

Abnormal T-Cell Receptor Excision Circle Newborn Screen: What Next?



Benjamin T. Prince, MD, MSci^a, and John M. Routes, MD^b

INSTRUCTIONS

MOC as well as CME credit can now be obtained, free for a limited time, by reviewing this Difficult Cases presentation. Please note the following instructions.

1. Review the target audience, learning objectives, and author disclosures.
2. Follow the online instructions to review the full online version of the presentation.
3. Complete the post-test. At this time, you will have earned 1.00 AMA PRA Category 1 CME Credit™.
4. Approximately 4 weeks later you will receive an online assessment regarding your application of this article to your practice. Once you have completed this assessment, you will be eligible to receive 2 MOC Part II Self-Assessment credits from the American Board of Allergy and Immunology.

Method of Physician Participation in Learning Process: The core material for these activities can be found online at the *JACI: In Practice* Web site: www.jaci-inpractice.org/. The accompanying tests may only be submitted online at www.jaci-inpractice.org/. Fax or other copies will not be accepted.

Date of Original Release: January 1, 2018. Credit may be obtained for these courses until December 31, 2018.

Copyright Statement: Copyright © 2018-2020. All rights reserved.

Overall Purpose/Goal: To provide excellent case-based reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for 1.00 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Benjamin T. Prince, MD, MSci, and John M. Routes, MD (authors); Michael Schatz, MD, MS (editor)

Learning objectives:

1. To review the use of T-cell receptor excision circle (TREC) assay as a screen for severe combined immunodeficiency (SCID).
2. To identify appropriate next steps in evaluating patients with an abnormal TREC newborn screen.
3. To formulate a differential diagnosis and treatment recommendations in patients with an abnormal TREC newborn screen for SCID.

Recognition of Commercial Support: This CME has not received external commercial support.

Disclosure of Relevant Financial Relationships with Commercial Interests: B. T. Prince has received travel support from Nationwide Children's Hospital. J. M. Routes has received consultancy and travel support from CSL Behring. M. Schatz disclosed no relevant financial relationships.

The Difficult Cases Feature is based on the *Difficult Cases* Course presented at the AAAAI Annual Meeting and coordinated by the AAAAI New Allergist-Immunologist Assembly (NAIA). View the entire presentation and obtain CME or MOC credit by visiting the *JACI: In Practice* homepage www.jaci-inpractice.org.

CASE REPORT

An 8-day-old full-term boy born to a 34-year-old Somali mother presents with an abnormal newborn screen for severe combined immunodeficiency (SCID) using the T-cell receptor excision circle (TREC) assay. There was no history of fevers, rash, or infection. He had normal growth and development, and the physical examination was normal. Prenatal and family histories were unremarkable without any history of immunodeficiency or confirmed

consanguinity. Laboratory evaluation showed an absolute T-cell count of $58/\text{mm}^3$ (normal, 2500-5500), with only 34% expressing CD45RA, a naive T-cell marker. Absolute B-cell and natural killer cell counts were $5/\text{mm}^3$ (normal, 300-2000) and $183/\text{mm}^3$ (normal, 170-1100), respectively. T-cell proliferation studies could not be performed secondary to the severe, progressive pancytopenia, and a clinical diagnosis of SCID was made.

^aDivision of Allergy and Immunology, Department of Pediatrics, Nationwide Children's Hospital, The Ohio State University, Columbus, Ohio

^bDivision of Asthma, Allergy and Immunology, Department of Pediatrics, Medical College of Wisconsin, Children's Research Institute, Milwaukee, Wis

Conflicts of interest: B. T. Prince has received travel support from Nationwide Children's Hospital. J. M. Routes has received consultancy and travel support from CSL Behring.

Received for publication July 5, 2017; accepted for publication July 12, 2017.

Corresponding author: Benjamin T. Prince, MD, MSci, Nationwide Children's Hospital, Division of Allergy & Immunology, 700 Children's Dr, Columbus, OH 43205. E-mail: Benjamin.prince@nationwidechildrens.org.

2213-2198

© 2017 American Academy of Allergy, Asthma & Immunology
<http://dx.doi.org/10.1016/j.jaip.2017.07.047>

Intravenous immunoglobulin was administered prophylactically to maintain the total serum IgG level to more than 600mg/dL, and *Pneumocystis jirovecii* pneumonia prophylaxis was initiated at 1 month of life. Because this was a case of T[−]/B[−]/NK[−] SCID and chondroosseous dysplasia was noted on chest x-ray, a lysed erythrocyte adenosine deaminase (ADA) level was sent and found to be undetectable. Genetic testing demonstrated a homozygous, Q3X nonsense mutation within the ADA gene, confirming the diagnosis of ADA deficiency. The patient is currently doing well on immunoglobulin replacement 5 months after receiving a matched sibling donor hematopoietic stem cell transplantation (HSCT) without conditioning.

