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Opinion

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Approach to immunodeficiency disorders

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Opinion

Immunodeficiency disorders can be classified into primary and secondary immunodeficiency disorders. The incidence is found to be 1:10000 which is more than PKU for which screening is available. An immunodeficiency disorder is a blanket terminology suspected in any children with recurrent infections. In children recurrent infection is normal up to 0 to 15 episodes of URI per year is considered normal in a well child. So the clinician is always faced with a dilemma whether it is normal for the age or serious immunodeficiency disorder.

Basics of immune system

i. The immune system starts at skin and mucosal barrier. Normally intact skin and mucosa constitutes a good barrier. In mucosa additional protective mechanism like mucus secretion , ciliary clearance, macrophages also play a role in preventing infection

ii. When the mucocutaneous barrier is breached, the innate immunity comes into play. This system is not specific for the pathogen. This includes phagocytises system, complement, inflammatory mediators, NK cells & cytokines IL2 and interferon gamma.

iii. If the pathogen is not cleared by innate immunity, then Antigen presenting cells (dendritic cells) stimulate CD 4 T cells. It can stimulate either Th1 or Th2 response. Th1 stimulates CD8 cells which are cytotoxic cells. Th2 response is hypersensitivity reaction. T cells are mainly utilized to activate B cell responses and to cope with intracellular pathogens

iv. CD4 T cells also stimulate B cells which mature to plasma cells & memory B cells. Plasma cells secrete antibodies. Memory B cells facilitate subsequent response to the same pathogen to be fast. Antibody-mediated defence is important against pathogens that produce toxins (eg, Clostridium tetani) or have polysaccharide capsules that interfere with phagocytises (eg, the pneumococci). It applies mainly to extracellular pathogens and their toxins.

Broadly they are classified as

i. Defects of antibody

ii. Combine B & T cell defect

iii. Phagocytic defect

iv. Complement defect

When to suspect primary immunodeficiency disorders: When > 2 of the following signs:

1. Four or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or fungal infection on skin.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections including septicemia.
10. A family history of PI.

Questions to be answered:

1. Age of onset?
2. Pattern of infection
   - Pneumonia
   - Skin abscess
   - CSOM
   - Persistent diarrhoea
   - Persistent Oral thrush
   - Meningitis
   - Sepsis
   - Disseminated BCGosis
3. Failure to thrive
4. Family history & pattern of inheritance
5. Associated features (Thrombocytopenia, eczema, skeletal abnormality, persistence of primary dentition)
6. H/O atopy

Combined B & T cell defect:

1. Age of onset? à From birth
2. Pattern of infection: Predominantly viral infection , fungal infunction, protozoal & OI

- Pneumonia à PCP/CMV
- Persistent diarrhoea
- Persistent Oral thrush
- Disseminated BCGosis

3. Failure to thrive
4. Family history: Previous sibling death , X linked SCID , WAS

This group includes SCID, Digeorge syndrome, Ataxia Telengectasia, Wiskot Aldrich syndrome

Predominantly B cell defect:

1. Age of onset? By 6-9 months after the maternal antibody wanes off
2. Pattern of infection: Infection by encapsulated organisms (st. pneumonia, H.influenza, Niesseria meningitis), M.catarrahalis, Pseudomonas, Staph aureus, Mycoplasma
   - Pneumonia
   - Sinusitis, otitis media
   - Skin abscess
   - Persistent diarrhoea (Giardia)
   - Meningitis (chronic meningitis by enterovirus in Agammaglobulinemia)
   - Sepsis
3. Failure to thrive: not common
4. Family history & pattern of inheritance: X linked - Agammaglobulinemia, Hyper IgM
5. Associated features: Common variable immunodeficiency has associated autoimmune disease & malignancy

It includes Bruton's Agammaglobulinemia, common variable immunodeficiency, Hyper IgM, selective IgA deficiency Phagocytic deficiency:

