

Thoracic Duct Injury Resulting in Abnormal Newborn Screen

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Measurement of T-cell receptor excision circles (TREC) in neonates has allowed for population-based screening of severe combined immunodeficiency and other disorders associated with T-cell lymphopenia. In addition to primary T-cell lymphopenic disorders, secondary causes of T-cell lymphopenia can be diagnosed with TREC analysis. We discuss the diagnostic evaluation of a patient with normal TREC analysis at birth that became abnormal after cardiac surgery. TREC analysis was performed by the Florida State Laboratory. Diagnostic evaluation and treatment were performed at All Children's Hospital, St Petersburg, Florida. We identified a 38-day-old female patient with thoracic duct injury, which caused chylothorax and chylous ascites diagnosed after an abnormal newborn screen. Chylothorax was secondary to thoracic duct injury after cardiac surgery and led to severe lymphopenia and hypogammaglobulinemia. Thoracic duct ligation led to improved lymphocyte counts and normalization of immunoglobulin levels. Secondary causes of lymphopenia are detected with TREC assay that lead to abnormal newborn screen results. Many secondary causes of lymphopenia can be acquired with normal initial newborn screens that become abnormal over time. © 2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2013;1:583-8)

Key words: Chylothorax; Newborn screen; Severe combined immunodeficiency; T-cell receptor excision circle; Thoracic duct

Over the past 50 years, newborn screening has grown tremendously from the original test for phenylketonuria described by Guthrie and Susi¹ to now include screening for more than 35

inherited potentially fatal diseases. This effort is supported by each state's public health program and leads to the diagnosis of rare but treatable conditions that would otherwise result in significant morbidity and mortality. Population-based screening for severe combined immunodeficiency (SCID) and other disorders associated with T-cell lymphopenia began in Wisconsin in 2008.²

SCID is a life-threatening disease of infants caused by more than 30 different genetic defects characterized by profound defects in cellular immunity and specific antibody production,³ and is estimated to occur in 1 in 50,000 to 1 in 100,000 live births.⁴ Regardless of the genetic defect, infants with SCID have absent or extremely low numbers of naive T cells that recently emigrated from the thymus. Variable decreases in B and natural killer (NK) cells occur and help with the classification and diagnosis of a specific genetic defect. The combined defects of T, B, and NK cells severely compromise the infant's ability to resist and fight infections, particularly opportunistic, viral, fungal, and bacterial infections.⁵ Infections from live-attenuated vaccines such as rotavirus, poliovirus, varicella, and Bacillus Calmette-Guerin are also common and can be fatal.^{6,7} The diagnosis of SCID is frequently delayed or missed due to multiple factors, primarily the normal physical appearance of most infants with SCID and the relative health of the infant, initially protected by transplacentally derived maternal IgG. However, superior outcomes have been shown repeatedly in infants with SCID diagnosed and treated at a young age.^{5,8-10}

Development of the T-cell receptor excision circle (TREC) assay in 2005 by Chan and Puck⁴ allowed for the initiation of population-based screening for SCID. TRECs are nonreplicative pieces of DNA formed during T-cell receptor gene rearrangement. TRECs are formed in 70% of thymocytes that will ultimately express $\alpha\beta$ -T-cell receptors.¹¹ The TREC assay enumerates the number of TRECs by using real-time quantitative PCR from DNA extracted from blood spots on newborn screening Guthrie cards. TREC quantification directly correlates with the number of circulating naive T-cell emigrants leaving the thymus. After a confirmed positive newborn screen result, the patients are referred to an immunologist where evaluation for SCID and treatment ensues.¹²

CASE PRESENTATION

We were referred a 38-day-old African-American female infant with complete absence of TRECs on newborn screening. This screening was performed on day of life (DOL) 31 and was her third screen. Newborn screens on DOL 2 and 5 were normal. In many states, it is standard to repeat newborn screens in hospitalized infants. In Florida, newborn screens on critically ill infants are routinely performed upon admission to the intensive care unit, at 48-72 hours of life, and on DOL 28.

