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Successful Newborn Screening for SCID in the Navajo Nation

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Abstract

Newborn screening (NBS) for severe combined immunodeficiency (SCID) identifies affected infants before the onset of life-threatening infections, permitting optimal treatment. Navajo Native Americans have a founder mutation in the DNA repair enzyme Artemis, resulting in frequent Artemis SCID (SCID-A). A pilot study at 2 Navajo hospitals assessed the feasibility of SCID NBS in this population. Dried blood spots from 1,800 infants were assayed by PCR for T-cell receptor excision circles (TRECs), a biomarker for naïve T cells. Starting in February 2012, TREC testing transitioned to standard care throughout the Navajo Area Indian Health Service, and a total of 7,900 infants were screened through July 2014. One infant had low TRECs and was diagnosed with non-SCID T lymphopenia, while 4 had undetectable TRECs due to SCID-A, all of whom were referred for hematopoietic cell transplantation. This report establishes the incidence of SCID-A and demonstrates effectiveness of TREC NBS in the Navajo.

Keywords

Artemis; Navajo; newborn screening; primary immunodeficiency; SCID; TREC

1. Introduction

Severe combined immunodeficiency (SCID) encompasses a group of genetic disorders characterized by a profound deficiency in both humoral and cell-mediated immunity [1].

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

SCID occurs in about 1/50,000 births, as assessed by unbiased, population based newborn screening [2-4]. Infants with SCID lack T cells and most have non-functional B cells, but 15-30% lack both T and B cells while retaining normal natural killer (NK) cells (T-B-NK+ phenotype) [5,6]. Most genetic mutations causing T-B-NK+ SCID disrupt antigen receptor recombination, required for development of a normal, diverse repertoire of T and B cells. In addition to lymphocyte restricted recombinase activating genes RAG1 and RAG2, DNA repair proteins expressed in all cells participate in antigen receptor rejoining; defects in these proteins can result in SCID as well as sensitivity to ionizing radiation and alkylating agents. The most common cause of radiosensitive SCID is mutation of *DCLRE1C*, the gene encoding the protein Artemis [7,8].

Over 3 decades ago, a high incidence of T-B-NK+ SCID, estimated at 1/2,000 births, was reported in Navajo and Apache Native Americans from the southwestern U.S. [9], and in 2002 the cause was discovered to be a Y192X truncation mutation in *DCLRE1C* [10]. This autosomal recessive trait was presumably present in survivors of the Long Walk in 1864, from Fort Defiance, Arizona, to Fort Sumner, New Mexico, a forced relocation by the U.S. government [11]. The ensuing Navajo population reduction and subsequent recovery may have increased the SCID allele frequency [12]. Although awareness of SCID led to carrier testing and prenatal diagnosis for SCID in some families with previously affected infants [13], the non-specific nature of presenting diarrhea and failure to thrive often delayed diagnosis. Early recognition of SCID is crucial for avoiding life-threatening infections that usually occur within the first 6 months of life. In contrast, definitive treatment by hematopoietic cell transplantation (HCT) leads to excellent survival in infants with SCID identified before the onset of infections [6].

The advent of a newborn screening (NBS) test for SCID presented an opportunity to implement population-based detection of affected Navajo infants before onset of infections. T-cell receptor excision circles (TRECs), circular byproducts of TCR V(D)J recombination, serve as a biomarker for newly formed naïve T cells [14]. Low or absent TRECs in DNA isolated from dried blood spots (DBS) already universally collected indicate low numbers of circulating naïve T cells regardless of the underlying genetic basis [15]. This is important because SCID from etiologies other than a *DCLRE1C* mutation has occurred among the Navajo [16].

Infants born at 2 hospitals in Chinle and Tuba City, Arizona, were invited to participate in a pilot study of TREC test implementation, beginning in March 2009. After successful completion of this study, SCID NBS was transitioned to standard clinical care throughout the Navajo Nation in February 2012, and is currently ongoing. We present the introduction of SCID NBS and outcomes of screening 7,900 infants through July 2014, including successful detection of 4 infants with SCID-A and one with T cell lymphopenia (TCL).

