Approach to primary Immunodeficiencies

By: Tooba Momen

Clinical Allergist & Immunologist

The primary immunodeficiency diseases are a group of disorders in which the primary defect appears to be intrinsic to one or more components of the immune system.

Frequency of the Primary Immunodeficiency Diseases

- The primary immunodeficiency diseases were originally thought to be quite rare.
- some of the primary immunodeficiency diseases are relatively common.
- For example, Selective IgA deficiency occurs in as many as 1/500-1/1000 individuals.

Frequency of the Primary Immunodeficiency Diseases

- Other primary immunodeficiency diseases are much less common and occur with a frequency of between 1/10,000 and 1/100,000.
- Because there are so many primary immunodeficiency diseases, when taken together as a group of disorders, they become a significant health problem,
- occurring with a frequency comparable to leukemia and lymphoma in children and four times as frequently as cystic fibrosis.

The immune system functional compartments

- The B-lymphocyte system
- The T-lymphocyte system
- The Phagocytic system
- The Complement system

Suspecting Immunodeficiency

- Look for infections that are:
  - Frequent
  - Recurrent/chronic
  - Unusual organisms
  - Organisms that respond poorly to therapy
  - Growth retardation
  - Family history

Clinical Manifestations of the Primary Immunodeficiency Diseases

- INFECTIOUS DISEASES
- AUTOIMMUNE AND RHEUMATIC DISEASES
- GASTROINTESTINAL DISEASE
- HEMATOLOGIC DISEASES

INFECTIOUS DISEASES

- An increased susceptibility to infection is the hallmark of the primary immunodeficiency diseases.
- In most patients, this is manifested by recurrent infections.
- Typically, the infections do not occur only in a single anatomic site, but usually involve multiple organs or multiple sites within the same organ.

INFECTIOUS DISEASES

- The type of infectious agent and the location of the infection may give valuable insight into the nature of the immunologic defect.
- For example, individuals who have B-cell deficiencies characteristically have an increased susceptibility to infection with encapsulated pyogenic bacteria, such as the pneumococcus and H.influenzae, and to enteroviruses.
- Patients who are deficient in T-cells may have infections with a variety of microorganisms but appear especially susceptible to fungi, viruses and Pneumocystis.

AUTOIMMUNE AND RHEUMATIC DISEASES

- rheumatoid arthritis, systemic lupus erythematosus, and/or dermatomyositis.
- Autoimmune and rheumatic diseases are more commonly seen in some of the primary immunodeficiency diseases than in others.
- For example, they are relatively common in Selective IgA Deficiency, Common Variable Immunodeficiency and deficiencies of the complement system
- Relatively uncommon in X-linked agammaglobulinemia.

GASTROINTESTINAL DISEASE

- Chronic diarrhea, malabsorption and even malnutrition may be important manifestations of primary immunodeficiency diseases, especially in infants and young children.
- infectious. Chronic giardiasis, rotavirus and cryptosporidium, among other infections, have each been significant problems in patients with primary immunodeficiency diseases.
- non infectious etiology includes inflammatory bowel disease, enteropathy, atrophic gastritis with pernicious anemia and nodular lymphoid hyperplasia.

HEMATOLOGIC DISEASES

- Anemia, thrombocytopenia, or leukopenia are seen frequently in patients with primary immunodeficiency diseases.
- For example, the Wiskott-Aldrich Syndrome is characterized by variable defects in B-lymphocyte and T-lymphocyte function. These patients also have intrinsic abnormalities of their platelets which result in small platelets and significant thrombocytopenia.

HEMATOLOGIC DISEASES

- hematologic abnormalities in consequence of the autoimmune diseases that are seen in patients with primary immunodeficiency. For example, a significant proportion of patients with autoimmune hemolytic anemia or ITP
- Autoimmune hemolytic anemia, and/or thrombocytopenia, and/or neutropenia are often seen in patients with Common Variable Immunodeficiency or Selective IgA Deficiency, and the hyper IgM Syndrome

1. Eight 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 elsewhere on skin, after age 1.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections.
10. A family history of Primary Immunodeficiency.

