

Newborn Screening for Severe Combined Immunodeficiency: Changing the Landscape of Pediatric Primary Immunodeficiencies

Andrew S. Nickels, MD^a, and Roshini S. Abraham, PhD^b Rochester, Minn

Practice Options from Beyond Our Pages focuses on identifying, critiquing, and placing into context research studies published in other journals that have the potential to change our clinical practices. It is written by Allergy-Immunology Fellows partnered with faculty members, and does not require an invitation for submission. This feature is coordinated by Editorial Board members Matthew Rank, MD and Julie Wang, MD.

BACKGROUND

Newborn screening (NBS) for severe combined immunodeficiency (SCID) using T-cell receptor excision circles (TRECs) is recommended on the Uniform Screening Panel by the US Department of Health and Human Services since 2010.¹ TRECs are a biomarker for T lymphopoiesis and are measured by real-time molecular analysis (PCR) using dried blood spots. Infants with absent or low TREC are referred for secondary testing, including but not limited to T, B, and NK lymphocyte subset quantitation by flow cytometry and distribution of naïve and memory T cells. At the time of the study, more than two-thirds of the births in the United States were part of NBS SCID. Previous work has given a limited glimpse into the progress of state screening.^{2,3} The present study is the largest report to date of TREC-based NBS for SCID.

METHODS

Retrospective observational study using data collected from active TREC-based SCID NBS programs in the United States that participated in the study.⁴ Because there was considerable variability in TREC cutoff and decision making for additional flow cytometry-based testing, the study attempted to provide homogeneous definitions (using the Primary Immunodeficiency Treatment Consortium criteria) and grouping for data analysis.

RESULTS

The study collected data from 3,030,083 births from 10 states (California, Colorado, Connecticut, Delaware, Massachusetts, Michigan, Mississippi, New York, Texas, Wisconsin) and the public health service for the Navajo Nation, based on availability to participate at the time. Fifty-two infants with SCID were

identified (42 with typical SCID, 9 with leaky SCID, and 1 with Omenn syndrome). The overall incidence of SCID in the population screened was 1/58,000 (95% CI 1/46,000-1/80,000). The incidence of SCID was similar in all programs, except for the Navajo Nation, which showed an increased incidence at 1/3500 births. No cases of SCID were diagnosed in the screened population that were missed by the TREC screen. Three patients did not receive definitive treatment of SCID (ie, bone marrow transplant, gene therapy, or adenosine deaminase enzyme treatment) because of early deaths from perinatal complications. Of those who received treatment, overall survival was 92% (45 of 49) at the time of publication.

Gene defects detected among the infants with SCID were notable. Eight cases had no molecular defect in known SCID-related genes. A defect associated with an SCID phenotype was identified because of mutations in the tetratricopeptide repeat domain 7A (*TTC7A*) gene. Cases of X-linked SCID, due to mutations in the common gamma chain (*IL2RG*), were found only in 19% (10 of 52) of patients, which is significantly less than the previously described incidence of this gene defect in the SCID population.⁵ In the Navajo nation, mutations in the *DCLRE1C* (Artemis) gene confirmed a previously suspected founder effect.⁶

There was heterogeneity observed between programs with regards to number of TREC copies considered abnormally low. This led to variable rates of referral to secondary screening ranging from 15 to 135 infants per 100,000 screened. Similarly, there was heterogeneity between programs with regard to cutoff values for what was considered significant T-cell lymphopenia (normal 2500-5000 cells/ μ L). Six programs used <1500 T cells/ μ L, 3 programs used <2500 T cells/ μ L, 1 program used <3505 T cells/ μ L, and 1 program had no defined cutoff (New York). Acknowledging this variation in definition, the incidence of T-cell lymphopenia differed between programs, ranging from 1/2,100 to 1/32,000. In the 6 programs with the most stringent T-cell cut point (<1500 cells/ μ L), the false-positive rate of TREC newborn screening for T-cell lymphopenia was 64% (95% CI 59-68).

Recognizing the inherent variability between programs in defining TREC and T-cell cutoffs, the report identified 411 infants who had non-SCID T-cell lymphopenia, providing evidence for detection of other conditions, beyond SCID, associated with low T cells at birth. Congenital syndromes such as

^aDivision of Allergic Disease, Department of Medicine, Mayo Clinic, Rochester, Minn

^bDepartment of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minn
No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts.

Received for publication June 5, 2015; accepted for publication June 8, 2015.

Corresponding author: Andrew S. Nickels, MD, Division of Allergic Disease, Department of Medicine, Mayo Clinic, Rochester, MN 55901. E-mail: Nickels.andrew@mayo.edu.