2. Patients, materials and methods

2.1 Navajo pilot study

All research was approved by the Navajo Nation Human Research Review Board (NNHRRB) and the University of California San Francisco (UCSF) Committee on Human

Research. An information pamphlet was approved for distribution in prenatal clinics and given to postpartum mothers (see Supp Text). Navajo study workers provided information to mothers, obtained face-to-face written informed consent, logged and tracked samples, and encoded samples to maintain confidentiality. Following routine heel-stick for standard NBS, an extra dried blood spot (DBS) was obtained on a "SCID TEST" blotter (ID Biological Systems, Greenville, SC). SCID blotters were couriered weekly to UCSF, and tested within a week of arrival. Residual study DBS material were destroyed after analysis, with documentation provided to the NNHRRB.

DNA was isolated robotically (AutoGenPrep 965, Autogen, Inc) using 96-well deep plates (Corning, Sigma Aldrich) from 3.2mm punches from control cord blood and study DBS [15]. After 16h at 65°C with proteinase K (0.5mg/mL), samples underwent organic extraction, DNA precipitation, 2 washes with 70% ethanol, and suspension in TE buffer 50μL. Quantitative PCR was performed using 5μL DNA in 20μL reactions containing 1x Taqman Gene Expression Master Mix (Applied Biosystems, Life Technologies), 0.5μM TREC or 0.25μM β-Actin primers, 150μM FAM-TAMRA labeled probe (Supp Table 1) and 0.04% BSA (New England Biolabs) [14, 15]. PCR conditions were 2m at 50°C, 5m at 95°C, followed by 40 cycles (30s at 95°C, 60s at 60°C) (7900HT Real-Time PCR System, Applied Biosystems). Serial dilutions of plasmids encoding TREC and β-Actin gene sequences ($1x10^5$–12.5 and $1x10^7$–100 copies/reaction, respectively) and a plasmid dilution (1,000 copies of each amplicon) were included on each plate. In addition to local quality monitoring, proficiency testing was performed (through the Newborn Screening and Molecular Biology Branch, Center for Disease Control and Prevention, Atlanta, GA).

Samples with ≥100 TRECs/punch (equivalent to 33 TREC/μL of blood) were considered normal based on analysis of anonymous DBS from the California Department of Public Health Genetic Disease Screening Program (kindly supplied by Fred Lorey, PhD), while those with fewer TRECs had a second punch analyzed for TRECs and β-Actin copies (Supp Fig. 1A). Samples with 2 poor PCR results or low TRECs with normal β-Actin were reported to the study workers at enrolling hospitals, enabling local physicians to contact infants as needed for clinical evaluation.

2.2 TREC screening as standard of care

In February 2012, TREC testing for SCID became part of routine clinical NBS for infants born in the Navajo Nation, reflecting the recommendations of the U.S. DHHS Secretary in 2010 [17] as well as the Navajo Area Indian Health Service Pediatric Advisory Board. Clinical TREC testing was performed at PerkinElmer Genetics, Inc. using a testing algorithm similar to the study procedure above (Supp Fig. 1B) [18].

2.3 Statistics

Confidence intervals (1-sided) were derived from inversion of the cumulative binomial distribution.

3. Results

3.1 Pilot study

TREC newborn screening was initiated at Tuba City Regional Health Care Corporation and Chinle Comprehensive Health Care Facility, serving a large area with a mostly rural Native American population. During the enrollment period, 2,931 infants were born at the hospitals, of whom 61% had TREC screening completed; 2,796 (95%) of the infants' mothers were visited by a Navajo study coordinator. Reasons that mothers were not interviewed included maternal or infant medical complications, infant out-of-hospital transfers for conditions requiring intensive care, and discharges prior to 24h. Consent from 1,837 mothers was obtained (66% of those interviewed), and 1,800 "SCID TEST" samples were collected and tested. Mothers who did not enroll their infants for SCID NBS cited a range of reasons (Table 1). Despite incomplete enrollment, the feasibility of integrating the TREC test into regular infant care in this setting was demonstrated.

In the first summer of the study a decline in mean TREC number occurred in samples from both sites between May (398 and 422 TRECs/μL for Tuba City and Chinle, respectively) and June (185 and 203, respectively) (Supp Fig. 2). Although no samples during June had TRECs below the normal cutoff, a procedural review was conducted. PCR artifacts were excluded based on standard curves and controls that accompanied every assay. Further investigation revealed that in the Arizona desert summer, evaporative coolers were used where the DBS samples were being stored. To reduce effects of humidity, likely to degrade DBS DNA quality based on observations from other NBS tests (Fred Lorey, personal communication), the study procedure was modified to require sealing each sample in a Mylar bag containing desiccant discs. With this change the TREC copy numbers returned to baseline by July (Supp Fig. 2), exhibiting no further variation.

