



Neonatal Review

In this issue... Volume 2, Number 11

The primary immunodeficiency diseases comprise a family of diseases which have in common intrinsic defects in the individual components of the immune system. There are over 125 of these disorders, most of which are genetically determined, with the most common clinical presentation being an increased susceptibility to infection. However, some of the primary immunodeficiency diseases are also found as part of a larger clinical syndrome, and their initial clinical presentations relate to the other clinical findings of the syndrome rather than to the immunodeficiency per se. Further, in addition to presenting with clinical manifestations, many patients can be ascertained based exclusively on a positive family history of a previously affected family member.

Two of these primary immunodeficiency disorders are of special interest to the neonatologist:

describes over a dozen molecular genetic defects which result in a severe deficiency of both T and B lymphocyte number and function. In spite of the different molecular genetic defects responsible for the disorder, patients are almost uniformly susceptible to a wide variety of common and opportunistic infections, and, if left untreated, usually succumb by one year of age (if not earlier). Therefore, presymptomatic diagnosis and therapy are critical.

The describes children with developmental defects relating to the 3rd and 4th pharyngeal pouch, which may result in variable degrees of hypoparathyroidism, conotruncal cardiac defects, thymic aplasia with T cell deficiency, and a variety of facial, gastrointestinal and developmental defects. Infants with this primary immunodeficiency usually present in the first few weeks of life and therefore are often diagnosed by the neonatologist.

In this issue we review important new contributions to the understanding of these two primary immunodeficiency diseases as they relate to neonates.

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Learning Objectives

The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing take responsibility for the content, quality, and scientific integrity of this CE activity.

At the conclusion of this activity, participants should be able to:

- Recognize which primary immunodeficiency diseases may likely present in the neonatal period;
- Evaluate the potential outcomes advantages of presymptomatic diagnosis of Severe Combined Immunodeficiency disease;
- Recognize the clinical presentation of the DiGeorge Syndrome.

Program Information

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LENGTH OF ACTIVITY
0.5 hours

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Guest Editor of the Month



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Guest Faculty Disclosure

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COMMENTARY

The age at which primary immunodeficiency diseases first present clinically depends on whether the deficient component of the immune system crosses the placenta and is at least initially supplied by the mother. For example, pure B lymphocyte defects, such as X-linked agammaglobulinemia, usually don't present until the second 6 months of life, since maternal transfer of IgG effectively supplies adequate replacement therapy during the prior 6 months. In contrast, virtually all phagocytic disorders, such as Chronic Granulomatous Disease and Leukocyte Adhesion Defect, can present in the neonatal period. Although uncommon, deficiencies of the complement system also can present in the neonatal period, as individual components of complement do not cross the placenta. In addition, T cell defects may also present in the immediate neonatal period, since there is normally no maternal transfer of T cells, or, if there is, such maternal transfer is inadequate to correct the infant's deficiency.

Therefore, neonatologists may be the first to encounter and diagnose infants with these primary immunodeficiencies. The critical criteria in the diagnoses of these disorders are knowledge of the disease state plus a high index of suspicion.

In spite of many advances in the diagnosis and therapy of patients with SCID, a significant portion of patients are not diagnosed until after they develop serious infections; their survival is therefore compromised even if they are provided immune reconstitution (e.g. via stem cell transplant). While obtaining a positive family history would be advantageous in families with a previously affected infant, this is not always possible. For example, in some instances, the family may be unaware of an uncle or great uncle who died of the X-linked recessive form of the disease many years before, while in other instances an older sibling may have died without a definitive diagnosis. In addition, over half of SCID patients are born into a family without a positive family history for the disorder because the molecular genetic form is inherited as an autosomal recessive trait.

In the absence of a positive family history, the presence of significant lymphopenia (<3,500

lymphocytes/mm³ for newborns), a nearly constant feature of SCID, can be an important clue to the presence of the disorder; however, not all newborns have a CBC and differential performed, and not all physicians are alert to the significance of lymphopenia. Thus, there has been a great deal of consideration given to screening for SCID, especially since recent evidence documents what seems clinically intuitive: that early diagnosis and therapy improve survival.

The Buckley, Myers, and Chan articles reviewed this issue provide important information about how early diagnosis and treatment of SCID patients can improve long-term outcomes. These additions to our SCID knowledge-base should help increase the incidence of presymptomatic (before infection occurs) identification and diagnosis, thereby significantly improving the survival of these infants.

