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Primary Immuno-Deficiencies in Pediatrics

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ABSTRACT

Introduction: There are many different types of primary immunodeficiency syndromes, with an overall prevalence of one in every 2,000 children in the United States. These syndromes are broadly classified as B-cell, T-cell, phagocytic, complement, or combined immunodeficiency disorders, mainly affecting children from a very young age.

Methodology: We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE from January 1987 to March 2017. The following search terms were used: immunodeficiency syndromes, B-cell disorder, T-cell disorder, complement disorder, phagocytic diseases, diagnosis of primary immunodeficiency, newborn screening

Aim of the work: In this study we aimed to understand the various common types of primary immunodeficiency syndromes, and also study their diagnosis and screening methods.

Conclusion: Early diagnosis with the help of newborn screening and data recording can help in reducing significant mortality and morbidity of children born with such disorders. Primary health care providers and pediatricians must keep a high degree of suspicion as many times the presentation can be subtle.

Keywords: B-cell disorder, T-cell disorder, complement disorder, phagocytic diseases, diagnosis of primary immunodeficiency, newborn screening

INTRODUCTION

Over 180 primary immunodeficiency diseases had been identified, and that number is increasing as the genetic technology advances allowing further identification of detailed defects of immunity. The prevalence of these diseases differs. In the United States, the overall prevalence of confirmed and diagnosed primary immunodeficiency disease is assessed to be one in 1,200 persons; while among individuals younger than 18 years of age, it is rounded to be one in 2,000[1]. The most common types of primary immunodeficiency disease in pediatric population in the United States are antibody disorders, and then followed by combined B-cell and T-cell disorders, phagocytic defects, and lastly complement disorders[2].

METHODOLOGY

• Data Sources and Search terms

We conducted this review using a comprehensive search of MEDLINE, PubMed and EMBASEfrom January 1973 to March 2017. The following search terms were used: immunodeficiency syndromes, B-cell disorder, T-cell disorder, complement disorder, phagocytic diseases, diagnosis of primary immunodeficiency, newborn screening.

• **Data Extraction**

Two reviewers have independently reviewed the studies, abstracted data and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was done after approval of ethical board of King Abdulaziz University

B-cell/Antibody Disorders

Across the world, antibody disorders are the most prevalent type of primary immunodeficiency disease. Antibody disorders constitute 55% of primary immunodeficiency diseases amongst patients who are entered in the European Society for Immunodeficiency's (ESID) registry; in the United States, 78% comprise an antibody disorder.

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Antibody disorders can be generally characterized by either the absence or presence of B cells[1].When B cells are existent, disorders are further classified by whether the B cells are of normal quantity or quality or not. Clinically, children who have an antibody disorder clinically manifest with recurrent or severe bacterial infections of the sinuses, ears, and lungs, predominantly with encapsulated organisms containing Streptococcus
pneumoniae and Haemophilusinfluenzae. Antibody disorders typically present three months after birth, once maternal immunoglobulin from placental transmission is gone[3].

1. X-linked (Bruton's) a gamma globulinemia

X-linked a gamma globulinemia (XLA) / hypo gamma globulinemia, classically known as Bruton's a gamma globulinemiais; a prototype of humoral immunodeficiency first termed by Bruton in the year 1952. It is an infrequent congenital disease,but is the major primary immunodeficiency recognized in childhood. As an x-linked recessive disorder, the occurance rate of XLA is around 0.5/100,000.[2] XLA happens as a result of mutations in the Bruton tyrosine kinase (Bkt) gene. Patients characteristically show less than 2% of the peripheral B cells and reduced levels of all immunoglobulins that make the affected patients vulnerable to repeated, severe bacterial infections, predominantly invasive extracellular pyogenic microbes. The most usual presenting problems is bronchiectasis, recurrent upper respiratory tract infections, including sinusitis, otitis media and pharyngitis, and recurrent pneumonia. Children who have agammaglobulinemia are born with a complete absence of B cells in their peripheral circulation and in umbilical cord blood. On physical examination, the infant may have no tonsils or lymph nodes. Upon investigation, all immunoglobulin subtypes are diminished, and there is a lack of B cells on lymphocyte subset analysis[4].

