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RESEARCH ARTICLE

Conditions Other than Severe Combined Immune Deficiency Found on SCID Newborn Screening

Joudeh B. Freij MD[1] and Elizabeth Secord MD*[2]

[1.] University of Michigan, Department of Pediatrics, Ann Arbor MI
[2.] Wayne State University, Department of Pediatrics, Division of Allergy and Immunology, Detroit MI 48201

* esecord@med.wayne.edu

ABSTRACT
Severe combined immune deficiency (SCID) is caused by a wide variety of genetic variants that result in absent or diminished levels of mature and functional T cells. SCID Newborn Screening programs that detect T cell receptor excision circles have resulted in early intervention and improvement in survival rates in infants with SCID but have also identified other conditions with low T cells. These conditions trigger what could be thought of as false positive tests for SCID, but for the most part they do reflect low T cells in conditions other than SCID. The scope of this review is entities other than severe combined immune deficiency that cause low T cell receptor excision circles (TRECs) and are thus identified on newborn screening. Secondary immune deficiencies from prematurity, neonatal medical conditions, hypomorphic or incomplete variants of SCID, transient T cell lymphopenia of infancy, and primary immune deficiencies that do not qualify as SCID are all elaborated. Identification and treatment options for these conditions leading to low TRECs are discussed.

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Scope: The scope of this review is entities other than severe combined immune deficiency that cause low T cell receptor excision circles and are thus identified on newborn screening.

Aims:

1. To describe the T cell receptor excision circle assay utilized for newborn screening for severe combined immune deficiency and the confirmatory testing utilized.
2. To delineate conditions other than severe combined immune deficiency that result in low T cell receptor excision circles that may be identified on newborn screening.
3. To discuss differentiation of these other conditions from severe combined immune deficiency and to discuss treatment approaches for each condition.

Abbreviations

- CT: Computerized Tomography
- DGS: DiGeorge Syndrome
- GVH: Graft versus Host
- HLA: Human Leukocyte Antigen
- IL: Interleukin
- LBW: Low birth weight
- NICU: Neonatal Intensive Care Unit
- NBS: Newborn screening
- NEC: Necrotizing enterocolitis
- NK: Natural Killer
- PCR: Polymerase chain reaction
- PHA: Phytohemagglutinin
- PIDD: Primary Immune Deficiency Disorder
- RAG: Recombinase activating gene
- SCID: Severe Combined Immunodeficiency
- TCR: T cell receptor
- VLBW: Very Low Birth Weight

Background:

Severe combined immune deficiency (SCID) is caused by a wide variety of genetic variants that result in absent or diminished levels of mature and functional T cells. Some variants of SCID have absent B cells, but even if present, B cells do not function in SCID because of the lack of T cell help and SCID patients, therefore, lack all adaptive immunity. Lymphocyte enumeration is variable in SCID depending on the genetic variant, and the delineation of B and Natural Killer (NK) cell presence helps with identification of SCID phenotype.[1, 2] SCID Newborn Screening (NBS) programs implemented throughout the USA, and now in several other countries, have resulted in early intervention and improvement in survival rates in infants with SCID. [3] T cell receptor excision circles (TRECs) are a by-product, and convenient biomarker for, T cell maturation in the thymus.[4,5] TRECs can be identified in blood collected on NBS cards by performing a polymerase chain reaction (PCR) assay. This screening has allowed early identification of SCID and, therefore, early intervention and improved outcomes.[4,6,7] It has also identified other conditions with low T cells. These conditions trigger what could be thought of as false positive tests for SCID, but for the most part they do reflect low T cells in conditions other than SCID and are not in that sense true false positives. This review elaborates the conditions other than SCID that result in low or undetectable levels of TRECs. Secondary immune deficiencies from prematurity or medical conditions can result in low TRECs. Defects in the same genes that cause SCID can also lead to hypomorphic or incomplete variants of SCID. Some infants, we now realize, have a transient T cell lymphopenia near birth. DiGeorge syndrome (DGS) is associated with varying levels of T cell lymphopenia, as are some other primary immune deficiencies (PIDD) that do not qualify as SCID. Identification and treatment of these conditions leading to low TRECs is discussed.

Secondary Immune Deficiencies:

Algorithms for TREC follow-up and referral to specialty centers vary by state. In some states a low TREC that is not near zero would be further differentiated as low or borderline. Borderline results often trigger a repeat screening before any work-up is done. A result that is low but not near zero may trigger some work-up depending on circumstances. False positives, more accurately, low TRECs that are not SCID are usually in the borderline or low category, but not the very low range. There are a few exceptions.

