated thrombocytopenia is most often benign. It is due, as in WAS, to anomalies in the WASP gene (11, 12). Between X-linked thrombocytopenia and WAS, a
continuum of disease severity can be seen (13). No clear relationship exists between disease severity and the type of mutation responsible, even though the mutations that allow residual expression of the protein WASP tend to cause less severe forms of the disease (14). Activated WASP associates with actin and plays a role in the reorganization of the cellular cytoskeleton (15).

Incidence
The incidence is 1/20,000 births/year.

Clinical description
This deficiency occurs early in childhood, during the first decade and usually before the age of 3 years. Several clinical signs can orient this diagnosis. The subject is a young boy with hemorrhagic signs (purpura, petechiae, ecchymoses, epistaxis, bloody diarrhea or others), recurrent infections (bronchial, pulmonary, ENT (ear, nose, throat), eczema and, sometimes, signs of autoimmunity (2).

Methods of biological diagnosis
A complete blood count shows severe thrombocytopenia, often fewer than 50,000 platelets. Analysis of platelet size shows them to be small (4-5 microns). When performed, the bone-marrow biopsy does not reveal the presence of a central mechanism.

Management/treatments
Children with WAS should be followed in pediatric centers specialized in immunology and hematology. Management consists of treating and preventing infections. When the thrombocytopenia is very severe, splenectomy may be beneficial (3). Only a bone-marrow transplantation can cure this pathology (4). Its success depends on the availability of an HLA-identical donor. Good management of infections can considerably lower the risk of the disease evolving towards the development of lymphoma or tumors (5).

Etiology
WAS is a disease with X-linked recessive inheritance whose gene has been localized to chromosome Xp11.22-p11.23 and is linked to polymorphic markers (6-7). The gene responsible has been characterized (8). The anomalies of this gene found in patients vary widely and differ from one family to another (9,11-15).

Genetic counseling/prenatal diagnosis
When the mutation in the family at risk has already been identified, analysis of the gene responsible for WAS enables early prenatal diagnosis on a trophoblast biopsy at 11 weeks of amenorrhea. In the familial forms (more than 1 member affected), it is also possible to use the polymorphic markers linked to the locus of the disease to evaluate the risk of a woman being a carrier or to perform an early prenatal diagnosis. Women carriers of WAS have a specific pattern of chromosome X inactivation in all their hematopoietic cell lines (10).

References

