Review

Primary immunodeficiency in the neonate: Early diagnosis and management

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SUMMARY

Many primary immunodeficiencies (PIDs) manifest in the neonatal period but can be challenging to diagnose and manage optimally. In part, the difficulty stems from the natural immaturity of the neonatal immune system that may mask immune deficits and/or complicate interpretation of clinical findings and laboratory assays. The great diversity of PIDs — from innate immune system defects to those that impact the humoral and/or cellular components of the adaptive immune system — and the rapid rate at which new PIDs are being discovered makes it challenging for practioners to stay current. Moreover, recent appreciation for immune deficiencies that lead to autoinflammation and autoimmunity have broadened the spectrum of neonatal PID, adding additional complexity to an already intricate field. This article serves to highlight the deficiencies in the neonatal immune system, while providing a review of the more common PIDs that present in the neonate and guidelines for diagnosis and supportive care.

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1. Introduction

More than 200 novel primary immunodeficiencies (PIDs) are currently recognized by the World Health Organization [1]. Many of these disorders are rare. However, collectively PIDs in the USA are estimated to occur in one in 1200 live births [2], emphasizing the need for all practioners, including those caring for neonates, to be vigilant for immune deficiencies. Recognizing and managing immunodeficiency in the neonate is challenging. Nonetheless, the early diagnosis of PIDs is critical for optimal treatment and improved outcomes. This review serves to outline physiologic immune deficits in the neonate and, more importantly, to highlight concepts in recognizing PIDs while providing guidance for the initial steps in management for the practising neonatologist.

2. Physiologic immune deficits in the neonate

Much like the other organ systems, the neonatal immune system — both the innate and adaptive arms — develops in phases throughout gestation starting in early embryogenesis and continuing its maturation for months to years in the postnatal period.

The neonatal innate immune system relies on granulocytes (predominantly neutrophils), antigen-presenting cells such as macrophages, natural killer (NK) cells and complement. The kinetics of neutrophil production in the newborn differ from those of older children and adults. Immediately following birth, neonates have a surge of neutrophils in the peripheral blood, reaching levels as high as 14,500–28,000 cells/μL for term and 14,000–41,000 cells/μL for preterm infants before gradually returning to near-normal adult levels by 10 days of life [3,4]. Preterm infants of <32 weeks of gestation have reduced neutrophil production, reduced total body neutrophil mass and reduced surplus proliferative capacity of granulocyte precursors at birth translating into an inability to adequately increase phagocyte production under stress, e.g. sepsis [5]. In addition to the quantitative defects described, neutrophils in the neonate are also flawed functionally with appreciable defects in adhesion [6], chemotaxis [7], production of free oxygen radicals [8] and neutrophil extracellular trap formation [9].

Similarly, neonatal macrophages demonstrate a decreased response to pathogen-derived products, e.g. lipopolysaccharide and stimulatory cytokines [10], resulting in less effective pathogen killing [11]. NK cells are present in adequate numbers but their cytotoxicity is diminished and cytokine production altered, limiting their effectiveness [12]. Lastly, whereas neonates express

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components of the complement system including C3, C4, and total hemolytic complement (CH50), their levels do not reach adult thresholds until 12–18 months of life, decreasing the quality of opsonization. These defects in the neonatal innate immune system place infants at risk for serious bacterial, viral, and fungal infections including group B streptococci, *Escherichia coli*, herpes simplex virus, cytomegalovirus (CMV), varicella-zoster virus, respiratory syncytial virus (RSV), and *Candida* species [13].

The adaptive arm of the immune system consists of B- and T-lymphocytes, which respectively contribute to the humoral and cellular immune responses. The humoral immune system remains underdeveloped at birth. B-cells are present in higher numbers in infants than in adults [14]. However, the neonate is almost exclusively dependent on passively acquired maternal immunoglobulin G (IgG), which passes through the placenta predominantly during the third trimester of gestation [15], until several months of age. Preterm infants at <32 weeks of gestation have significantly less serum IgG and nadir lower and earlier than their term counterparts [16]. Maternally derived IgG may wane faster with repeated phlebotomy, surgery and infection. IgA, IgM and IgE do not pass through the placenta and are present only in low levels in all neonates. Neonates can mount antigen-specific antibody responses, although at a lower intensity than adults and often with delayed isotype switching. These deficits in antibody production render the neonate less competent at opsonization and more vulnerable to infection.

With regards to the cellular immune system, all newborn infants have a highly significant increase in absolute numbers of T-cell as compared to normal adults [14]. A total absolute lymphocyte count of <2500 cells/μL or a total CD3 T-cell count of <1500 cells/μL in the neonatal periods suggests a T-cell deficiency. T-cell function is partially intact at birth, although T-cells have decreased effective cytotoxicity and preterm infants have a less robust mitogen proliferative response. This physiologically diminished T-cell function leaves the neonate susceptible to both infection and autoimmunity.