Of the 1,800 initial DBS samples, 1,787 (99.3%) had normal TRECs (Supp Fig. 1A). At the study hospitals, a second DBS was obtained routinely at each infant's 2-week pediatric visit, allowing for collection of repeat TREC samples where required. Eleven infants with initial inconclusive DBS had a second DBS showing normal TRECs. Two infants were initial positive cases with low TRECs and normal β-Actin; one infant was withdrawn from the study because the parents did not want repeat TREC testing. The other initial positive case (Patient 1, Table 2) had TCL by flow cytometry (discussed in Section 3.3).

3.2 Expansion to standard care

In February 2012, SCID NBS was rolled out as part of the routine NBS at all Navajo Nation maternity hospitals in Arizona and New Mexico. DBS samples for TREC testing were collected and stored according to established study protocol and sent weekly to PerkinElmer Genetics, Inc. for SCID screening. Results were returned to designated local pediatricians and also reported to the senior pediatric consultant in Tuba City (Supp Fig. 1B). By June 2012, all infants born at participating hospitals and present at 24h of age were screened, as were infants born elsewhere but enrolling for care by 6 weeks of age at Navajo Reservation clinics; none of 6,100 DBS screened were inconclusive, but 4 infants had undetectable TRECs and proved to have SCID-A. A summary of the first 17 months of standard care

screening with a single SCID-A case in 3,498 infants (Pt 2 here) was included in a publication on SCID NBS in 11 programs [4]. This current, comprehensive report reaches back to include findings from the pilot (1,800 infants) as well as 13 more recent months of screening 2,602 previously unpublished infants, including 3 more with SCID-A.

3.3 Infants with low TRECs

Five infants, 1/1,580 births (95% CI 1/870-3,300) were identified as abnormal, one with low TRECs and TCL associated with congenital anomalies during the pilot phase and 4 with undetectable TRECs and mutation-proven SCID-A during standard care screening (Table 2). All 5 infants presented with low absolute lymphocyte counts (ALC) and no visible thymus tissue on initial chest radiographs. SCID-A patients received treatment at UCSF.

Pt 1—this term female had 11 TRECs/μL blood, with normal β-Actin on NBS (Table 2). Family history was negative. In addition to lack of a thymic shadow, chest radiogram showed thoracic scoliosis with incomplete fusion of T7 and a T10 hemivertebra. She developed neonatal tetany due to primary hypoparathyroidism, responding to calcium supplementation. Flow cytometry showed only 632 CD3 T cells/μL (normal >2,500/μL), but proliferation to PHA was normal, as was the diverse T cell repertoire demonstrated by spectratyping. A chromosome copy number array, fluorescent in-situ hybridization for DiGeorge syndrome and *TBX1* gene sequence were normal. Live rotavirus vaccination was given without sequelae, and routine killed vaccines elicited robust antibody responses at 7 months. Despite persistent TCL she has experienced no severe infections.

Pt 2 (listed in [4])—this term female had undetectable TRECs with normal β-Actin on NBS; immune studies were consistent with T-B-NK+ SCID (Table 2). Although no family history of SCID was recorded before the NBS result, upon review 2 distant cousins had succumbed to SCID, one with complications following attempted HCT and the other with an infection before HCT could be performed. Physical examination at 4 weeks was normal except for an oral ulcer, a previously described non-infectious characteristic of SCID-A [19]. At 2 months she received a haploidentical, CD34 selected, T cell depleted peripheral HCT from her mother without pre-conditioning, followed by a stem cell boost at 7 months. She developed mild graft vs. host disease (GVHD), autoimmune hemolytic anemia and thrombocytopenia, all resolving with steroids. Her CD3 T cell count was 304/μL at 20 months of age, with normal proliferation to PHA. She is healthy, but remains B-lymphopenic, and requires gammaglobulin support.

