FT03

Immunodeficiency In The Human Newborn

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Abstract

The normal neonate's immune system is anatomically intact, antigenically naive, and shows somewhat decreased role of a number of immunological pathways. Aside from anatomic characteristics (eg, thin skin and mucosal barriers) of newborn, weakened proinflammatory and T helper cell type 1 (Th1) cytokine release and lessened cell-mediated immunity predispose the neonate more susceptible to all types of infections. However, most of the newborn stand this period without sickness due to intact innate immunity with other adaptive defense mechanisms, and maternally transferred immunoglobulin G (IgG).

Besides unique immunity of the premature baby and normal newborn; risk factors, clinical features and laboratory evaluation of primary immunodeficiency diseases (PIDs) are told in this presentation. Moreover, most important PIDs of the newborn including antibody deficiencies, cellular/combined immunodeficiencies, phagocytic diseases, complemento-pathies and innate immune system disorders are briefly mentioned here as well.

Background

The premature and normal newborns have a unique immunity. The innate and adaptive immune systems modify as they grow old. Many parts of the immune system in the healthy newborn are dissimilar since it is intended to facilitate the transition from intrauterine to outside world.

Prematurity:

Premature infants have immune defects consistent with their degree of immaturity. Accordingly, it can be hard to differentiate a premature infant with PID from an infant who is just premature, unless there is a positive family history of PID. Compared with the term infant, the preterm demonstrates fragile skin, moderate to severe hypogammaglobulin-emia, lower lymphocyte counts, weaker proinflammatory / Th1-polarizing cytokine responses, and lower plasma complement and antimicrobial protein / peptide levels, rendering the preterm infant particularly susceptible to infection.

Physiologic hypogammaglobulinemia of infancy (PHI):

Maternal IgG is existent at birth and disappears over several months, with a steady maturation of B cells to plasma cells able to synthesize immunoglobulins in the infant. This leads to PHI, with serum IgG levels <400 mg/dL from roughly 3 to 6 months of age.

Risk Factors For Primary Immunodeficiencies

Factors increasing mostly risk of PID in a neonate include: The most predictive factor for a PID is a family history of immunodeficiency, confirmed or suspected, leading to early death or recurrent/chronic illness in one of more family members. Some newborns inherit a genetic immune defect manifesting at birth or early infancy, named as PID. PIDs are occurring in up to approximately 1 out of 1.200 individuals. Certain ethnic groups with founder mutations (eg, severe combined immunodeficiency [SCID] in Navajos, ataxia-telangiectasia in Amish, and Bloom syndrome in Ashkenazi Jews) or countries or populations where there is a high incidence of consanguinity (Amish, many Arab countries) have a higher incidence of immunodeficiency.

CLINICAL FEATURES SUGGESTIVE OF PRIMARY IMMUNODEFICIENCIES

A newborn at birth or during the first months of life might exhibit signs and symptoms indicative of immunodeficiency, below. These signs and symptoms are following: Syndromic look (abnormal facies); infection at any location; infection as a result of live vaccines (eg, rotavirus, Bacille Calmette-Guerin [BCG], oral polio); failure to thrive; chronic diarrhea; abdominal distention; lymphadenopathy and/or hepatosplenomegaly; lung or cardiac disorder; mucosal diseases eg thrush, mouth sores, and ulcerations; skin rashes, pigmentary disorders, or alopecia; petechiae, melena, bleeding; and late separation of umbilical cord.

Laboratory Evaluation For Primary Immunodeficiencies Of Newborn

Screening laboratory tests and preliminary evaluation should be done if one or more of the risk factors for immunodeficiency are available. PIDs may also be demonstrated on neonatal screening.

