

X-linked severe combined immune deficiency; T- B+

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Abstract

X-linked severe combined immunodeficiency disease (SCID-X1) is characterized by severe and recurrent infections, occurring during the first months of life of a boy, associated with diarrhoea and failure to thrive. Immunological findings are lymphopenia with the absence of T and NK cells, while B cells are present in normal or high number. SCID-X1 results from a defect in the gene encoding the common gamma chain. The absence of gamma chain expression at the surface of hematopoietic cells allows to diagnose most of the patients. Prenatal diagnosis of this disease can be performed by genetic approaches. The disease incidence is approximately 1/200,000 births/year. Today, bone-marrow transplantation is the only treatment for this severe immunodeficiency.

Keywords

T-, B+, NK- phenotype / common gamma chain / bone-marrow transplantation

Name of the disease and synonyms

X-linked severe combined immune deficiency;
SCID-X1

Definition

X-linked severe combined immune deficiency (SCID-X1) (MIM: 300400) is an immune deficiency with recessive inheritance that accounts for 50% of SCID observed in children.

Incidence

The incidence of this disease is approximately 1/200,000 births/year.

Clinical description

This deficiency occurs since the first months of life, with recurrent bacterial or viral (cytomegalovirus, *Pneumocystis carinii*) infections, sometimes BCG-itis if the infant had received BCG vaccination during the neonatal period, severe diarrhea and failure to thrive (1, 2). The same clinical signs are seen in children with SCID with autosomal recessive inheritance, regardless of the type of genetic anomaly (alymphocytosis, deficit of the protein (RAG) encoded by the recombination-activating gene, janus kinase 3 (JAK3) deficit, interleukin-7 receptor (IL7R) deficit, adenosine deaminase (ADA) deficit or another).

Differential diagnosis

Study of the segregation of the disease in the familial forms and analysis of the different lymphocyte populations can help distinguish among them. In X-linked SCID (3, 4), evaluation of lymphocyte populations demonstrates the absence of CD3+, CD4+ and CD8+ T cells and natural killer (NK) cells, while B cells are present in normal or higher numbers (T-, B+, NK- SCID). This lymphocyte deficit leads to agammaglobulinemia, sometimes with IgM. This same clinical and immunological phenotype (T-, B+, NK- SCID) is found in autosomal recessive forms of SCID and, in particular, that caused by a tyrosine kinase defect, JAK3 protein (5). However, NK cells are present in the rare cases with an IL7R deficit (T-, B+, NK+ SCID) (11). Immunological evaluation of SCID type alymphocytosis (MIM: 202500) demonstrates the absence of T and B lymphocytes with resulting agammaglobulinemia, and the presence of NK cells (T-, B+, NK+ SCID) (2, 6). In all forms of SCID, circulating maternal T lymphocytes that crossed the placental barrier during pregnancy can be detected in some patients. HLA typing of this population can determine its true origin (7).

Management

SCID can only be adequately managed in units specialized in immunology and hematology. Children suspected of having SCID must not receive live vaccines or transfusions of non-irradiated blood products. SCID is treated with bone-marrow transplantation. Its success depends on finding an HLA-identical donor (8).

Etiology

The genetic anomaly responsible for SCID-X1 is the gamma chain common to several lymphokine receptors IL2, IL4, IL7, IL9 and IL15. IL7, IL7R seems to be essential for the differentiation of T lymphocytes and IL15, IL15R for that of NK cells; their respective functional defects are responsible for the absence of T and NK populations observed in SCID patients. Mutations of the common gamma chain, already identified in patients, differ widely and are often localized in the extracellular region of the molecule, which is normally expressed on all hematopoietic cells, leading to an absence of detection of the molecule by an antibody specific to CD132 (9). Mutations in the intracytoplasmic region of the molecule generally affect its function but not its expression.

Prenatal diagnosis

This immune deficiency can be diagnosed prenatally at 11 weeks of amenorrhea on a trophoblast biopsy by direct detection of the

mutation, when it has been previously identified in the family. In the familial forms, the polymorphic markers linked to the common gamma chain gene (gc gene) can be used to study segregation. In all cases of SCID in a child and especially when transmission by the X chromosome is in question, an immunological investigation to demonstrate the absence of the different T lymphocyte and NK cell populations can be undertaken to obtain the diagnosis. This analysis is performed on fetal blood drawn at 20 weeks of gestation (10).

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