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Abbreviations used

CHARGE- Coloboma, heart defects, choanal atresia, growth or developmental retardation, genitourinary and ear abnormalities

DOL- Day of life

IVIG- Intravenous immunoglobulin

LDH- Lactate dehydrogenase

NK- Natural killer cell

PCO₂- Partial pressure of carbon dioxide

RBC- Red blood cell

SCID- Severe combined immunodeficiency

TREC- T-cell receptor excision circle

WBC- White blood cell

The patient was born full term via spontaneous vaginal delivery. There were no prenatal complications. At 36 hours of life, she became apneic, limp, and bradycardic. Intubation quickly followed due to respiratory failure and acidosis; blood gas measurements showed profound acidosis, with a pH of 6.5 and PCO₂ of 101 mm Hg. Cardiac evaluation revealed D-transposition of the great arteries. Despite treatment with prostaglandins and antibiotics for possible sepsis, she remained hypoxic and acidotic, and so an emergent septostomy was performed.

Acute kidney injury with poor urine output, azotemia, and anasarca led to placement of a peritoneal catheter for dialysis. A Lecompte arterial switch procedure with closure of the atrial septostomy was performed on DOL 27. This procedure involves a midline sternotomy and direct arterial switch of the pulmonary artery and aorta to their correct anatomic positions. The coronary arteries also are separated from what had developed into the aorta and connected to the neo-aorta. As often happens in cardiac surgery, thymic tissue was removed. Immediate postoperative complications included development of pleural effusions, which required bilateral chest tube placement, midline incision clots, and hypoalbuminemia. The midline incision eventually became infected with *Enterobacter cloacae*. Significant drainage from the peritoneal catheter also occurred, which caused concern for a possible connection between the thoracic and abdominal cavities.

Four days after surgical repair of transposition of the great arteries, the newborn screen was abnormal, with 0 TRECs measured. In Florida, TREC counts <25/μL are considered abnormal and cases are referred for evaluation. Initial immunologic evaluation showed profound hypogammaglobulinemia and T, B, and NK lymphopenia (Table I). Of all cell counts, NK (CD56⁺) cells were the least decreased. Naive CD4⁺ and CD8⁺ T cells were preferentially low compared with memory CD4⁺ and CD8⁺ T cells. Fluid from the chest tubes and peritoneal catheter appeared chylous and were sent for analysis. Both samples were very cellular, with more than 93% lymphocytes, and showed elevated protein, glucose, and triglycerides. Lactate dehydrogenase was elevated in the pleural fluid but low in the peritoneal fluid. At the time that these samples were taken, the patient was receiving all nutrition parenterally. Lymphocyte subset analysis from a different sample of pleural fluid revealed a predominance of lymphocytes (61%). Twenty-seven percent were CD4⁺ T cells, 15% CD8⁺, 7.6% CD56⁺, and 7.8% CD19⁺. By DOL 31, when the newborn screen was performed, an average loss of 58 mL/kg/day of chylous fluid through both chest tubes had occurred. Other immunologic evaluation performed included measurement of normal maternal

immunoglobulins, a chromosomal microarray that showed no deletions within 22q11 suggestive of DiGeorge syndrome, and robust T-cell responses to phytohemagglutinin.

The patient was initially managed with reverse isolation; intravenous immunoglobulin (IVIG); and antibacterial, antiviral, and antifungal prophylaxis. She remained on immunoglobulin replacement due to profound hypogammaglobulinemia. Medical management of thoracic duct injury included frequent albumin infusions and total parenteral nutrition with removal of triglycerides from the diet. Twenty-four days after surgery, octreotide was started. The chylous appearance of the fluid improved, but the total amount of drainage was unchanged. Forty-one days after initial surgery, thoracic duct ligation was performed. During surgery, large amounts of chyle were visualized within the right chest. Over the next several days, chest tube drainage significantly decreased and immunoglobulin levels and lymphocyte counts improved (Figure 1). Approximately 1 week after thoracic duct ligation, chest tube drainage increased again to approximately 18 mL/kg/day. Over the next month, chest tube drainage significantly decreased to 2.5 mL/kg/day but lymphopenia continued. This continued drainage along with loss of thymic tissue during cardiac surgery are likely contributing to her continued T-cell lymphopenia.

DISCUSSION

Newborn screening for SCID began in Wisconsin in 2008 and has now been instituted in 15 states and the Navajo Nation. Published data on initial results from the first several years of screening from Wisconsin¹³ and California¹⁴ are available. In the first 3 years of newborn screening in Wisconsin, 34 patients were diagnosed with SCID or other causes of T-cell lymphopenia; further testing was refused for 1 patient. Three cases of lymphatic malformations that led to T-cell lymphopenia and abnormal newborn screen results were reported.¹³ Of 993,724 births over 2 years, California identified 11 infants with typical SCID, 3 with leaky SCID or Omenn syndrome, and 1 with complete DiGeorge syndrome. All 15 infants underwent immune restoring therapies with either hematopoietic stem cell transplantation, thymus transplantation, or gene therapy. Thirty-five other cases of T-cell lymphopenia were diagnosed with newborn screening; 6 were secondary to congenital or postnatal major congenital heart disease and 1 was secondary to chylothorax.¹⁴