Pt 3—this male infant born at 36 weeks' gestation had two NBS (repeated for preterm birth) with undetectable TRECs, but normal β-Actin, and absent T and B cells (Table 2). He was healthy at 4 weeks of age except for an oral ulcer that interfered with feeding. Review of the family history revealed a deceased older sibling who had experienced recurrent pneumonias with fatality at age 6 months, but for whom no immunologic studies were done. At 5 weeks he received a haploidentical, CD34 selected, T cell depleted peripheral HCT from his mother without pre-conditioning. His course was complicated by infection with HHV6 and refractory GVHD treated with sirolimus, prednisolone, basiliximab and methylprednisolone. Because of persistent T-lymphopenia, he received a second maternal HCT at 13 months with

reduced-intensity conditioning chemotherapy. He continued to have further complications including venoocclusive disease, ongoing GVHD, HHV6, pulmonary infiltration causing respiratory distress and eventual demise at 15 months.

Pt 4—this term female was discharged after birth without SCID NBS collected and failed to return for this test until 2 months of age. At this visit, a TREC test was obtained, but 2-month vaccinations were also given, including live attenuated rotavirus oral vaccine. Within two days, her NBS showed undetectable TRECs. At her local hospital, she had loose stools that tested positive for rotavirus antigen, and further studies confirmed SCID-A (Table 2). At 3 months she received a haploidentical, CD34 selected, T cell depleted peripheral HCT from her mother without pre-conditioning, with a stem cell boost at 5 months. She has developed donor CD3 T cell engraftment at 8 months, but remains on immunoglobulin infusions.

Pt 5—this healthy term female had undetectable TRECs with normal β-Actin on NBS, undetectable T or B cells, and normal NK cells (Table 2). At 8 weeks, following serotherapy with rabbit anti-thymocyte globulin, she received a haploidentical, CD34 selected, T cell depleted peripheral HCT from her mother. Due to failure to engraft a second HCT with a matched unrelated donor was performed at age 5 months.

4. Discussion

This report describes the successful implementation of newborn screening for SCID in the Navajo Nation, and emphasizes the importance of mandatory SCID NBS in this population with increased frequency of SCID due to the founder mutation in Artemis. The initial pilot study with informed consent was undertaken to establish whether SCID NBS could be accomplished in this rural population with its distinctive traditions and values. A face-to-face written consent process was mandated during the study phase to assure that participants were fully informed and knew that participation in research was voluntary [20, 21]. Only two-thirds of new mothers agreed to enroll their infant, with refusals reflecting attitudes shared across cultures [22] as well as deriving from traditional values (Table 1); nonetheless sufficient enrollment occurred to demonstrate DBS sample collection, TREC testing and follow-up could be integrated into pediatric care, provided DBS were protected from humidity. Based on the pilot study, together with the known high risk for SCID among the Navajo, the health benefits of screening were judged sufficiently important that this test was adopted as standard care. The high specificity of the TREC test throughout both phases reported here, with 0.2% indeterminate results, is comparable to other SCID NBS programs [2-4]; repeat DBS testing where needed was facilitated by the existing practice of obtaining a routine second DBS sample from all infants during the first month of life.

The benefit of this public health measure to the Navajo people has been realized, with detection of absent TRECs in 4 infants leading to otherwise unsuspected diagnoses of SCID-A. TREC screening in one infant was delayed, resulting in exposure to live rotavirus vaccine that caused diarrheal illness [23], emphasizing the importance of complete implementation and physician awareness to avoid infectious exposures in infants whose screening tests have not been reported as normal [23]. The remaining 3 SCID infants were diagnosed early and

protected from infectious exposures with isolation, prophylactic antibiotics, and prompt referral for HCT. Given the known DNA repair defect of SCID-A, DNA damaging chemotherapy and radiation were minimized. Unfortunately persistent HHV6 in Pt 3 was associated with prolonged lymphopenia and refractory GVHD, ultimately leading to his demise.

One case of non-SCID TCL and associated anomalies was also found by NBS; Pt 1 received prompt follow up, avoided serious infections, and remained healthy at 2.5 years of age.

NBS has confirmed that the incidence of SCID-A in the Navajo Nation is very close to the original estimate of 1 per 2,000 births, nearly 30-fold higher than in the general population [4]. In contrast to screening programs in many states [2-4], most abnormal TREC screens in Navajo infants, 1/1,580 births, are due to SCID because the incidence of SCID-A is high and that preterm and ill infants, a major source of abnormal TREC tests and TCL in other screening programs, are transported to high level care beyond the Navajo Nation before newborn screening tests are sent. Continuation and expansion of SCID NBS is particularly important in areas where Navajo and Apache infants at high risk for SCID are born, but universal implementation will afford early detection for all forms of SCID and other TCL conditions to all infants.