Secondary immune deficiencies account for the majority of low TREC results that are not SCID and the most common secondary immune deficiency resulting in low TRECs is prematurity. In infants who are preterm and otherwise healthy the first response of most hospitals, is to repeat the NBS card per state and/or hospital protocol. As prematurity triggers positive results in many NBS tests, not just TRECs, Neonatal intensive care units (NICU) usually have protocols for repeating cards at fixed intervals. [8] In cases such as SCID, where definitive intervention could not reasonably proceed until a very low birth weight (VLBW) or low birth weight (LBW) infant has grown, waiting on the second NBS card before drawing labs for T cell enumeration and function is the usual response. NICU protocols are already in place to avoid infections in these VLBW and LBW preterm infants. Positive low TREC screens in preterm infants are not usually associated with very low TRECs and the index of suspicion for SCID is not high. If the TREC is zero or near zero secondary labs may be done as prematurity itself does not preclude SCID.

If a preterm infant has sepsis, the question of which came first, the low TREC or the infection, must be considered. There is some evidence that low TRECs predict infant mortality in preterm infants, but it is usually theorized that severe illness in the form of necrotizing enterocolitis (NEC), sepsis, etc., associated with the prematurity causes the low TREC rather than immune deficiency causing the

co-morbidities, especially infection.[9] Because intervention for SCID, specifically stem cell transplant, would not be plausible in VLBW or LBW or even many preterm infanta, and because blood draws are limited due to weight and other pressing co-morbidities, secondary tests may be somewhat delayed.

If the infant has other signs of SCID, or if the screen is strongly positive, flow cytometry should be done as soon as possible, and further precautions should be considered while waiting for flow cytometry results. Protective isolation in a laminar flow room until flow cytometry is obtained may be recommended. Minimally, all staff should be alerted for extra precautions with the infant and nursing assignments altered to assure that the nurse assigned is not assigned to any infants being treated for infection.

If a pre-term infant with a positive TREC is getting breast milk the usual precaution of stopping breastfeeding to prevent cytomegalovirus transmission from mother to infant is more complex than it would be with a full-term infant and this recommendation should be delayed until a definitive diagnosis of SCID has been made. If the screen is a strong positive and SCID is highly suspected, the precaution of holding breastmilk should be discussed with the family and the treating physician. Breastmilk is an established part of treatment protocol for pre-term infants when it is available and has been shown to reduce the incidence of NEC, and stopping it could do harm.[10] Again, flow cytometry should be obtained as soon as possible if TRECs are very low. The determination of what is considered very low, or highly suspicious for SCID varies by the state or country protocol.

Maternal Immune Suppression:
T cell lymphopenia secondary to maternal immune suppression is another cause for a low TREC on NBS. Initially reports of low TRECs due to maternal steroids were reported.[11,12] Since that time cases of maternal purine analog use resulting in low TRECs in the newborn have also been reported.[13] Pre-term infants are often exposed to prophylactic steroids given to mothers before birth to prevent infant intracranial hemorrhage and to assist with infant lung maturation. Although lymphopenia is a consequence of this treatment, recovery is not prolonged in most cases. It is postulated that many of the borderline positive TREC screens in preterm infants may be attributable to maternal steroids.[14,15] Women with systemic lupus, inflammatory bowel disease, or other chronic illnesses with poorly controlled inflammation may require more prolonged immune suppression in the form of steroids and/or purine analogs, and these agents have been reported to cause low TREC screens.[3, 11, 13, 14] The effects of maternal immune suppression on infants is not a new concern, but the TREC screen does afford us an opportunity to identify those infants whose exposure to maternal immune suppression significantly lowers the T cell count. Infants with history of maternal immune suppression who have been reported as having low TREC screening have recovered within a matter of months. [11, 12]

Severe Disease:
Secondary immune deficiency from chylothorax, edema, NEC, or exchange transfusion may cause low TRECs because the lymphocytes are removed from the circulation.[3, 12, 16] Cases of neonatal leukemia and other malignancies resulting in low TRECs have been reported.[3, 9] The question arises as to whether the low T cells contribute to the severity of the underlying disorder.[9]

Primary Immune Deficiencies other than SCID Revealed by TREC:

DiGeorge Syndrome:
DiGeorge Syndrome (DGS), or 22q11.2 deletion syndrome, is a PIDD other than SCID that is a frequent cause of low TRECs. DGS causes low T cells because of decreased or absent thymic output. This syndrome has significant variation but involves the deletion of multiple genes from the 11.2 loci of chromosome 22.[17, 18] Some individuals with deletions in this region are asymptomatic, others have cardiac defects, midline facial anomalies, parathyroid abnormalities leading to low calcium and seizures, and of particular importance to immune function, low or absent T lymphocytes due to poor thymic output. A total absence of T cells in DGS is the most severe form and is very rare, accounting for only about 1-2% of all case of DGS. [17,18]

