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History and current status of newborn screening for severe combined immunodeficiency

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ABSTRACT

The development of a T-cell receptor excision circle (TREC) assay utilizing dried blood spots in universal newborn screening has allowed the early detection of T-cell lymphopenia in newborns. Diagnosis of severe combined immunodeficiency (SCID) in affected infants in the neonatal period, while asymptomatic, permits early treatment and restoration of a functional immune system. SCID was the first immunodeficiency disease to be added to the Recommended Uniform Screening Panel of Core Conditions in the United States in 2010, and it is now implemented in 26 states in the U.S. This review covers the development of newborn screening for SCID, the biology of the TREC test, its current implementation in the U.S., new findings for SCID in the newborn screening era, and future directions.

Introduction and background

Severe combined immunodeficiency (SCID), popularly known as the "bubble boy disease," is characterized by severe defects of cellular and humoral immunity that renders affected infants susceptible to opportunistic and recurrent infections. As the most severe form of primary immunodeficiency (PID), SCID is generally fatal in the first year of life unless recognized and treated.[1,2] SCID is a collection of individual heritable PID diseases, resulting from defects in genes controlling the maturation of elements of the adaptive immune system. Regardless of the molecular cause, infants born with SCID typically appear normal at birth, are characterized by a severe deficiency of naïve T cells, and are at a high risk of serious infections after waning of maternal antibody at around 4–6 months of age. If untreated, SCID-affected infants are susceptible to recurrent and opportunistic infections, persistent diarrhea, faltered growth, and early demise.

Established treatments for SCID include restoring the faulty immune system by means of an allogeneic hematopoietic cell transplant (HCT) from HLA-matched related or unrelated donors, haploidentical parental donors, or cord blood; enzyme replacement therapy for the adenosine deaminase (ADA)-deficient form of SCID; or experimental gene therapy for X-linked SCID and ADA-SCID. By and large, HCTs have been successful over the past decades, and outcomes following HCT for SCID-affected infants are optimized by earlier HCT and by effective prevention and treatment of infections prior to HCT.[3–6]

Studies have shown that infants identified in the neonatal period by a positive family history have better outcomes compared to index or sporadic cases.[4,5] Optimal survival and health outcomes for SCID are associated with treatment early in infancy before the development of uncontrollable infections.[3–6] Because SCID-affected infants appear healthy at birth, in the past, only those who had a recognized family

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history of SCID could have the diagnosis made early, and such infants comprise fewer than 20% of all cases.[5,7,8] Early diagnosis and treatment for all infants, whether with a positive family history or sporadic, is possible only upon institution of population-based screening for SCID.[9]

Epidemiology of SCID

Prior to newborn screening, SCID had been estimated to occur at an incidence of 1 in 100,000,[7,10] though specific ethnic populations were recognized to have a higher incidence of certain types of SCID due to founder mutations. For example, ADA-SCID in the Somali population has an incidence of ~1 in 5000[11]; DCLRE1C (Artemis) gene mutations occur in Navajo Americans at a rate of ~1 in 2000[12]; and RAG1-, RAG2-, ADA-, IL7R-, CD3-, and ZAP-70-mutant alleles have been noted in the Amish and the Mennonite populations.[13,14] However, SCID-affected infants may succumb to opportunistic infections prior to a diagnosis of immune deficiency, and it was widely acknowledged that reported incidence was likely an underestimate of the true incidence of SCID.[15]

Genetic heterogeneity of SCID

Understanding the genetic heterogeneity of SCID is necessary in order to appreciate the development of the various screening tests that were initially proposed for SCID, the limitations of tests, and the range of conditions identified.

SCID and combined immunodeficiency (CID) comprise a spectrum of genetic disorders of the immune system in which T-cell and B-cell immune responses are impaired.[16] Many proteins are essential for T-cell development, and as many as 20 known genes have been associated with SCID due to deleterious mutations that abrogate or alter protein expression and prevent the development and maturation of T cells (Table 1). Impaired development of a diverse repertoire of functional T cells combined with inability to produce specific antibodies, either due to impaired B-cell development or due to lack of T-cell help, leads to combined impairment of cellular and humoral immunity.[1,2]

Previous reports from transplant centers show almost 50% of SCID cases to be caused by *IL2RG* mutations, while all other known SCID defects are caused by mutations in autosomal recessive genes.[7,10] Different gene mutations characteristically give rise to particular phenotypic profiles. All SCID forms have low or absent T cells, but different gene defects are associated with the presence or the absence of B cells and NK cells, and in some instances, they are associated with non-immunological manifestations such as radiosensitivity or skeletal, dermatologic, or neurologic abnormalities.[16] Hypomorphic mutations of genes can give rise to leaky SCID in which non-null mutations allow for some T-cell development, but cellular immunity remains impaired. Attention to such features can facilitate the search for the causative gene mutations in a given SCID case.

Despite this genetic heterogeneity, the common phenotype of impaired T-cell immunity means that infants with SCID present with recurring opportunistic infections, classically described in textbooks to include *Pneumocystis jiroveci* pneumonia; disseminated BCG infection secondary to vaccination; recurrent diarrhea that may be caused by inadvertent administration of live rotavirus vaccine[17]; persistent and severe cytomegalovirus, adenovirus, or other viral infections; oral thrush; and invasive bacterial, mycobacterial, and fungal infections. Without diagnosis of the underlying problem and provision of a functional immune system, SCID-affected infants cannot survive.

Development of screening test for SCID

Criteria for newborn screening

The premise of newborn screening (NBS) is to detect disorders pre-symptomatically, such that effective treatments can be applied. Phenylketonuria (PKU) provided the paradigm for disorders in which pre-symptomatic treatment would be effective.[18] Public, state-based newborn screening programs began in the U.S. over 50 years ago, with the development of the filter paper-based testing technology by Robert Guthrie, which is still currently in use. Guthrie's innovation of heel-stick blood spotted onto a filter and dried facilitated the development of state-based NBS programs because the samples were easy to obtain and stable, while his assay for phenylalanine was reproducible, inexpensive, and accurate; these are all necessary components for an effective population-based public health program. NBS using biochemical markers to detect certain congenital conditions has become a means for early identification of affected newborns in an effort to reduce infant morbidity and mortality. It is a comprehensive system of education, screening, follow-up, diagnosis, treatment/management, and evaluation, which must be institutionalized and sustained within state governments often challenged by economic, political, and cultural considerations.[19,20]

Criteria were developed for screening additional conditions beyond PKU as follows: (1) a sensitive and specific test was available and affordable, (2) the condition evaded clinical recognition early in its course, and (3) harmful health consequences could be prevented or reduced by early treatment. Since the advent of tandem mass spectrometry, the number of diseases efficiently screened by this means has expanded greatly, and core disease panels for screening were established, which included PKU and other inborn errors of metabolism, hypothyroidism, hemoglobinopathies, and additional disorders.[21]

SCID as a disease fits the screening criteria established by Wilson and Jungner[22]—SCID is an important health problem, acceptable diagnosis and treatment are available, there is a recognized latent pre-symptomatic stage, and the natural history of SCID including development from latent to declared disease is well understood. The prospect of preventing death from life-threatening infections by identifying at-risk infants before the onset of such infections makes SCID an excellent target for NBS. What remained was the establishment of a suitable test that is cost-effective, acceptable to the population, and economically balanced. If at all possible, newly developed screening tests should take advantage of dried blood spot (DBS) samples to avoid cost of getting a