The TREC assay has the ability to diagnose conditions associated with significant T-cell lymphopenia (<1500 T cells/μL). Typical, leaky, and variant SCID are all associated with T-cell lymphopenia and abnormal T-cell function. Variant SCID, defined as no defect in a known SCID-associated gene and measurements of 300-1500 T cells/μL that demonstrate impaired function, is a new subgroup of patients identified due to results of newborn screening. Syndromes with variable effects in cell-mediated immunity such as DiGeorge syndrome and ataxia-telangiectasia also can lead to abnormal TREC levels in the newborn (Table II). Secondary T-cell lymphopenia as a result of thymectomy after neonatal cardiac surgery; neonatal leukemia; lymph losses from gastroschisis, chylothorax, and third spacing; and extreme prematurity all can lead to abnormal TREC analysis. Some secondary causes of T cell lymphopenia are reversible, as in the cases of lymphatic loss and prematurity.¹²

The initial assessment of our patient revealed profound hypogammaglobulinemia and lymphopenia with a T-B-NK-phenotype with 0 TRECs on newborn screening and a history of

TABLE I. Laboratory analysis

Test	Patient's results (age 38 d)	Mother's results
IgG	<33 (250-1200 mg/dL)	1610 (528-2190)
IgA	<7 (<7-60 mg/dL)	332 (44-441)
IgM	<4 (29-107 mg/dL)	126 (48-226)
Absolute lymphocytes	200 (3400-7600/ μ L)	
CD3	38 (2500-5500/ μ L)	
CD4	23 (1600-4000/ μ L)	
CD8	6 (560-1700/ μ L)	
CD19	19 (300-2000/ μ L)	
CD56	97 (170-1100/ μ L)	
CD4/CD45RA	5 (1200-3700/ μ L)	
CD4/CD45RO	18 (600-900/ μ L)	
CD8/CD45RA	5 (450-1500/ μ L)	
CD8/CD45RO	1 (300-330/ μ L)	
TREC from dried blood spot (copies/ μ L)	152 (DOL 3); 483 (DOL 5); 0 with normal β -actin (DOL 31)	
Pleural fluid analysis	RBC 174,150 cells/ μ L, WBC 833 cells/ μ L, lymphocyte 93%, monocyte 4%, eosinophil 3%, protein 3500 mg/dL, glucose 90 mg/dL, LDH 459 IU/L, triglyceride 31 mg/dL	
Pleural fluid lymphocyte analysis*	61% lymphocytes: 27% CD4 ⁺ , 15% CD8 ⁺ , 7.6% CD56 ⁺ , and 7.8% CD19 ⁺	
Peritoneal fluid analysis	RBC 5,130 cells/ μ L, WBC 540 cells/ μ L, lymphocyte 90%, monocyte 10%, eosinophil 3%, protein 2600 mg/dL, glucose 102 mg/dL, LDH <30 IU/L, triglyceride 79 mg/dL	
Chromosome microarray	No clinically significant imbalance or deletions	

RBC, Red blood cell; WBC, white blood cell; LDH, lactate dehydrogenase.

*A different sample from initial pleural fluid analysis.

2 normal newborn screens. The absence of TRECs and the degree of lymphopenia were suggestive of SCID but seemed less likely with 2 previously normal newborn screens. In addition, lymphocyte proliferative responses to mitogens were normal. The T-B-NK-phenotype is characteristic most often of adenosine deaminase or purine nucleoside phosphorylase deficiencies. In both adenosine deaminase and purine nucleoside phosphorylase deficiencies, lymphopenia can develop after birth as toxic metabolites that lead to lymphocyte death increase. Adenosine deaminase and purine nucleoside phosphorylase activity were measured and normal in this patient. Also, in all forms of SCID, IgG levels are typically maintained in the first 6 months of life because they are transplacentally acquired from the mother. Our evaluation included measuring maternal immunoglobulins to ensure that there was no hypogammaglobulinemia in the mother that could have led to hypogammaglobulinemia in the infant.