2213-2198

<http://dx.doi.org/10.1016/j.jaip.2015.06.007>

TABLE I. Diagnoses and associated conditions of 411 infants identified as having non-SCID T-cell lymphopenia by T-cell receptor excision circle newborn screen

Category of T-cell abnormality	Condition	No. of infants
Syndromes with T-cell impairment		136
	DiGeorge	78
	Trisomy 21	21
	Ataxia telangiectasia	4
	Trisomy 18	4
	CHARGE	3
	Jacobsen	2
	CLOVES	1
	ECC	1
	Fryns	1
	Nijmegen breakage	1
	Noonan	1
	Rac2 defect	1
	Renpenning	1
	TAR	1
	Not specified	10
	Cytogenetic abnormalities	6
Secondary T-cell impairment		117
	Cardiac anomalies	30
	Multiple congenital anomalies	23
	Loss into third space	15
	Gastrointestinal anomalies	15
	Neonatal leukemia	4
	Not specified	30
Preterm birth alone		12
Variant SCID		29
Unspecified/idiopathic T cell lymphopenia		117

CHARGE, Coloboma, heart defect, atresia choanae, retarded growth and development, genital and ear abnormality; CLOVES, congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and spinal/skeletal anomalies; ECC, ectodermal dysplasia, ectrodactyly, and clefting; SCID, severe combined immunodeficiency; TAR, thrombocytopenia and absent radius. Adapted from Kwan et al.⁴ Used with permission.

DiGeorge and CHARGE among others with T-cell impairment were the most common, accounting for 136 (33.1%) of the cases. One hundred and seventeen (28.5%) were determined to have secondary T-cell lymphopenia for causes other than an intrinsic immune anomaly (eg, gastroschisis, third-spacing, chylothorax among other conditions). Thirty (7.3%) cases had no cause identified. The label of idiopathic T-cell lymphopenia was used for 117 cases (28.5%). Twelve (2.9%) infants were classified as having “variant SCID,” which was defined as having T-cell counts ranging from 300 to 1500 cells/ μ L with no known SCID genetic defect and abnormal T-cell function, who may or may not need hematopoietic transplantation. In other states, the term “idiopathic T-cell lymphopenia” has been used to categorize infants with low T-cell counts (range not always defined) with preserved T-cell function. Prematurity as a cause for T-cell lymphopenia and low screening TREC was identified for 29

(7.1%) cases of this cohort. Table I shows the complete breakdown of causes of non-SCID T-cell lymphopenia.

CRITICAL APPRAISAL

This study took a pragmatic approach to define the incidence of SCID and compare data obtained from various state screening programs. The study was limited by the interprogram variability in defining TREC and T-cell lymphopenia cutoffs and heterogeneity in non-SCID T-cell lymphopenia definitions. The authors made every effort to collect objective information that would be broadly applicable to assessing the efficacy of NBS SCID.

RECOMMENDATION

This report is the largest to date to describe the performance of newborn screening for SCID using the TREC assay. For the stated purpose of detecting SCID, it performs exceptionally well and, to date, has not missed a case of SCID. Population-based screening has changed our understanding of the diagnosis and epidemiology of this disease. Findings of interest include new data on the distribution of known SCID defects with a lower than predicted incidence of X-linked SCID, identification of a new gene defect associated with an SCID phenotype (*TTC7A*), and confirmation of the higher frequency of SCID in the Navajo population.

This study quantifies the experience of both the public health state laboratories and clinicians in states performing TREC-based NBS SCID. Some important points emerge from this study: (1) the majority of infants with positive (abnormal) TREC screens do not have T-cell lymphopenia on follow-up testing; (2) only a minority of those infants identified as having T-cell lymphopenia have SCID (14%). Currently, there is limited consensus on management of non-SCID T-cell lymphopenia, particularly those infants with idiopathic lymphopenia. This report provides an evidence-based differential diagnosis for neonatal T-cell lymphopenia, which is a novel contribution to the literature and further highlights the need for improvement in diagnostic algorithms across screening programs and the need for further research into non-SCID T-cell lymphopenia.

REFERENCES

1. Recommended Uniform Screening Panel Core Conditions; 2013. Available from: <http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendedpanel/>. Accessed February 8, 2015.
2. Kwan A, Church JA, Cowan MJ, Agarwal R, Kapoor N, Kohn DB, et al. Newborn screening for severe combined immunodeficiency and T-cell lymphopenia in California: results of the first 2 years. *J Allergy Clin Immunol* 2013;132:140-50.
3. Gaspar HB, Hammarstrom L, Mahlaoui N, Borte M, Borte S. The case for mandatory newborn screening for severe combined immunodeficiency (SCID). *J Clin Immunol* 2014;34:393-7.
4. 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;312:729-38.
5. Dvorak CC, Cowan MJ, Logan BR, Notarangelo LD, Griffith LM, Puck JM, et al. The natural history of children with severe combined immunodeficiency: baseline features of the first fifty patients of the primary immune deficiency treatment consortium prospective study 6901. *J Clin Immunol* 2013;33:1156-64.
6. Jones JF, Rittenbaugh CK, Spence MA, Hayward A. Severe combined immunodeficiency among the Navajo. I. Characterization of phenotypes, epidemiology, and population genetics. *Hum Biol* 1991;63:669-82.

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