Suspecting Immunodeficiency

- Humoral (antibody) deficiency associated with:
  - Recurrent infections with encapsulated bacteria
  - Chronic sinupulmonary infections
- Cell-mediated deficiency characterized by:
  - Recurrent infections with
    - Viruses
    - Fungi
    - Opportunistic organisms (PCP)
  - Diarrhea, wasting, growth retardation
- Combined immunodeficiency

Humoral Immunodeficiency (B cells)

- Transient hypogammaglobulinemia of infancy
  - Slow to develop normal levels of antibody
  - Asymptomatic, minor infections
  - Low levels of IgG, IgA (IgM usually normal)
  - Resolves by 3-6 yo
- IgA deficiency
  - Most common humoral antibody deficiency
  - 50-80% asymptomatic
  - Recurrent sinopulmonary infections most frequent manifestation
  - May have severe malabsorption (chronic diarrhea)
  - Isolated low IgA level
  - Increased risk of autoimmune disorders

Bruton's X-linked Agammaglobulinemia

- No B cells
- Child clinically well for first 6 months of life
- Recurrent upper/lower respiratory tract infections with encapsulated bacteria (*S. pneumo*, *H.flu*)
  - Bronchiectasis → chronic cough/increased sputum
- Sepsis, meningitis, skin infections
- Paucity of lymphoid tissue (tonsils, adenoids)
- Markedly decreased IgG, IgA, IgM
- Treatment: IVIG, antibiotic therapy

Common Variable Immunodeficiency

- B lymphs don’t differentiate into plasma cells
- Recurrent sinopulmonary infections
- Low IgG, IgA, IgM
- Treatment: IVIG
- ***Associated with autoimmune disease, lymphoma***

DiGeorge Syndrome

- No T cells secondary to thymic hypoplasia
- “CATCH 22”
- Overwhelming infections with viruses, fungi, bacteria
- Treatment: correct hypocalcemia, cardiac defects, fetal thymus transplant

SCID

- Defects in stem cell maturation
- Adenosine deaminase deficiency (toxic insult to T and B cells)
- Manifestations seen in first 3 months of life
  - Recurrent, severe bacterial, viral, fungal, and protozoan infections (usually respiratory infections)
  - Failure to thrive, diarrhea, dermatitis, candidiasis
- Most have lymphopenia, decreased IgG, IgA, and IgM
  - Diagnosis made by analysis of T, B, and NK cell subsets
- Treatment: isolation, treat underlying infections, bone marrow transplant

Wiskott-Aldrich Syndrome

- X-linked recessive
- ***Symptoms in infancy***
  - ***Recurrent, severe infections***
  - ***Eczema***
  - ***Thrombocytopenia (petechiae)***
- Low levels of IgM
- Increased risk for hematologic malignancy
- Treatment: manage bleeding/infections, BMT

Ataxia Telangiectasia

- Autosomal recessive deficiency in DNA repair affecting T and B cells
- ***Progressive ataxia, telangiectasia, variable immunodeficiency*** (recurrent sinopulmonary infections common)
- Increased risk of malignancy (leukemia, lymphoma)

Hyper IgE (Job) syndrome

- Symptoms/signs
  - Coarse facial features/skeletal abnormalities
  - Recurrent staph infections
    - Impetigo (resistant)
    - Pneumonia with pneumatocele formation
  - ***3 E's: Elevated IgE, Eosinophilia, Eczema***

Hyper IgM Syndrome

- T cell abnormality preventing IgM → IgG

- Frequent sinopulmonary infections, diarrhea, opportunistic infections (PCP)
- Low levels of IgG/IgA,nl or high levels of IgM
- Treatment: Ig replacement

Phagocytic Disorders

Chronic Granulamatous Disease (CGD)