Another consideration was that this result was a false-positive newborn screen, especially with the presence of 2 previously normal screens with normal TREC analysis. California reported that in 0.08% of all newborns screened, a second newborn screen was requested. These instances occurred when there was a question regarding the validity of the assay and were mostly in preterm infants within the neonatal intensive care unit.¹⁴ In Wisconsin, 38 infants with abnormal newborn screens had normal T-cell counts that led to a false-positive rate of 0.018%.¹³ False-positive results can occur due to premature evaluation in preterm infants (<37 weeks gestation), low-birth-weight infants (<1500 g), or a sample being obtained before 24 hours of life.⁴ Also, poor sample quality as occurs with expired filter paper; degradation of DNA with exposure to alcohol, heat, or sun; and exposures to oxidizers or heparin can cause false-positive results.¹⁵ Our patient was a term baby with a weight of approximately 4000 g; there was no evidence of poor sample quality.

The most pertinent part of our patient's history was her cardiac defect and the timing of corrective surgery relative to the positive newborn screen (0 TRECs). Also the presence of 2 prior normal newborn screens suggested the possibility of acquired lymphopenia. Congenital heart disease is the most common congenital abnormality in the newborn, with a prevalence of 6-13 per 1000 live births,¹⁶ with cyanotic lesions that occur in approximately 15%. Congenital heart disease is not usually associated with SCID or other primary immunodeficiencies except in the cases of DiGeorge and CHARGE (coloboma, heart defects, choanal atresia, growth or developmental retardation, genitourinary and ear abnormalities) syndromes. Both are associated with T-cell lymphopenia and abnormal T-cell function and have been diagnosed in patients with low TRECs from newborn screening.¹⁴ Associated heart defects are typically conotruncal, such as interrupted aortic arch, truncus arteriosus, tetralogy of Fallot, atrial and septal defects, and vascular rings.^{17,18} The first 3 of these are cyanotic heart lesions. Transposition of the great arteries is the most common cyanotic heart defect among newborns and is not associated with lymphopenia or primary immunodeficiencies. It is a defect in which the aorta arises from the right ventricle and the pulmonary artery originates from the left ventricle.¹⁶ Chromosomal microarray showed no microdeletions within chromosome 22q11 suggestive of DiGeorge syndrome, and the patient had no somatic features consistent with CHARGE syndrome.

Removal of thymic tissue commonly occurs during corrective cardiac surgery for patients with congenital heart disease, which leads to lymphopenia and, therefore, was a diagnostic consideration in our patient. Thymic removal can cause progressive lymphopenia, with a very significant reduction in CD3⁺, CD4⁺, and CD8⁺ T cells in the first 3 years after surgery. The decline in CD4⁺ T cells is more pronounced than CD8⁺ T cells and

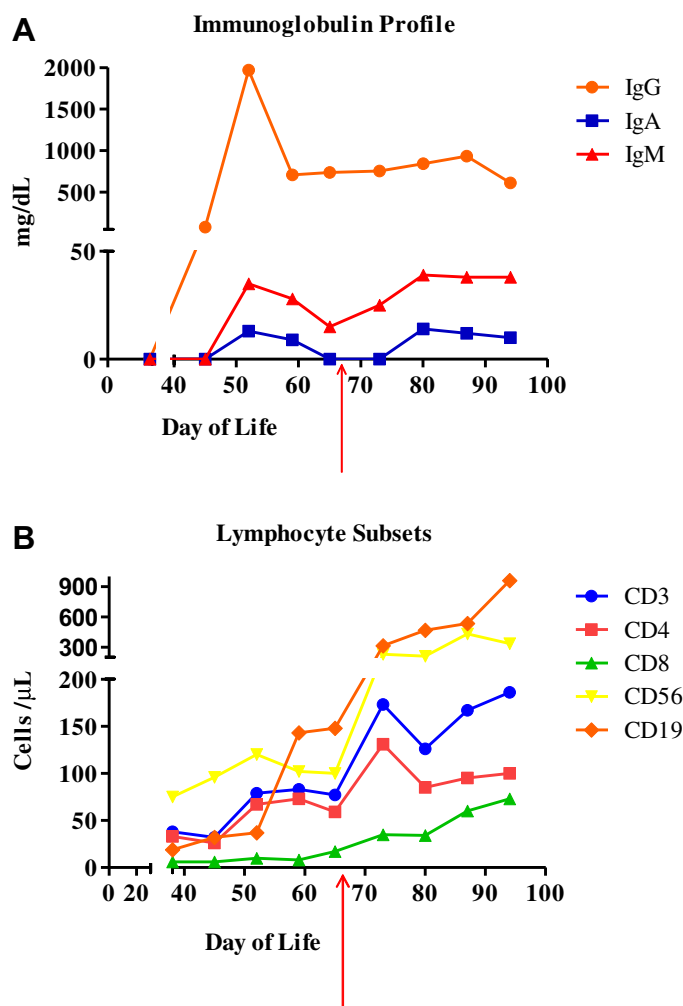


FIGURE 1. A, Immunoglobulin levels. B, Lymphocyte subset analysis. Arrows indicate time of thoracic duct ligation.