The DiGeorge Syndrome — with its associated cardiac abnormalities, hypocalcemia, and gastrointestinal defects usually presenting in the first few weeks of life — is the most common primary immunodeficiency encountered and diagnosed by Neonatologists. Although significant and persistent T cell defects are found in a small minority of patients, the early identification of the T cell deficiency, when it occurs, is important. These patients are usually diagnosed as immunodeficient before they develop infections. The presence of conotruncal defects, hypoparathyroidism as a cause of the hypocalcemia and/or the abnormal facies and GI defects are the usual clinical findings that lead to the diagnosis of DiGeorge — which in turn leads to the presymptomatic diagnosis of the immunodeficiency. While lymphopenia may be present in some patients with the most severe immunodeficiency, it should be noted that only 90-95% of patients who have the clinical syndrome have a large enough deletion to be picked up by Fluorescent In Situ Hybridization (FISH). Thus, a FISH test that fails to show the deletion does not rule out the diagnosis.

The Sullivan, Yagi, and Markert articles reviewed herein enlarge and clarify the clinical and immunologic findings in this interesting disorder, provide insight into the newest molecular genetic analysis, and offer a new and novel therapy that is of benefit to those patients with significant and persistent T cell defects.

Patients with primary immunodeficiency undoubtedly benefit from early diagnosis and treatment, and it is we NICU providers who will play a most critical role in the diagnosis and initiation of therapy.

SEVERE COMBINED IMMUNODEFICIENCY (SCID)

Buckley, RH

Molecular defects in human severe combined immunodeficiency and approaches to immune reconstitution.

Ann Rev Immunol 2004;22:625-55

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Myers, LA, Patel, DD, Puck, JM, Buckley, RH.

Hematopoietic stem cell transplantation for severe combined immunodeficiency in the neonatal period leads to superior thymic output and improved survival.

Blood 2002; 99:872-8.

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Chan K, Puck, JM.

Development of population-based newborn screening for severe combined immunodeficiency.

J Allergy Clin Immunol. 2005;115:391-8.

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Reporting on advances in understanding, diagnosing, and treating this disorder.

Buckley et al provide critical information about the most recent advances on the molecular genetic bases of this uncommon primary immunodeficiency disease. The authors report that there are at least 9 different molecular genetic defects responsible for this clinical syndrome, each of which results in a severe deficiency of both T and B lymphocyte number and function. Three of the defects affect important components of cytokine receptors, three are essential for T cell antigen receptor rearrangement, one affects the delta component of CD3 antigen receptor, one affects the intracellular metabolism of the T cell, and one affects the signaling threshold of lymphocytes. The authors discuss bone marrow transplantation (HLA identical unfractionated and T cell-depleted HLA haploidentical), both of which have been very successful in effecting immune reconstitution. They note that these interventions produce the best results if done in the first 3.5 months of life without pretransplant chemotherapy. Of particular importance is that, while gene therapy had been highly successful in nine infants with X-linked SCID, trials have currently been placed on hold due to complications (leucemia) in two of the children.

Myers et al performed a retrospective chart review on SCID patients transplanted at a single center (Duke). While there are a variety of stem cell transplantation techniques that are available for immune reconstitution of SCID - HLA identical (usually from an HLA identical sib), haploidentical (usually from a parent), and matched unrelated (usually from an unrelated but HLA matched donor entered into a world wide computer data base) — this review focused not on comparing one technique to another, but on determining whether infants transplanted early (<1 month of age) did better than those transplanted later (>1 month of age).

The authors report that infants who received transplants before 28 days developed higher T lymphocyte counts and higher lymphocyte responses to mitogens than did infants who were transplanted after the immediate neonatal period of 28 days. Importantly, survival of those patients transplanted in the first 28 days of life was 95% (versus 74% in the >28 day group). Also noted is that 6.6 months is the mean age at which children are diagnosed with SCIDS, a point where most of the patients have already suffered from recurring infections with weaning from maternal antibody protection. The authors conclude that prenatal screen of affected families and/or general screening of all newborns using cord-blood white blood cell count and a manual differential count could lead to earlier diagnosis and therapy and improved long-term outcomes.

Seeking to produce a proof of principal that early diagnosis and therapy of SCID can result in improved survival, the pilot study by Chan et al sought to develop a screening method to detect newborns with SCID before they acquired infections that could compromise their survival. As T lymphocytes mature, T cell receptor excision circles (TRECs) are produced as a result of DNA rearrangement and excision. These accumulate in the T lymphocyte as it develops and are an indirect measure of T lymphocyte maturation and development that can be analyzed and quantified by PCR.

In this study, dried blood spots obtained from normal neonates and from 2 patients with known SCID were analyzed for TRECs. Normal newborns had an average of 1020 TRECs in two 3-mm punches, while infants with SCID had <30 TRECs. These results allowed the authors to estimate an incidence rate for SCIDS (1/105,000 births); as importantly, they were able to demonstrate the potential superiority of TREC screening (dried blood) over lymphocyte count screens which requires liquid blood collection.

THE DIGEORGE SYNDROME

Sullivan KE.

The clinical, immunological and molecular spectrum of chromosome 22q11.2 deletion syndrome and DiGeorge Syndrome.

Curr Opin Allergy Clin Immunol 2004;4:505-12.