DGS is characterized as complete or incomplete, based on the absolute T cell count. It is estimated that about 1 in 3000-6000 individuals have 22q11.2 deletions.[17, 18, 19] Ten percent of the cases of DGS are estimated to be inherited in an autosomal dominant fashion, but the other 90% are the result of spontaneous mutations.[17,18,19] Most infants with incomplete DGS will not be identified

on the TREC screening because their T cells are not low enough. Those with lower thymic output will be positive on the TREC screen, but the majority of those who screen positive will not be strong positives, that is, they will not be in the very low range. Only 1-2% of individuals with DGS will be characterized as complete DGS.[17,18] Infants with complete DGS arguably meet the criteria for SCID as they lack T cells, but their treatment differs, and this genetic disorder is considered as separate from SCID.

When flow cytometry in a DGS infant reveals less than 50 CD3+ T cells/ul complete DGS is suspected. Complete DGS is anatomical athymic, and although chest x-ray may be utilized to evaluate for thymic tissue ("sail sign" or thymic shadow), it is not a reliable tool for diagnosis because thymic tissue may be very small or in an ectopic location.[17,18] Flow cytometry can reveal the presence of lymphocytes with T cell markers and is less invasive than x-ray or computerized tomography (CT) scan. Flow cytometry is utilized to enumerate CD3+ T cells in absolute numbers as well as naïve (CD45+RA+) and memory (CD45+RO+) T cells in circulation. Mitogen proliferation, especially to phytohemagglutinin (PHA), is utilized to determine if the T cells are functional.[17] Infants without cardiac anomalies who have complete or near complete DGS were sometimes overlooked prior to TREC screening and identified only when they developed infection.

Treatment for complete DGS is either thymus transplant or stem cell transplant.[17,18,19] Currently the preferred treatment is thymus transplant as this supplies the missing thymus stromal tissue needed for T cell maturation, is associated with survival rates of 58-75%, and allows broader recovery of T cell subsets and functions[18] Thymus transplant is not, however, readily available for all complete DGS patients as it is approved at only a few treatment centers. Stem cell transplant is another alternative with similar survival rates, but the functional T cell recovery is not as complete as with thymic transplant.[17] A major issue for either procedure is that DGS patients most often have other conditions that must be treated prior to therapy for the immune deficiency, especially unstable congenital heart disease. It is often a challenge to stabilize the patient so that she/he can receive a transplant.

Many infants with DGS syndrome and low but not absent T cells are identified on TREC screening and T cell numbers often normalize or approach normal with time in these infants. Lymphocyte function assessment by PHA proliferation will advise whether the infant may require prophylaxis against *Pneumocystis jirovecii*. Checking for antibody response if the T cell function is low will advise whether the B cell function is secondarily affected so that replacement immunoglobulin is warranted. There is also evidence that persons with incomplete DGS are more likely than the general population to develop autoimmune disease later in life, and they are advised to continue to be monitored for signs of autoimmunity.[20]

Hypomorphic SCID:

There are genetic mutations that are associated with hypomorphic or partial SCID. These can be heterozygous forms of mutations that in their homozygous forms are associated with SCID or can be a partially active mutation either of which may cause a combined immune deficiency or leaky SCID. A leaky SCID is defined as a SCID with some T cells present that are usually of low function by PHA assay, but may be autoreactive.[21] In 2014 the Primary Immune Deficiency Treatment Consortium sought to establish clearer diagnostic criteria for SCID, leaky SCID and Omenn syndrome.[21] The terms Leaky SCID and Omenn Syndrome were sometimes used synonymously prior to the 2014 definitions, and there remains overlap. Omenn syndrome and leaky SCID both have T cells present that are autoreactive and not of maternal origin, both have low T cell function by PHA mitogen assay, and both present clinically with rash and enlarged lymph nodes with more prominent symptoms seen in Omenn syndrome.[21] Additionally, in clinical practice the cut-off for SCID versus leaky SCID are not always clear.