Btk mutation also plays a significant role in signal transduction of pre-B-cell receptor (BCR). In one such case report, it was noted that XLA is also linked with precursor B-cell acute lymphoblastic leukemia, which is also the most common malignancy in children. XLA is caused by 600 unalike mutations in the Bruton tyrosine kinase (Bkt) gene. The Bkt gene is mapped on X chromosome at the site Xq21.3-Xq22. It has five domains (PH, TH, SH3, SH2, and TK) and XLA happens as a result of mutation in all these five structural domains[5].

Flow cytometric analysis via the anti-Btk antibody is a powerful diagnostic tool for screening XLA patients to quantify Btk expression in peripheral monocytes.Current treatment options for XLA consist of life long prophylactic therapy with IVIG that maintains some of the missing antibodies, suitable antibiotics for avoidance of acute and chronic infections, nutritional rehabilitation as well asimmunization. If the disease is diagnosed timely, patients can have a good quality of life. With the purpose to decrease the recurrences, amount of hospital admissions and severity of infections, early management with immunoglobulin replacement therapy is essential.Live viral vaccines must be avoided. There is no definitive treatment for XLA, yet the probability of using gene-corrected hematopoietic stem cells to complement the immune defects in mouse models is being studied. It may be encouraged to initiate stem cell-based treatment for XLA using gene-corrected autologous hematopoietic stem cells[4].

2. Common Variable Immunodeficiency

Hypo gamma globulinemia is characterized by low or scarce levels of any of the immunoglobulin including immunoglobulin A [IgA], IgE, IgG and IgM, or by an uncharacteristic response of immunoglobulins to vaccinations. In the ESID registry, 82% of all cases of antibody disorders include a hypo gamma globulinemia, the most described of which is common variable immunodeficiency, adding up to 46% of hypo gamma globulinemias. In common variable immunodeficiency, levels of a minimum of two immunoglobulin types are decreased[6].

In the United States, IgA deficiency is the most prevalent type of B-cell disorder accounting for 30%, followed by IgG subclass deficiency (which are IgG2, IgG3, and IgG4) at 26%, hypo gamma globulinemia (comprising IgG1 subclass) at 23%, common variable immunodeficiency adding to 15%, and both transient hypo gamma globulinemia of infancy and a selective antibody deficiency totaling to 3%. Reasons for the dissimilarities in the rates of antibody disorders between patients in the United States and Europe are not understood, but they primarily relate to variances in the ethnicities of populations, and modifications in data collection[7].
The nadir for IgG levels in infants happens at three months of age, but a transient hypo gamma globulinemia can continue because of a prolonged nadir of IgG. Clinical infections during this time are usually insignificant. Serum IgG and IgA levels are

reduced, but B-lymphocyte levels are normal on further investigation[6].

As with other antibody disorders, ear, sinus, and pulmonary infections are typical; while gastrointestinal problems such as diarrhea, malabsorption, and symptoms of irritable bowel syndrome also befall in children who have common variable immunodeficiency.Causative entities for infection include Clostridium difficile, in addition to species

of Giardia, Salmonella,Yersinia,

and Campylobacter[8].

3. IgA Deficiency

Immunoglobulin IgA deficiency (OMIM 137100) is described as reduced or absent level of serum IgA in the occurrence of normal serum levels of IgG and IgM in a patient often older than 4 years of age, in whom additional causes of hypo gamma globulinemia have been ruled out. In general, serum IgA level of lower than 7 mg/dL (or 0.07 g/L) is measured as *selective IgA deficiency* since this concentration is the bottom of most detectable limit recognized by most of the laboratories. When serum IgA level is greater than 7 mg/dL but two standard deviations lower than normal for age, the condition may be referred to as partial IgA deficiency, which is quite prevalent. The threshold of 4 years of age is used to elude premature diagnosis of IgA deficiency which may be temporary in younger children because of delayed ontogeny of IgA system after birth[9].