DISCUSSION

SCID is a severe, life-threatening immunodeficiency characterized by markedly decreased, autologous T-cell number (<300/mm³) and function (<10% normal PHA response), resulting in a lack of specific lymphocyte-dependent adaptive immunity.¹ ADA is a purine salvage enzyme that is expressed in all tissues of the body. SCID results in ADA-deficient individuals from the accumulation of toxic substrates within lymphocytes and other rapidly dividing cells leading to their death.² Because of an increased carrier frequency of a nonsense mutation, ADA deficiency is significantly more common among individuals of Somali decent.³

Historically, most patients with SCID were identified after presenting with recurrent and opportunistic infections; however, the implementation of newborn screening (NBS) for SCID using the TREC assay has led to the identification of patients during the first weeks of life, before the development of life-threatening infections. TRECs are small circles of non-replicating DNA formed during T-cell receptor rearrangement that are a biomarker of recent thymic emigrants. The TREC assay enumerates the number of TRECs in dried blood spots by real-time PCR and screens for low numbers of naive T cells.⁴ Currently, 44 US states have active screening programs in place with 4 additional states piloting TREC screening. A recent systemic review of the TREC assay in NBS found the sensitivity to be 100% for typical SCID.⁵ Prematurity is a common cause of false-positive results, but other syndromes associated with T-cell lymphopenia have also been identified with TREC NBS.^{5,6}

Although TREC NBS has been highly successful, it can miss infants with hypomorphic mutations in SCID-causing genes and other combined immunodeficiencies in which naive T cells are present at birth such as delayed-onset ADA deficiency, MHC class II deficiency, and Wiscott-Aldrich syndrome.⁵

Although there are several monogenic defects that lead to SCID, the clinical diagnosis of SCID does not require a genetic diagnosis.¹ Once a diagnosis of SCID is established, it is important to implement appropriate infection precautions and prophylaxis. HSCT is the most common treatment strategy; however, gene therapy and enzyme replacement are other options depending on the underlying molecular defect and donor availability. The significance of early identification can be demonstrated by evaluating the 5-year survival rate of patients with SCID undergoing HSCT. Infants transplanted by age 3.5 months have a survival rate of 94%. In contrast, when HSCT is performed on infants older than 3.5 months with active infection, the 5-year survival rate drops to 50%.⁷

REFERENCES

1. Shearer WT, Dunn E, Notarangelo LD, Dvorak CC, Puck JM, Logan BR, et al. Establishing diagnostic criteria for severe combined immunodeficiency disease (SCID), leaky SCID, and Omenn syndrome: the Primary Immune Deficiency Treatment Consortium experience. *J Allergy Clin Immunol* 2014; 133:1092-8.
2. Baffelli R, Notarangelo LD, Imberti L, Hershfield MS, Serana F, Santisteban I, et al. Diagnosis, treatment and long-term follow up of patients with ADA deficiency: a single-center experience. *J Clin Immunol* 2015;35: 624-37.
3. Sanchez JJ, Monaghan G, Børsting C, Norbury G, Morling N, Gaspar HB. Carrier frequency of a nonsense mutation in the adenosine deaminase (ADA) gene implies a high incidence of ADA-deficient severe combined immunodeficiency (SCID) in Somalia and a single, common haplotype indicates common ancestry. *Ann Hum Genet* 2006;71:336-47.
4. Puck JM. Laboratory technology for population-based screening for severe combined immunodeficiency in neonates: the winner is T-cell receptor excision circles. *J Allergy Clin Immunol* 2012;129:607-16.
5. van der Spek J, Groenwold RHH, van der Burg M, van Montfrans JM. TREC based newborn screening for severe combined immunodeficiency disease: a systematic review. *J Clin Immunol* 2015;35:416-30.
6. Kwan A, Abraham RS, Currier R, Brower A, Andruszewski K, Abbott JK, et al. Newborn screening for severe combined immunodeficiency in 11 screening programs in the United States. *JAMA* 2014;312:729.
7. Pai S-Y, Logan BR, Griffith LM, Buckley RH, Parrott RE, Dvorak CC, et al. Transplantation outcomes for severe combined immunodeficiency, 2000–2009. *N Engl J Med* 2014;371:434-46.

Reproduced with permission of copyright owner. Further reproduction prohibited without permission.