Initial screening in the newborn includes a complete blood count with differential and Ig levels. However, measuring quantitative Ig levels (IgG, IgA, IgM, and IgE) is less useful in neonate because they produce only small amount of Igs and most of the IgG in early **infancy is transferred IgG from the mothers.**

Leukopenia is described as a white blood cell (WBC) count: <4.000 cells/ µL. Lymphopenia is described as an absolute lymphocyte count <2.500 (3.000) cells/µL in infants and suggests a T- and/or B- cell defect. Mild neutropenia is described as a neutrophil count 1.000-1.500 cells/µL, moderate neutropenia 500-1.000 cells/µL, and severe neutropenia <500 cells/µL. Neutropenia <100 cells/µL is life threatening. Neutropenia in the neonate can be triggered by sepsis, necrotizing enterocolitis, maternal autoimmune disorders or medications, or primary phagocyte disorders. Thrombocytopenia may be owing to PID (eg, in Wiskott-Aldrich syndrome [WAS]) or related with infection (eg, fungal or cytomegalovirus [CMV] infection).

T-, B-, and natural killer (NK)- cell identification by flow cytometry is requested if lymphopenia is observed on a CBC with differential, or if SCID is assumed even in the case of a normal lymphocyte count. This procedure enumerates CD3+ cells (T lymphocytes), CD3+CD4+ cells (T helper cells), CD3+CD8+ cells (T cytotoxic cells), CD19+ or CD20+ cells (B lymphocytes), and CD3-CD16/56+ cells (NK cells). This test will discover most infants with SCID or complete DiGeorge syndrome and may give guidance as to the character of the T-cell defect. If a T-cell defect is thought, the preliminary test for T-cell function is a lymphocyte proliferation assay. Neonates demonstrate lymphoproliferation to nonspecific stimuli, such as the mitogen phytohemagglutinin or anti-CD3, but not to most antigens.

Newborn screening:

T-cells are released from the neonatal thymus in a large amount, hence accounting for the high numbers of circulating lymphocytes in the neonatal blood. T-cells constitute nearly fifty percent of the lymphocytes in the first year of life. Circulating T-cells in the neonate's blood (including heel stick blood) can be predicted by determining T-cell receptor excision circles (TRECs), a derivative of thymic production of freshly made T-cells.

Specific (Primary) Immunodeficiency Disorders Of Neonate

Once an immunodeficiency disorder is doubted, the next phase is to define whether the immunodeficiency is likely to be the normal physiologic susceptibility of a newborn and/or heightened by additional factors causing a secondary/acquired immunodeficiency (eg, prematurity, blood loss due to phlebotomy or surgery), or a PID owing to an underlying genetic defect changing the immune system function.

Antibody Deficiencies:

Antibody deficiency typically causes to frequent, often severe, upper and lower airway infections with encapsulated bacteria (eg, *Streptococcus pneumoniae, H. influenzae*). Children usually are brought with recurrent otitis media, sinusitis, and pneumonia. Frequent

accompanying findings in children include poor growth, failure to thrive, recurrent fevers, and chronic diarrhea.

A neonate with hypogammaglobulinemia (serum IgG: <400 mg / dL, severe <200 mg / dL) is infrequent, even regardless of low or absent B cells. The most common reason is prematurity with exaggerated physiologic hypogammaglobulinemia. Another explanation may be a low maternal IgG level with lessened transplacental IgG passage.

Infants including neonates with congenital agammaglobulinemias usually have low B cells and absent or very low IgM and IgA and do not become hypogammaglobulinemic until after the 3rd month of life, because of the existence of transplacental maternal IgG. However, the diagnosis can be made prenatally in families with a history of agammaglobulinemia by genetic testing or assaying B cells on a fetal blood sample. The presence of a female fetus on ultrasound or chromosome analysis on prenatal blood makes X-linked agammaglobulinemia very unlikely. Routine kappa-deleting recombination excision circles (KRECs) testing at the time of birth is a planned screening method.

Cellular/Combined Immunodeficiencies:

Infants with cellular immunodeficiency have deficiencies of both T-cell immunity and antibody immunity (combined immunodeficiency [CID]). They characteristically manifest in early infancy due to the defect in cellular immunity, especially those with a severe defect.

Severe Combined Immunodeficiencies (Scids):

SCIDs are defined by severe defects in both cellular and antibody deficiency. Most affected infants seem to be normal at birth, but develop severe infections with organisms that include viruses, bacteria, and fungi within the first few months of life. Stark complications may happen after routine immunization with live-virus vaccines. Related findings include chronic diarrhea and failure to thrive. Other motives to think SCID are lymphopenia on a routine CBC or a chest radiograph demonstrating no thymic shadow. A few infants are noticeable with graft-versus-host disease (GVHD) as a result of transplacental passage of alloreactive maternal T cells or unintentional delivery of viable lymphocytes from a blood transfusion. Manifestations of acute GVHD include maculopapular rash, vomiting, and diarrhea.