In IgA deficiency, B cells express IgA; nonetheless, they are of immature phenotype along with the co-expression of IgM and IgD, and they cannot completely develop into IgA-secreting plasma cells. The defect look like it involves the stem cells because IgA deficiency can be improved by bone marrow transplantation. An intrinsic B cell defect, T helper cell dysfunction, and suppressor T cells have all been described in IgA deficiency. Aberrations in the cytokine network such as lack of IL-4, IL-6, IL-7, IL-10, TGF-β, and most newly IL-21 have also been suggested to play a role in IgA deficiency[10].

There is a widespread spectrum of clinical manifestation in IgA deficiency. Patients with IgA deficiency must be recognized among blood bank donors, without any apparent clinical findings. In fact, 85–90% of IgA-deficient individuals remain asymptomatic. This high percentage is interesting and still relics a puzzle to be solved since IgA is such an important immunoglobulin in immune defense system. Some patients with IgA deficiency have a predisposition to develop recurrent sinopulmonary infections, gastrointestinal infections and disorders, autoimmune conditions, allergies, and malignancies[11].

Assessment of a suspected IgA deficiency would normally include a complete blood count with differential, serum IgG subclasses, quantitative serum immunoglobulin levels, specific antibody response to protein and polysaccharide antigens, and lymphocyte subsets. Furthermore, relevant laboratory testing for the accompanying conditions, such as, recurrent infections, allergies, and celiac disease, should be implemented. IgA-deficient patients who are diagnosed unexpectedly and/or who do not have any symptoms do not require any treatment. Nevertheless, awareness and education are of prime significance, particularly to prevent a possible anaphylactic reaction secondary to blood transfusion. In IgA deficiency, the backbone of treatment is the treatment of accompanying diseases. If the patient experiences repeated infections, daily prophylactic antibiotics on anuninterrupted or seasonal intermittent basis may be advantageous[10].

T-Cell Disorders

T-cell disorders constitute 9% of primary immunodeficiency diseases in the ESID registry while10.5% in the United States. T-cell disorders are regarded as by the absence or presence of T lymphocytes. Furthermore, T cells are important to the standard functioning of B cells. As a result, most T-cell deficiencies lead to a combined T-cell and B-cell disorder[12].

T-cell disorders typically present early in life. The gravest form of T-cell disorder is severe combined immunodeficiency (SCID) which presents in infants as an emergency condition with life-threatening infections. Failure to thrive, diarrhea, opportunistic infections, and severe repetitive infections in a child younger than three months of agemust raise suspicion for SCID[13].

Phagocytic Disorders

Phagocytic disorders are the outcome of abnormalities in neutrophils and monocytes. These types of disorders constitute 12.5% of primary immunodeficiency diseases in the ESID registry while 8.5% in the United States.Chronic

granulomatous disease is the most prevalent phagocytic disorder in the ESID registry. It is typically diagnosed by five years of age, and is categorized by pneumonia, abscesses, suppurative adenitis, along with gastrointestinal infections. The leading manifestation may be omphalitis in infants[14]. Other common appearances of chronic granulomatous disease as well as of other phagocytic disorders comprise recurring pyogenic or fungal skin infections, or abscesses. Infections are associated with the inability of the phagocytic system to destroy catalase-positive organisms, comprising Staphylococcus aureus; Burk holder iacepacia; and Nocardia, Aspergillus, Serratia, and Candida species. Invasive fungal infection such as disseminated Candida, Aspergillus, or Nocardia species, or invasive Staphylococcus aureus orBurkholderiacepaciasepticemia, should increase suspicion for a phagocytic disorder[15].