primarily consists of naive cells (CD4/CD45RA⁺). Significant decreases in TREC quantity also occur with a decline plateauing at approximately 12 months after surgery. There is no impact on T-cell function as measured by lymphoproliferative responses to mitogens, expression of CD19⁺ B cells or CD56⁺ NK cells, or production of immunoglobulin. Generally, patients are not at increased risk of infections related to T-cell immunodeficiency. By 3 years after surgery, T lymphocyte subsets are maintained in low numbers.¹⁹ TREC or lymphocyte subset analysis are not performed routinely in patients after surgical repair of congenital heart defects. However, in states such as Florida that continue to repeat newborn screen panels, including TREC analysis in hospitalized infants, TREC analysis may indirectly become part of routine testing in cardiac patients after surgery. TREC analysis could be used in this patient population as a surrogate marker for thymopoiesis and the diagnosis of acquired lymphopenia related to thymic tissue removal or thoracic duct injury.

Because of the large amount of chylous drainage from the chest tubes and peritoneal catheter along with pan lymphopenia (T, B, and NK), and profound protein loss with hypogammaglobulinemia, there was a strong suspicion of a thoracic duct injury, which resulted in chylothorax. Evaluation of pleural and peritoneal fluid

confirmed chylous drainage, and our suspicion of thoracic duct injury was confirmed. She eventually required surgical repair with thoracic duct ligation. After surgery, all immunoglobulin levels (IgG, IgM, and IgA) increased and were maintained, with no further gammaglobulin replacement. CD19⁺ B cells and CD56⁺ NK cells normalized, but she remains T-cell lymphopenic.

Chylothorax is a known complication of cardiothoracic surgery and most commonly occurs secondary to direct injury to the thoracic duct. The thoracic duct originates in the cisterna chyli and runs superior along the vertebral column, terminating in the junction of the left subclavian artery and internal jugular vein.²⁰ The main function of the thoracic duct is to transport alimentary fats into the systemic circulation. It does this by draining chyle that originates in the gastrointestinal tract, liver, abdominal wall, lower extremities, upper left extremity, and left side of the head and neck. Lymphatic flow depends on diet, drug intake, gastrointestinal absorption, and the degree of motility.²¹

The incidence of chylothorax has increased to more than 5% in the past decade and is a significant cause of morbidity and mortality in patients with congenital heart disease. Chylous fluid typically appears milky white or turbid but may appear clear, depending on the level of fat in the diet. Chyle is rich in

TABLE II. Conditions with low or absent TRECs and T-cell lymphopenia*

Condition
Primary T cell lymphopenia
Typical SCID
Leaky or variant SCID
Idiopathic T cell lymphopenia
Secondary T-cell lymphopenia
Lymphocyte extravasation
Thoracic duct ligation
Chylothorax or chyloperitoneum
Gastroschisis
Hydrops
Neonatal cardiac surgery with thymectomy
Known disorders
DiGeorge syndrome (22q11.2 microdeletion syndrome)
Ataxia telangiectasia
Trisomy 21
CHARGE syndrome
Jacobsen syndrome
Phagocyte defect associated with RAC2 [−] mutation
DOCK8-deficient hyper-IgE syndrome
Cartilage-hair hypoplasia
Congenital anomaly
Gastrointestinal atresia
Others
Extreme prematurity
Neonatal leukemia

*Adapted from reference 12.

triglycerides, cholesterol, fat soluble vitamins, digestive enzymes, lymphocytes, and immunoglobulins.²¹ Pleural fluid analysis assists with the diagnosis of chylothorax. A pleural fluid triglyceride concentration higher than 110 mg/dL supports the diagnosis, but many cases of chylothorax with low pleural fluid triglyceride levels have been reported.^{22,23} Enteral fat intake strongly contributes to the high triglyceride counts within the pleural fluid. Chyle electrolyte content is similar to that of plasma and typically has a high protein concentration and low lactate dehydrogenase levels. Cell counts typically demonstrate higher than 80% lymphocytes.²⁴ Varying amounts of hypogammaglobulinemia and lymphopenia can be associated.²⁵ Chest radiograph may demonstrate pleural effusion but is unable to elucidate the etiology of the accumulated fluid.²⁶ Computed tomography of the thorax and abdomen may be useful in evaluating the thoracic duct route, lymphadenopathy, masses, or lymphangioma-appearing cystic lesions.²⁷ Lymphatic imaging, such as lymphangiography and lymphoscintigraphy, may be performed when the etiology and leakage location are unknown.^{28,29}