- Defective NADPH oxidase
- ***75% X-linked recessive***, 25% autosomal recessive
- Severe, recurrent staph aureus infections of lymph nodes, and skin (granulomas, heal slowly), pneumonitis, osteomyelitis, hepatosplenomegaly
- ***Dx: Nitroblue tetrazolium (NBT) test & DHR test***
- Treatment: antimicrobial prophylaxis, IFN-gamma, BMT

Leukocyte adhesion deficiency (LAD)

- Deficient chemotaxis
- Recurrent soft tissue, skin, respiratory infections, impaired wound healing (typically ***no pus, minimal inflammation***)
- ***Delayed umbilical separation***
- Increased WBC count
- Treatment: BMT

Complement System Disorders

- Defects of early components (C1-C4) associated with infections with encapsulated bacteria
  - Present similarly to humoral immune deficiencies
- Defects of late components (C5-C9) associated with *Neisseria* infections
- Also associated with autoimmune-like conditions
- CH50 functional assay assesses entire complement cascade
  - Also may use individual components
- Treatment: treat infectious and autoimmune sequelae

Laboratory Diagnosis of Immunodeficiency

- EVALUATION OF B-LYMPHOCYTE FUNCTION:
  The initial screening test for B-lymphocyte function is the measurement of serum immunoglobulines.
- Quantitative measurements of serum IgG, IgA and IgM will identify patients with panhypogammaglobulinemia as well as patients who have a deficiency of an individual class of immunoglobulin, such as selective IgA deficiency.

Laboratory Diagnosis of Immunodeficiency

- There are four subclasses of IgG
- In some instances, the total serum IgG may be normal or near normal but the patient may still have an IgG subclass deficiency.

Laboratory Diagnosis of Immunodeficiency

- assessment of antibody function is a necessary part of the evaluation of humoral immunity.
- Antibody titers after immunization with protein antigens (e.g. tetanus or diphtheria toxoids) and polysaccharide (e.g. pneumococcal capsular polysaccharides) are most convenient.
- If immunoglobulin levels and/or antibody titers are decreased, the evaluation should proceed with more advanced tests of B-lymphocyte numbers and function.

Laboratory Diagnosis of Immunodeficiency

EVALUATION OF T-LYMPHOCYTE FUNCTION:

- lymphocyte count
- CXR: thymus size
- Delayed type hypersensitivity (DTH) skin tests using a panel of ubiquitous antigens can be used as a screening test in older children and adults.
- The presence of a positive DTH skin test generally indicates intact T-cell function and cell mediated immunity.

Laboratory Diagnosis of Immunodeficiency

More specialized tests of T-cell function

- assessment of lymphocyte proliferation in response to nonspecific mitogens (e.g. phytohemagglutinin), specific antigens (e.g. candida) and/or mononuclear cells from an unrelated, histoincompatible individual (mixed leukocyte reaction).
- measure the production of a number of different cytokines that are involved in T- and B- lymphocyte regulation (e.g. Interleukin 2, interferon-gamma).

Laboratory Diagnosis of Immunodeficiency

EVALUATION OF PHAGOCYTIC FUNCTION

- reductions in phagocytic cell number in the peripheral blood and, therefore, can be detected by using a white blood cell count and differential.
- measuring the reduction of nitroblue tetrazolium (NBT test).

EVALUATION OF THE COMPLEMENT SYSTEM

- CH50 assay , this assay requires the functional integrity of C1 through C9.
- The identification of the individual component which is deficient rests on specialized functional and immunochemical tests which are specific for each component.

- 10 m/o infant presented with recurrent otitis media & common cold
- IgG ↓, IgM↓, IgA; nl , IgE : nl

اقدام بعدی چیست؟

- a 3 y/o boy with recurrent pneumonia,persistent diarrhea
- P/E; no tonsils & L.N
- IgG ↓, IgM↓, IgA↓ , IgE : ↓
- anti tetanus ab titer↓
- Flowcytometry : 1% B cell, nl T, NK cell

- A 4 M/O infant presented with persistent diarrhea , FTT, refractory pneumonia, organomegaly
- CBC; WBC; 5300, 30% LYMPHOCYTE, 70% neutrophil
- IgG ↓, IgM↓, IgA↓ , IgE : ↓
  - اقدام بعدی چیست؟