Leukocyte adhesion deficiency type 1 andsevere congenital neutropenia are phagocytic disorders that frequently present within the first few weeks of life. Delayed separation of the umbilical cord (for more than four weeks after delivery), or erosive perianal ulcers, can be initial signs of leukocyte adhesion deficiency type 1.Omphalitis can happen in severe congenital neutropenia as well as leukocyte adhesion deficiency type 1[16].

Complement Disorders

Complement disorders constitute 2% of primary immunodeficiency diseases in the ESID registry where as 3% in the United States. Over 25 proteins are involved in the complement pathway, which supplements the action of antibodies to destroy bacteria[17].

These disorders consist of infections with encapsulated organisms .An insufficiency of C3 is associated with repeated pyogenic infections with S. pneumoniae and H. influenza. Deficiencies in C5 through C9 are supplementary to Neisseria meningitidis infections for instance meningitis, sepsis, and arthritis[18].

DIAGNOSIS

Clinical Signs

The most usual presentations of a primary immunodeficiency disease in children are recurring ear, sinus, and pulmonary infections as well as diarrhea and failure to thrive. These conditions are also found in children who do not have an immunodeficiency disease, which puts forward the question of how to identify children in need of assessment[19].

A thorough evaluation from the United Kingdom found that the three most supportive warning signs for primary immunodeficiency disorder were[2]:

1. a positive family history (relative risk [RR] = 18; with 95% confidence interval [CI],
2. Failure to thrive (RR = 22; with 95% CI, 8 to 60 for T-cell disorders), and
3. a diagnosis of sepsis managed with intravenous antibiotics (RR = 5; 95% CI, 1.4 to 15 for the phagocytic disorders)

Many primary immunodeficiency disorders are inherited (most hereditary disorders are autosomal recessive inherited or could be X chromosome–linked).A child with recurrent severe infections who has a positive family history of such types of illnesses or who is from an ethnicity connected to higher parental consanguinity (for example, the Middle East,northern and sub-Saharan Africa; some regions of western, central, and southern Asia) must be screened for an immunodeficiency disease[2].

A child presenting with recurrent infections in a single anatomic location is more expected to have an anatomic defect rather than an immunodeficiency. If repeated infections are present in two or more sites, on the other hand, an immunodeficiency disease can be suspected. Additionally, children have a tendency to "outgrow" their infections, with less infections as they get older. An immunodeficiency should be suspected if a child's infections increase in regularity or become more serious as he or she gets older[19].

Repeated, serious infections with similar pathogens may be a sign of an immunodeficiency syndrome. Similarly, any uncommon infections, such as meningitis, sepsis, or fungal and opportunistic infections, should increase suspicion for an immunodeficiency disease[20].

Investigation

1. HUMAN IMMUNODEFICIENCY VIRUS

HIV infection must be considered in newborns and adolescents who present with diarrhea, unusual opportunistic infections, and failure to thrive. HIV infection clinically looks like a T-cell immunodeficiency disorder. For children older than 18 months, HIV antibody testing for diagnosis is adequate[21].

Because maternal antibodies to HIV cross through the placenta, viral testing is necessary in children younger than 18 months. HIV RNA assay testing and HIV DNA polymerase chain reaction testing in newborns is suggested during the first 14 to 21 days

of life, after one month of age, and again at four to six months of age in order to identify those who have perinatal-acquired HIV infection[20].

2. COMPLETE BLOOD COUNT

A complete blood count with differential must be achieved to screen for a T-cell or phagocytic disorder. T-cell disorders are described by lymphocytopenia. Newborns typically have a lymphocytosis. An absolute lymphocyte count of below 3,000 per mm^3 in a newborn can be used as the cut off for considering a T-cell disorder[22].

Absolute lymphocyte count is relatively age-dependent. In the applicable clinical situation, if the absolute lymphocyte count is two standard deviations below the average, a T-cell disorder may be deliberated. For instance, an absolute lymphocyte count in a four-month-old infant of less than 2,800 per mm^3 has 86% sensitivity and 94% specificity for identifying severe combined immunodeficiency (SCID) syndrome[23].