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Yagi, H, Furutani y, Hamada H, et al

Role of TBX1 in human del22q11.2 syndrome.

Lancet 2003; 362:1342-3.

 [view journal abstract](#)

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Markert ML, Sarzotti M, Ozaki DA et al

Thymus transplantation for complete DiGeorge Syndrome: Immunologic and safety evaluation in 12 patients.

Blood. 2003 Aug 1;102(3):1121-30. Epub 2003 Apr 17.

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Exploring the clinical spectrum of the disorder, its genetic determinant, and a novel therapeutic approach.

The DiGeorge Syndrome, or 22q11.2 deletion syndrome, is one of the most common genetic syndromes found in the NICU, with an incidence (under)estimated at 1:6000 births. The disorder is characterized by hypoparathyroidism and hypocalcemia, conotruncal cardiac defects, thymic hypoplasia or aplasia, and a variable concurrent T cell deficiency and abnormal facies. In addition, affected patients have a variety of midline gastrointestinal defects including esophageal atresia and malrotation, cleft lip and palate, and CNS developmental abnormalities.

The Sullivan article provides a thorough overview of this disorder, discusses its variable phenotype and penetrance, and presents a comprehensive review of its clinical presentation, diagnosis, and therapy. The author notes that familiarity of providers with the disease doubles the likelihood of early detection and is critical in the timely diagnosis and treatment.

While the DiGeorge Syndrome has long been appreciated to involve a gene residing on the 22nd chromosome (since deletion of 22q11.2 has led to the clinical syndrome), the exact identity of the gene responsible for this complex developmental embryonic defect has been unknown. Yagi et al explored the molecular genetic findings relating to this area of chromosome 22 in 235 patients with the 22q11.2 deletion syndrome, examining in detail the genes residing in the area of chromosome 22 that is commonly deleted in this syndrome. As they could not examine each of these genes for mutations in those patients who carried the deletion (since the gene would not be there!), they focused on the relevant genes in patients who had classic DiGeorge Syndrome but did not have a deletion.

Based on their own analysis of patients with the deletion, one specific candidate gene was . They therefore examined 10 families with clinical features of DiGeorge Syndrome but no deletion and found a strong association with mutations in the gene. The authors' results strongly suggest that is a major genetic determinant of the 22q11.2 deletion syndrome, accounts for its clinical presentation in a significant number of patients with DiGeorge Syndrome, and is likely responsible for five major phenotypes — abnormal facies (conotruncal anomaly face), cardiac defects, thymic hypoplasia, velopharyngeal insufficiency with cleft palate, and parathyroid dysfunction with hypocalcaemia. Further, their results indicate that mutation is most likely not linked to the mental retardation that is commonly seen in patients with del22q11.2 syndrome.

The identification of as a cause of the DiGeorge Syndrome is a major step forward in diagnosis of these patients, especially since between 5 and 10% of patients with the DiGeorge Syndrome do not have a deletion and therefore have been diagnosed purely on

clinical grounds. In addition, the identification of _____ will also contribute significantly to our understanding of the pathogenesis of this complex syndrome as well as to the role of _____ in normal development.

Although thymic hypoplasia occurs with some regularity in the DiGeorge Syndrome, clinically significant T cell deficiency is relatively uncommon — nevertheless, complete T cell deficiency does occur in a small minority of patients with the DiGeorge Syndrome and can be an important cause of morbidity and mortality. Markert et al report on the result of thymic epithelium transplantation in the "complete DiGeorge Syndrome", a term used to indicate T cell deficient patients with this disorder. These patients possess stem cells but lack the thymic epithelium microenvironment that is necessary for the development of mature and functionally competent T cells. In this novel therapy, thymus is cultured in vitro until only thymic epithelium remains — it is this thymic epithelium that is transplanted.

The results in this first series of patients have been very encouraging, with over half of the patients receiving this transplant developing immunologic function. Deaths were almost exclusively related to non-immunologic problems associated with the DiGeorge Syndrome. As DiGeorge Syndrome, if left untreated, is usually fatal within 2 to 3 years, the remarkable survival rate of 58% with thymic epithelium transplant is a major achievement in the treatment of primary immunodeficiency — especially considering the fact that patients with DiGeorge often have other congenital problems that impact on overall survival. Despite these favorable outcomes, many questions remain, particularly in regards to the mechanism of "thymic education", and await resolution through long-term outcome studies.

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- Dr. Nogee has indicated a financial relationship of grant/research support with Forest Laboratories and has received an honorarium from Forest Laboratories.
- Dr. Lawson has indicated a financial relationship of grant/research support from the NIH. He also receives financial/material support from Nature Publishing Group as the Editor of the Journal of Perinatology.

All other faculty have indicated that they have not received financial support for consultation, research, or evaluation, nor have financial interests relevant to this e-Newsletter.

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