3. Recognizing and evaluating primary immunodeficiency in neonates

Identification of PIDs in neonates is extremely complex, yet it is critical to diagnose these disorders before severe infection and subsequent organ damage occurs. Physical exam findings outside of a handful of syndromic disorders are typically normal. Family histories may be unrevealing as many disorders are inherited in an autosomal recessive or X-linked fashion, but a history of early/unexplained deaths, multiple miscarriages, atypical infections, or immune dysregulation should raise suspicion for a PID. Many immunodeficiencies in older children are recognized by history of frequent, severe and/or atypical infections. However, neonates lack sufficient exposures to use infections as a singular guiding principle for initiating investigation. Immaturity of the neonatal immune system makes testing and interpretation of results difficult. Basic immune laboratory tests may be normal; sometimes, if they are abnormal, they may not discriminate between PIDs, necessitating more complex diagnostic assays that are not readily available. Recognition that autoinflammation and autoimmunity – referring to conditions with pathologic activation of the innate and adaptive immune systems, respectively – may also be associated with PIDs is important [17]. Although it is not intuitive that an immune deficiency can actually have the capacity to activate and cause significant disease, it is now appreciated that a functional immune system is also critical to maintain self-tolerance [17].

Initial work-up for PIDs consists of basic immunology testing as outlined in Table 1. Abnormal results and/or high suspicion of PIDs should trigger consultation by physicians with immunology

expertise. Also, disease manifestations may evolve over time, so close monitoring and follow-up immune evaluation should occur in patients with high suspicion but negative initial testing.

Special mention of the TREC assay should be made as its incorporation into newborn screening has been a tremendous advancement in the early diagnosis of PIDs. T-cell receptor excision circles (TRECs), circular fragments of DNA that form during T-cell development, can be detected via polymerase chain reaction from dried blood spots on Guthrie cards [18]. Absence of TRECs indicates concern for a T-cell maturation defect. At the time of this publication, 34 states, the District of Columbia, and the Navajo nation currently utilize the TREC assay with eight states planning to begin screening in 2015 [19]. The list of T-cell lymphopenic conditions identified by the newborn screen is long [20]. 22Q11.2 deletion syndrome and severe combined immune deficiency (SCID) are the most widely identified disorders followed by trisomy 21, ataxia-telangiectasia, CHARGE (coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, ear anomalies/deafness), and Jacobsen syndrome [20]. Neonates with very low TRECs should prompt evaluation of PIDs but may also result from a secondary cause of T-cell loss including egress of T-cells into third spaces, thymic removal following cardiac surgery, gastrointestinal disease resulting in T-cell loss, and neonatal leukemia [20].

4. Well-characterized primary immunodeficiencies that present in the neonatal period

The following section describes the more frequently occurring PIDs that may present very early in life and that are categorized based on the predominant defect or manifestation of disease.

4.1. Disorders of the innate immunity

4.1.1. Severe congenital neutropenia (SCN)

Severe congenital neutropenia is a heterogeneous group of disorders characterized by severe neutropenia with a peripheral blood absolute neutrophil count (ANC) < 500 cells/μL, maturation arrest of bone marrow myeloid precursors at the promyelocyte/myelocyte stage and recurrent bacterial infections [21]. The estimated frequency is one or two cases per million [22]. SCN may be identified incidentally on routine complete blood counts or present with sepsis, skin abscesses, gingivitis, aphthous ulcers and/or recurrent fevers. Diagnosis includes a bone marrow biopsy demonstrating maturation arrest of myeloid precursors followed by genetic testing. Autosomal dominant, X-linked, and sporadic causative gene mutations exist with the majority (50–60%) of patients having an *ELANE* mutation [23].

Before the introduction of modern therapies, SCN was highly fatal with 50% mortality in the first year of life from bacterial sepsis [24]. Treatment with granulocyte-stimulating factor (G-CSF) is standard treatment, but patients who avoid sepsis death may later develop myelodysplastic syndrome or leukemia [24]. A minority (10%) of patients fail to achieve sufficient increase in neutrophil count despite high doses of G-CSF [25] and should be considered for early hematopoietic cell transplantation (HCT).

4.1.2. Leukocyte adhesion deficiency, type 1 (LAD-1)

In response to tissue injury, neutrophils follow a chemotaxin gradient to the site of inflammation, roll along the endothelial border, attach at the site of inflammation, and squeeze through the endothelial cell wall barrier [26]. Defects in proteins necessary for this process result in LAD. LAD-1 is an autosomal recessive disorder due to mutations in the *ITGB2* gene, which results in loss of CD18, the β subunit of the leukocyte β2 integrins, necessary for cellular adhesion [26]. LAD-1 presents with severe and recurrent bacterial