1. Age of onset? From birth
2. Pattern of infection : It includes staph aureus, burkholderia, Serratia, Aspergillus, nocardia, Mycobacterium, Salmonella
   - Pneumonia with pneumatocoele
   - Skin abscess
   - CSOM
3. Failure to thrive: Not common
4. Family history & pattern of inheritance: X linked chronic granulamatous disease
5. Associated features eczema, skeletal abnormality, persistence of primary dentitionà seen in hyper Ig E, Obstructive features like pyloric stenosis, intestinal obstruction, Ureteric stenos is seen in chronic granulamatous disease, Delayed umbilical cord separation à LAD , Albinism à Chediak Higashi syndrome
6. H/O atopy à Hyper Ig E

It includes either qualitative or quantities Quantitative: Severe congenital neutropenia(Kostmann syndrome), cyclical neutropenia Quantitative: Chronic granulamatous disease, Leukocyte adhesion defect, Hyper IgE, Chediak Higashi syndrome Complement deficiency:

1. Age of onset? Any age
2. Pattern of infection: Early complement deficiency presents with autoimmune disorders & pyogenic infection while late complement deficeiency presents with Neissseria meningitides

Investigations

1. Complete blood count
   a. Neutropenia: Repeat weekly to differentiate Severe congental neutropenia from cyclical neutropenia
   b. Leukocytosis in the absence of infection: LAD
   c. Throbocytopenia: WAS
   d. (Neutropenia & thrombocytopenia can be present in Organic acidemia also!!!)
   e. Eosinophilia : severe allergy, ABPA, Job's syndrome/Hyper Ig E, Omenn's syndrome (A form of SCID)
   f. Lymphopenia for age: SCID
   g. Birth < 2500/µL
   h. 5–6 Months up to 1 year < 4000/µL
   i. Adult < 1000/µL
   j. Normal ESR rules out serious bacterial & fungal infection
   k. Morphology: Small platelet-WAS, giant neutrophilic granule-chediak higashi syndrome
2. B cell defect: Immunoglobulin profile:
   a. Ig A can be done as screening test since selective IgA deficiency is the commonest. Normal rules out T & B cell defect.
   b. It can be low in protein losing states like nephritic syndrome, protein losing enteropathy, burns. In these scenarios specific antibody measurement helps.
   c. Antibody response to protein & polysaccharide antigen, isohemagglutinin (Blood group antibodies in children > 2 years)
   d. Isolated elevated Ig E àsevere allergy, ABPA, Job's syndrome/ Hyper Ig E
3. T cell Defect
   a. Delayed hypersensitivity response to Candida antigen (not reliable in younger children who is not exposed to antigen). Presence of BCG scar is a marker of intact T cell immunity
   b. In vitro response of T cell to phytohemagglutinin & mitogen
4. T and B cell markers Flow cytometry:
   a. Absent immunoglobulin & absent B cell markers à Brutons aggamaglobulinema
   b. Low immunoglobulin & Positive B cell markers à CVID
   c. Absent T cell markers à SCID. Various types associated with variable combination of absence of B / NK cell markers or both

5. Phagocytic Function:
    a. Chronic granulamatous disease à NBT test, DHR flow cytometry assay
6. Comlement Function:
    a. CH50 (Classic & final pathway) & AH50 (Alternate pathway).

Other conditions to be which need to be considered

1. Immunodeficiency disorders not classified: IPEX (Immune Dysregulation, Polyendocrinopathy, Enteropathy and X-Linked Syndrome), X-Linked Lymphoproliferative Syndrome, Autoimmune Lymphoproliferative Syndrome ALPS.
2. Diseases Due to Defects in Interferon-gamma & Interleukin-12 Pathways (Mendelian susceptible mycobacterial disease).
3. Chronic mucocutaneous candidiasis.
4. Defects of DNA repair.
5. Where mucosal barrier is affected: Cystic fibrosis, immotile ciliary syndrome
6. Immune dysregulation: HLH.

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Conflicts of interest

The author declares that there are no conflicts of interest.