Inheritance of SCID is X-linked or autosomal recessive. A family history of the disease is often negative because new mutations are common. Early diagnosis can be made by prenatal tests of fetal blood, by neonatal TREC screening, or by recognition of early manifestations and confirmation by immunologic and genetic testing. Typical laboratory features on initial screening studies include profound lymphopenia with low T cells (<1.500 cells/μL) and absent antibody responses to vaccine antigens. Immunoglobulin synthesis is absent or minimal. Referral to a tertiary medical center for genetic analysis, tissue typing and hematopoietic stem cell transplantation is mandatory when SCID suspected.

Other (Less Severe) Combined Immunodeficiencies:

The most common CIDs that present in the newborn period, or are identified by newborn **screening, and their identifying features are as follows:**

●DiGeorge syndrome: The immunodeficiency can range from recurrent sinopulmonary infections to a SCID phenotype (complete DiGeorge). Associated features include conotruncal cardiac anomalies, hypocalcemia, hypoplastic thymus, and craniofacial abnormalities.

●Wiskott-Aldrich syndrome (WAS): WAS is an X-linked disorder distinguished by thrombocytopenia, small platelets, early onset of eczema, and a CID. The patients manifest with petechiae, melena, and soft tissue bruising, or bleeding after circumcision.

●X-linked hyperimmunoglobulin M syndrome (HIGM): X-linked HIGM often presents in the first few months of life with increased susceptibility to recurrent sinopulmonary infections, opportunistic infections, chronic diarrhea and/or failure to thrive.

●Chronic mucocutaneous candidiasis (CMCC): The patients typically present in the preschool years with chronic noninvasive *Candida* infections of the skin, nails, and mucous membranes, but a few patients manifest in the first months of life, especially those with familial candidiasis.
●Ataxia-telangiectasia (AT): Most AT patients are asymptomatic for the first several years, but a few patients have been identified on newborn TREC screening, in spite of the presence of some T cells.

Phagocyte Defects:
Infection spectrum from phagocytic disorders ranges from mild, recurrent skin infections to overwhelming, fatal, systemic infection. These patients are mostly vulnerable to bacterial (eg, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Nocardia asteroides*, *Salmonella typhi*) and fungal (eg, *Candida* and *Aspergillus* species) infections. Immune response to nontuberculous mycobacteria (NTM) may also be atypical, especially in chronic granulomatous disease (CGD).
●Congenital neutropenia(s): They start around birth and due to genetic defects causing primary bone marrow failure. They include severe congenital neutropenia (<200 cells/ µL; Kostmann syndrome), cyclic neutropenia, and Shwachman-Diamond syndrome.
●Chronic granulomatous disease (CGD): The X-linked type of CGD can present in infancy. It is a genetically heterogeneous disease known by life-threatening infection with specific bacteria and fungi causing to the formation of granulomata over the body.
●Leukocyte adhesion deficiency (LAD): The LADs are a set of disorders described by recurrent bacterial infections and weak wound healing due to defects of neutrophil adhesion and movement. A typical characteristic is delayed separation of the umbilical cord.

Complement Deficiencies:
Novel inherited complement deficiencies are infrequently defined in neonates without a family history of a complementopathy. Screening for a complement defect is necessary in neonates with a positive family history and severe encapsulated bacteria infections eg streptococci, meningococci, or *H. influenzae* type B.

Other Defects In The Innate Immune System:
They include NK cell deficiency syndromes and defects in cytokines and proinflammatory mediators released by innate immune cells, eg Mendelian susceptibility to mycobacteria disease (MSMD).

Conclusion
The normal neonate's immune system is anatomically complete, but antigenically naïve and functionally distinct, with lower inflammatory and Th1 responses, potentially making the newborn more susceptible to infection. Nevertheless, most newborn survive the period without disease because of imperfect innate immunity with other adaptive defense mechanisms and maternal IgG transferred through the placenta.

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