Criteria for SCID as set by The Primary Immune Deficiency Treatment Consortium are absent or "very low" CD3+ T cells that are not of maternal origin, specifically less than 300 CD3+ T cells/ul of infant's blood, and a PHA response of less than 5-10% of the control, while leaky SCID and Omenn syndrome may have PHA response up to 30% of the control.[21]

To establish whether CD3+ T cells are of infant or maternal origin (maternal engraftment) in cases where the CD3+ T cell count is higher than the established cut-off, but SCID is still suspected, the CD45RO memory T cells and CD45RA naïve T cell markers are helpful. The usual expectation is that

the CD45RA naïve cells will be predominant in infants. If CD45RO+ T cells are a significant percentage of the population they could be of fetal or maternal origin, and Human Lymphocyte Antigen (HLA) typing to detect chimerism will establish whether there is significant maternal engraftment. It is expected that in an infant with SCID without maternal engraftment, the naive T cells will be close to 90% of the T-lymphocyte pool, with 10% or less being memory cells.[11, 12, 21]

In cases of Omenn syndrome, the CD3+ T cell count will be higher than the usual cut-off for SCID and may even be normal. The T cells may have a higher percentage of memory cells of maternal origin with more CD45+RO cells as opposed to CD45+RA cells.[22,23] Omenn syndrome classically presents with erythroderma, eosinophilia, and hepatosplenomegaly. The rash was previously considered to be graft versus host (GVH) in origin secondary to maternal engraftment.[22] More recently autoreactive oligoclonal T cells that have persisted secondary to impaired thymic function and/or defective recombination-activating genes (RAG) are thought to be responsible.[22, 24] Omenn syndrome has previously been described as a variant of RAG deficiency but is now often described as secondary to hypomorphic RAG mutations.[25] It is no longer considered exclusive to RAG variants, and has been, more recently associated with other SCID variants. The Artemis gene, for example, which is also key to gene rearrangement in the adaptive immune system, has been described in cases of Omenn syndrome.[26] Hypomorphic genes for Ligase 4 deficiency, Interleukin 7 (IL-7), and multiple other SCID associated genes, as well as DGS, have now been associated with Omenn syndrome.[25] Prior to the onset of NBS by TRECs, these children were more difficult to diagnose because the T cell count was normal despite lack of function, and they were often missed. We now realize that not all Omenn syndrome is RAG variant in origin and not all RAG variants present as Omenn syndrome. This SCID variant, as well as leaky SCID variants may be treated with SCT.

The most commonly recognized hypomorphic mutations leading to low TRECs are in the RAG genes. There are reports of heterozygous RAG1 and RAG2 variants presenting as a combined immune deficiency. Since the start of newborn screening infants with heterozygous RAG deficiency may present early with low, but not necessarily zero, TRECs. Many of these patients will be candidates for the same treatment, i.e., SCT, as patients with SCID.

Transient T-cell Lymphopenia of Infancy:

The evaluation of low TRECs has led to the diagnosis of some true primary and secondary immune deficiencies but has also led to the discovery of an entity referred to as idiopathic or transient T cell lymphopenia of infancy.[23, 27, 28] These infants do not appear to be prone to increased infection, and the T cells return to normal by a year of life. This is thought to be analogous to transient hypogammaglobulinemia, and the lack of recognition prior to NBS suggests it is a benign condition. These infants are usually followed with serial T cell enumerations once other conditions have been ruled out, to assure that the T cells reach normal range. The issue with such infants is, however, to ensure that there is no other underlying condition responsible for the low T cells.

The criteria for transient T cell lymphopenia are not well established. The lower limit of normal for absolute T cell count varies significantly by laboratory. In one report from New York State the incidence of this condition was 30 per 485,912 births or approximately 1 per 16,000 births.[23]

The reports of infants with transiently low T cell counts have varied in recovery time analogous to transient hypogammaglobulinemia. The issue of live vaccines is handled differently at different centers without a clear standard at this time. Some centers clear infants for live vaccine when mitogen stimulation for PHA is near the control range while others wait for the absolute T cells to reach normal range.

Low TREC secondary to non-immunologic causes:

There have been a few case reports of true false positives on TREC screening from genetic mutations in the primer area used for the PCR assay. Primers are selected to attach to highly conserved areas of DNA, but in these cases mutations in the infants DNA was identified in the areas of attachment that rendered the assay unusable.[29] Such cases become suspicious because despite an abnormal TREC screen the lymphocyte enumeration for T cells, B cells and NK cells as well as for naïve and memory T cells (CD45RA and CD45RO) will remain normal. The mitogen proliferation will also be normal. Repeat TREC screens will continue to indicate absence of T cells. The discrepancy

should lead to scrutiny of the test and utilization of an alternate primer will reveal the cause.

Conclusion:

TREC NBS has saved lives, but it has also given us new challenges. We have now identified other disorders that present with low T cells that may have been missed or misdiagnosed without screening. Infants with hypomorphic, leaky SCID, or Omenn may have presented beyond infancy and been followed without intervention until severe illness. DGS that is complete or near complete may have been missed until severe infection, especially in infants without cardiac defects. Transient T cell lymphopenia is a separate challenge that appears to require no intervention but may be important to recognize as a normal variant. As more time goes by it is expected that we will be able to pool data and make informed recommendations for these infants.

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