Despite the extreme lymphopenia and hypogammaglobulinemia that can accompany patients with chylothorax, there does not seem to be increased risk of infection characteristic of patients with hypogammaglobulinemia or T-cell immunodeficiency.^{30–32} Orange et al²⁵ described the immunologic profile of 8 patients with chylothorax aged 1–25 months. Seven had undergone cardiac or thoracic surgery and 6 of the 7 had traumatic injuries of the thoracic duct that led to chylothorax. All the

patients were hypogammaglobulinemic with low IgG and normal IgA and IgM. Absolute lymphocyte counts, CD3⁺, CD4⁺, CD8⁺, and CD19⁺ cells were consistently low, but, in contrast, circulating NK cell counts (CD56⁺) were preferentially maintained and normal. There was preferential loss of naive CD4⁺ T cells (CD4/CD45RA⁺) in chyle that led to low levels of CD4⁺/CD45RA⁺ T cells in the serum. T-cell function was preserved as assessed by specific antibody levels and by mitogen and antigen proliferation assays.²⁵ Kovacikova et al³⁰ noted similar levels of T- and B-cell depletion and maintenance of NK cells among 16 study subjects, age 28 days to 5 years, with chylothoraces. All the patients in the study by Orange et al²⁵ and 4 in the study by Kovacikova et al³⁰ received immunoglobulin replacement. There was no increased incidence of infections in either patients who had or who had not received IVIG. In agreement with these data, our patient had no infections other than the development of an *Enterobacter cloacae* wound infection in the midline incision. *E. cloacae* is a gram-negative, catalase-positive anaerobic bacillus that is a common enteric flora and is a cause of common community acquired infections, including urinary tract infections and skin and soft tissue infections. More commonly, it is a cause of nosocomial bacteremia, pneumonia, wound infections, urinary tract infections, and meningitis. *Enterobacter* species are among the most common cause of surgical site infections in patients within the intensive care unit.³³ Although patients with lymphopenia associated with chylothorax are not at increased risk of opportunistic or bacterial infections associated with T-cell immunodeficiency or hypogammaglobulinemia, they are at increased risk of nosocomial infections. Wasmuth-Pietzuch et al³² showed that 4 of 7 patients with congenital chylothorax and lymphopenia developed 1 nosocomial infection; 2 developed a second nosocomial infection. Recurrent skin infections with gram-negative organisms may lead to consideration of immunodeficiency, but, *E. cloacae* wound infection in this patient was more consistent with a nosocomial postoperative complication and was not considered as a specific infection susceptibility related to immunodeficiency.

Treatment strategies for chylothorax are aimed at decreasing the flow of lymph to allow the thoracic duct to heal. Dietary modification with exclusion of all fats except medium chain triglycerides is the first-line treatment. Medium chain triglycerides enter directly into the portal circulation, bypassing the lymphatic system.³⁴ If low-fat medium chain triglycerides enriched diet fails, then total parenteral nutrition and enteral rest are recommended.³⁵ High-output chylothoraces that do not respond to dietary changes may be treated with octreotide, a somatostatin analog that decreases lymph production and splanchnic blood flow.³⁶ The use of IVIG in the management of chylothoraces has been controversial. Multiple studies have shown no reduction in the rate of infections in patients treated with IVIG.^{25,30,37,38} Surgical intervention, including thoracic duct ligation,³¹ pleuroperitoneal shunt, or pleurodesis, are typically considered after the patient fails 2 to 4 weeks of medical management.

In the age of newborn screening for SCID, allergists-immunologists will be faced with patients such as ours with abnormal newborn screens that lack a typical presentation of SCID. Although false positives can occur, they are rare, and there should be a high suspicion for immunodeficiency in patients with abnormal TREC analysis on newborn screens. Thoracic duct injuries are common complications of surgical repair of

congenital heart disease. Lymphatic loss can lead to profound but reversible lymphopenia and hypogammaglobulinemia that can be compounded by the loss of thymic tissue perioperatively. Secondary causes of lymphopenia are common among those patients with abnormal newborn screens and should be considered in patients with previously normal screens.

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