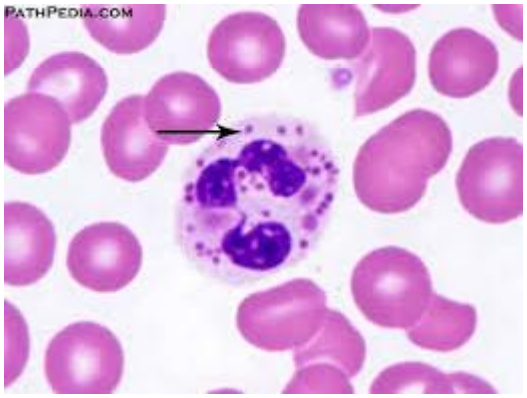
A 3 y/o girl with malar rash, severe skin vasculitic rash

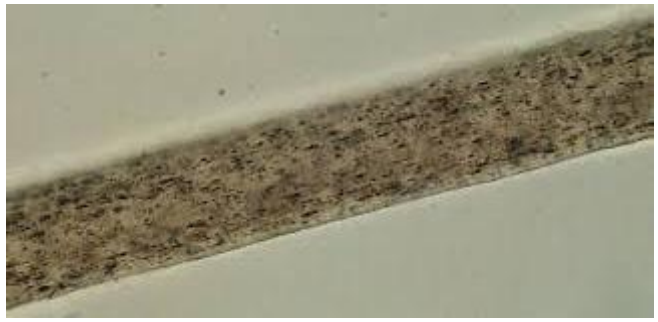
Thrombocytopenia, Dx : SLE

C3 ↓ C4 ↓ CH50: 0

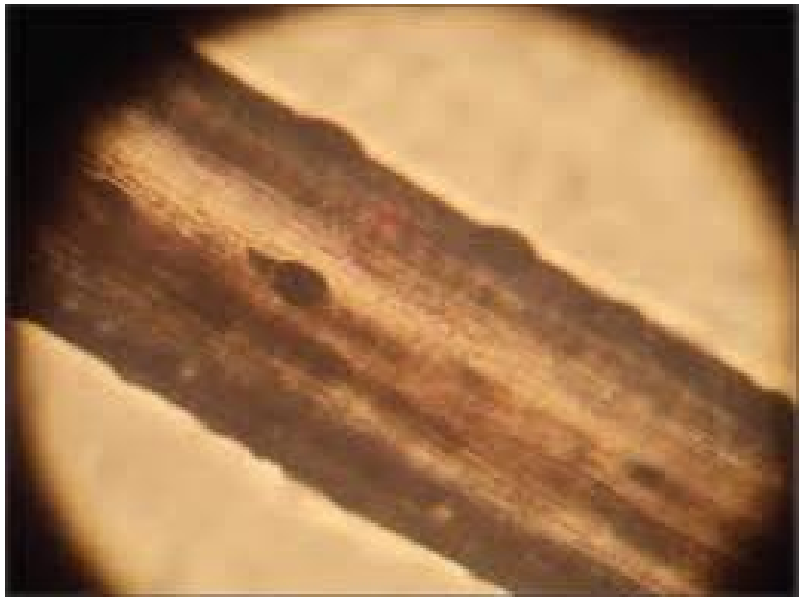
C1q ↓↓↓

- A 7 y/o girl with recurrent pneumonia albinism, nystagmus,





- grisceli



- A 4 y/o girl with generalized lymphadenopathy, skin rash, hepatosplenomegaly
- pancytopenia
- L.N Bx: positive acid fast, mycobacterium bovis
- Dx: disseminated BCGitis
  - تشخیص های افتراقی شما چیست؟

- A 1.5 y/o with severe oral mucositis, gingivitis, skin ulcer, past hx of repeated infections
- Wbc; 50000, 75% neutrophil, 30% lymphocyte
- تشخیص افتراقی و اقدام بعدی چیست؟