Severe Combined Immunodeficiency Disorders

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KEYWORDS

• Severe combined immunodeficiency disease • DiGeorge anomaly • Transplantation • Gene therapy • Newborn screening

KEY POINTS

- Severe combined immunodeficiency disease (SCID) is defined by (1) the absence or very low number of T cells (<300 CD3 T cells/mm^3) and no or very low T-cell function (<10% of the lower limit of normal) as measured by response to phytohemagglutinin (PHA) or (2) the presence of T cells of maternal origin.
- Fourteen molecular defects are recognized as causing SCID: *IL2RG*, *JAK3*, *RAG1*, *RAG2*, *DCLRE1C*, *PRKDC*, *IL7R*, *CD3D*, *CD3E*, *CD247*, *PTPRC*, *CORO1A*, *ADA*, and *AK2*. Several others are often considered to be associated with SCID as well.
- Definitive treatment options for SCID include hematopoietic bone marrow stem cell transplant or gene therapy. Transplant before 3.5 months of age remains essential for optimal survival and immune reconstitution. Conditioning should not be used in patients with active infections.
- Complete DiGeorge anomaly produces a T-negative, B-positive, natural killer (NK)-positive phenotype that can be confused with SCID. It is diagnosed clinically and cannot be excluded by negative genetic testing results. Allogeneic thymus transplantation provides the optimal long-term solution for complete DiGeorge anomaly but remains limited in availability.
- Newborn screening for SCID has proved highly successful in identifying infants with SCID and complete DiGeorge anomaly. It has demonstrated that the incidence of SCID in the United States is 1 per 58,000 live births and has led to life-saving treatment of affected children.

INTRODUCTION

Severe combined immunodeficiency disorders are characterized by a lack of protective T-, B-, and sometimes NK-cell responses to infections. As a result, affected individuals are born with marked susceptibility to pathogens that ultimately cannot be

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managed or controlled. Infection-related death typically occurs by 1 to 2 years of age in the absence of treatment. Thus, these disorders represent true pediatric emergencies.

Failure to generate T cells can result from either intrinsic defects in T-cell precursors that preclude their survival or from absence of the thymic environment necessary for thymocytes to properly mature into naive T cells. The former condition is broadly categorized into a condition known as SCID. The latter condition, congenital athymia, occurs in children with complete DiGeorge anomaly or, more rarely, *FOXN1* deficiency.

This article reviews both SCID and congenital athymia. For SCID, acknowledgment is given to the fact that increased screening of newborns for the condition in the United States quickly brings affected infants to the attention of medical providers, who must then counsel family members regarding options for treatment and anticipated prognosis. Thus, although some of the more common known molecular causes of SCID in North America are discussed, emphasis is placed on conditions that merit special therapeutic considerations, key clinical evaluations, and various approaches toward definitive therapy. For congenital athymia, complete DiGeorge anomaly and *FOXN1* deficiency are reviewed, including typical and atypical presentations. Treatment modalities are then presented. Finally, newborn screening for severe combined immunodeficiency disorders is discussed, including its utility and particular challenges that physicians may face when presented with abnormal results.

Severe Combined Immunodeficiency Disease

Definition

Because combined immunodeficiency diseases, which often do not require immediate correction, are sometimes mistaken for or misdiagnosed as SCID, criteria have been adopted by the Primary Immune Deficiency Treatment Consortium (PIDTC) to define the severe phenotype. Initial guidelines stated that in the absence of an established genetic defect, minimum criteria should include negative human immunodeficiency virus testing and at least 2 of the following 3 conditions: (1) Marked lymphocytopenia and/or T-cell (CD3) lymphopenia (based on age-appropriate reference ranges), (2) severe defect in T-cell proliferation to mitogens (<10% of the lower limit of the reference/normal response), and (3) marked decrease in thymic function (decreased/absent $CD4^+CD45RA^+$ naive T cells or T-cell receptor rearrangement excision circles).[1] Subsequently, the criteria were revised to define typical SCID as (1) absence or very low number of T cells (<300 CD3 T cells/mm^3) and no or very low T-cell function (<10% of the lower limit of normal) as measured by response to PHA or (2) presence of T cells of maternal origin.[2] Thus, enumeration of naive T cells or recent thymic emigrants remains important but not essential. These current criteria should be used to establish a diagnosis for clinical and research purposes.

Molecular defects

The first molecular cause of a primary immunodeficiency disease was identified in 1972 when Dr Robert A. Good serendipitously discovered that lack of adenosine deaminase (ADA) results in SCID. Clinical immunologists continued to puzzle, however, over the fact that ADA deficiency is inherited in an autosomal recessive pattern, but children with SCID are nonetheless predominantly boys. The next molecular cause of SCID would not be identified for another 3 decades, when investigators demonstrated that defects in *IL2RG* cause X-linked SCID.[3,4] With the development of advanced molecular cloning techniques and complete sequencing of the human genome, discoveries of the genetic causes of SCID rapidly progressed. Now, at least 14 molecular defects have been confirmed to cause SCID.[5]