5. Conclusion

In the Navajo population, where a founder mutation causes frequent SCID, benefit from SCID NBS has been demonstrated, with affected infants receiving prompt diagnosis and early referral for definitive treatment. The benefit of SCID NBS in this high-risk population demonstrates the importance of early detection and supports extending SCID NBS to newborns everywhere.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Abbreviations

DBS	dried blood spots
dsDNA	double strand DNA
GVHD	graft vs. host disease
HCT	hematopoietic cell transplant
NBS	newborn screening
SCID	severe combined immunodeficiency
SCID-A	Artemis deficient SCID
TCL	T cell lymphopenia
TCR	T cell receptor
TREC	T-cell receptor excision circle

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Highlights

- A research study found SCID newborn screening feasible for Navajo Native Americans.
- When face-to-face consent was required, only two thirds of infants were screened.
- Artemis-deficient SCID due to a founder mutation was identified by screening, permitting early treatment.
- Population-based screening confirmed SCID in 1 per 2,000 Navajo births.

Table 1

Reasons giving for declining to enroll infant in SCID screening study (959 of 2,796 mothers interviewed)

Reason	Proportion of mothers endorsing
Mother is not interested.	25%
Baby looks healthy, so test not required.	23%
Mother needs more time to consider it.	10%
If test is voluntary, mother does not want it.	9%
Enrolling would be against traditional beliefs.	7%
Baby has had enough testing.	4%
Father or other family members are against it.	3%
Mother is not Navajo.	3%
(Uncommon reasons, each)*	<2%
(No reason recorded)	11%

*Examples: prior baby already tested, privacy concerns, does not think SCID is a serious problem.

Table 2

Immunological profiles of infants with low TRECs identified by screening.

Values at diagnosis	**Pt 1**	**Pt 2**[a]	**Pt 3**	**Pt 4**	**Pt 5**
TRECs (>25 copies/μL)	**11**[b]	**0**	**0, 0**	**0**	**0**
WBC (>5,000 /μL)	**4700**	**4400**	**3500**	**1100**	**700**
Neutrophils (>1,000 /μL)	2540	2290	2120	8050	5500
Lymphocytes (>2,500 /μL)	**1290**	**350**	**480**	**1560**	**300**
CD3 T cells (>2,500 /μL)	**632**	**46**	**1**	**116**	**0**
CD4 T cells (>1,600 /μL)	**439**	**39**	**1**	**116**	**0**
CD8 T cells (>560 /μL)	**206**	**7**	**0**	**19**	**0**
CD19 B cells (>300 /μL)	310	**<4**	**0**	**<10**	**0**
CD16/56 NK cells (>170 /μL)	348	291	**96**	815	390
CD4 naive cells (>1,200 /μL)	**167**	**<1**	**4**	**<1**	**0**
CD45 cell proliferation to PHA (>50%)	>50%	**0.9%**	**0.4%**	**3.3%**	**0.5%**
Maternal T cell engraftment detected by short tandem repeat DNA markers (% of total T cells)	*Not done*	**1%**	**1%**	**55%**	Not detected
IgG (passive maternal IgG)	709	1030	1038	**<100**	684
IgA (8-45 mg/dL)	34	**620**	**<5**	**<8**	**<6**
IgM (10-40 mg/dL)	87	20	**<5**	<25	**<5**
Molecular diagnosis	None (see text)	**Homozygous mutation for SCID-A**[c]	**Homozygous mutation for SCID-A**[c]	**Homozygous mutation for SCID-A**[c]	**Homozygous mutation for SCID-A**[c]

Values at 7 months of age, after vaccinations	
CD3 T cells (>1,900 /μL)	**729**
Anti-pneumococcal titers, protective/total tested	8/12
Anti-tetanus titer (>0.2 protective)	3.2

[a] This patient was listed in a previous publication [4]

[b] Abnormal values for age in bold type

[c] *DCLRE1C* exon 8, cDNA 597 C>A , causing TAC (tyrosine) to become TAA (termination codon); p Y192X.