T-cell disorders can be further established by lack of a delayed hypersensitivity skin test response to mumps, Candida, or tetanus in children older than one year of age, and by lymphocyte subset analysis at any age. A lymphocyte subset analysis will detect for the number and percentage of B cells (CD19, CD20), T cells (CD3, CD4, CD8), and natural killer cells (CD16, CD56)[21].

Phagocytic disorders are categorized by neutropenia and abnormalities in lysosomal granules in neutrophils. Primary immunodeficiency disease must be expected if the neutrophil count is less than 1,500 per mm^3. If the neutrophil count is normal but there is yet suspicion of primary immunodeficiency disease, granulocyte function tests can be done[22].

3. SERUM IMMUNOGLOBULINS

Patients with B-cell disorders have decreased serum immunoglobulin levels and reduced production or response of immunoglobulin to the vaccines. Serum immunoglobulin levels differ with age, so age-specific cutoffs must be used while performing laboratory testing. If immunoglobulin levels are low, serum albumin level must be checked since low albumin indicates protein loss by the kidney or protein malabsorption through the bowel as causes of immunoglobulin deficiency[23].

IgG antibody titers to vaccine antigens can be tested to conclude responsiveness to vaccination. Testing is preferably performed four weeks after vaccination if the child was not before hand exposed to the vaccine antigen. In case if the child was previously exposed, a threefold upsurge in the titers against two antigens that is present three weeks after vaccination points to responsiveness of B cells. Protein antigens (tetanus, diphtheria, mumps, and rubella) can be checked at all ages; polysaccharide antigens (for example, H. influenzae, Pneumococcus species) can be detected if the patient is two years or older. If the physician is using a conjugated pneumococcal vaccine, specific serotype of IgG antibody titers are obligatory[24].

4. COMPLEMENT TESTING

Complement disorders are screened by detecting the components of the classic and alternative pathways. The classic pathway involves C1 through C9 and is analyzed with a CH_{50} assay. If the assay results are normal, the child does not have a clinically noteworthy complement deficiency. However, if the results are abnormal, the alternative pathway must be checked with an AH_{50} or CH_{100} assay. By means of the combination of the two test results, specific deficiencies can be recognized[21].

Newborn Screening for T-cell Disorders

From 2010, the U.S. Department of Health and Human Services endorsed routine screening for SCID in newborns. SCID is expected to occur in one in 100,000 live births. Even though SCID is rare, timely identification and management with hematopoietic stem cell transplantation can avoid infant deaths. In the United States, the survival rate is 94% if transplantation is accomplished in the first three-and-a-half months of the infant's life, but drops to 70% if transplantation takes place later than that. Death is primarily caused by viral illness present at diagnosis[25].

Five states presently necessitate screening for T-cell disorders in newborns; another 15 states are in the procedure of introducing testing. Screening involves recognition of T-cell receptor excision circles by polymerase chain reaction by the method of current newborn heel stick dried blood spot. T-cell receptor excision circles are certain pieces of DNA produced only by the T cells[26].

Applying a cutoff of less than 30 copies per μL, screening for T-cell receptor excision circles for T-cell disorder is 100% sensitive. The false-positive rate is 1.5% in term infants, while 5% in preterm

infants or those who require the intensive care unit.Testing protocols comprise resampling or first sampling at a rough gestational age greater than 37 weeks[27].

CONCLUSION

Primary immunodeficiency can be elusive and differ in their presentation, including recurrent or unusual infections, malignancies or autoimmune phenomena. Pediatricians and primary care providers are the first to evaluate and treat these patients. Documentation of all infections through imaging and microbial evidence is crucial in building the index of suspicion. When primary immunodeficiency is suspected, basic blood work (including complete blood count, immunoglobulin levels, and documenting the response to vaccines) is usually helpful, and a clinical immunologist can counsel on further diagnostic tests and management of these patients.

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