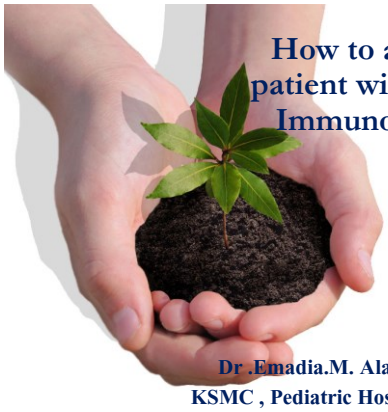


How to approach to patient with suspected Immunodeficiency

Dr .Emadia.M. Alaki
KSMC , Pediatric Hospital
Pediatric Consultant Allergist & Immunologist

- Immuno-competent kids may have up to six URIs per year. Ten URIs per year if they attend daycare.

Common Risk Factors for Frequent Infections

- Day-care, school-aged siblings
- Second-hand smoke
- Atopy
- Anatomic abnormalities including ciliary defects
- Retained foreign body
- Gastroesophageal reflux

Secondary Immunodeficiencies

- Malnutrition
  - Vit. A deficiency - Infections of GI and resp. tract
  - Zinc deficiency – Acrodermatitis enteropathica, SCID-like syndrome
  - B12 deficiency – impaired immunoglobulin production
  - Protein and caloric deficiency – impaired immune response
  - Iron deficiency

- Frequent or recurrent sinopulmonary infections, malabsorption, nasal polyps…

•Cystic Fibrosis

–1:2500

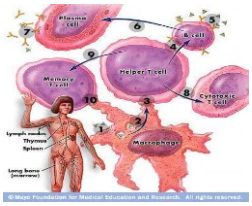
–More common than most of the immunodeficiencies

Secondary Immunodeficiency

Two most common •

– HIV infection – seventh leading cause of death in children 1-4 years in the US.
  - Third leading cause in black children 1-4 in the urban northeastern US.
  - Always think about it…

Primary Immunodeficiency



- A disorder in one or more components of the immune system.

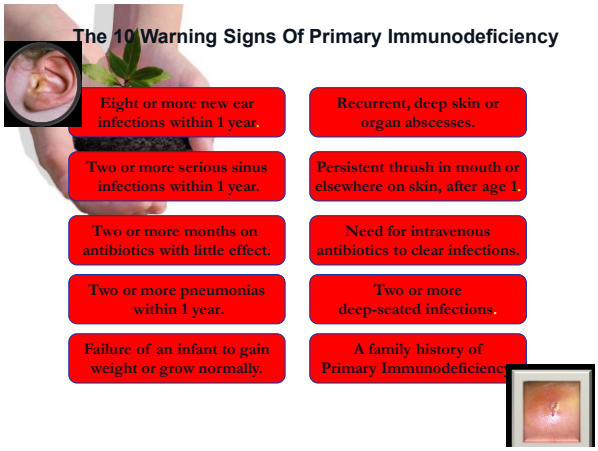
Components of Immunity

Classification of Immunodeficiency

1. **Humoral (B-cell)** – quantitative or qualitative defects in antibody production account for more than 50% of defects.
2. **Cellular (T-cell) –** usually combined with humoral; account for 20-30%.
3. **Phagocytic** – defects in migration, or killing; account for ~18%.
4. **Complement** – account for ~2%

History Our Guide

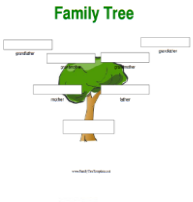
- Age of onset



CRUISE

Important historical points

- **CHRONIC**
- **RECURRANT**
- **UNUSUAL**
- **INVESIVE**
- **SEVERE**



History Our Guide

Important historical points

- Frequency, duration, severity, complications, response to treatment
- Risk factors
- Family history
- Infection with low-virulence or unusual organisms

Physical Exam

- A benign physical exam does not rule out immunodeficiency.
- Look for:
  - General appearance, weight, overall health
  - Hair,
  - Dysmorphic features
  - Gingivitis, dental erosions, signs of sinusitis

- Tonsillar tissue, adenopathy, splenomegaly
- Arthritis, ataxia, neuro deficits

Disease Specific Skin Findings

- Eczema and petechiae – Wiskott-Aldrich Syndrome
- Telangiectasia – Ataxia-Telangiectasia

- Oculocutaneous
- albinism --Chediak-Higashi
- Dermatomyositis-like rash –
- XLA
- Chronic dermatitis – Hyper-IgE
- Generalized molluscum, extensive warts, candidiasis – T-Cell defects

4 Stages of Testing for Primary Immunodeficiency

1	• History and physical examination, height and weight • CBC and differential • Quantitative Immunoglobulin levels IgG, IgM, IgA (related to age)
2	• Specific antibody responses (tetanus, diphtheria) • Response to pneumococcal vaccine (pre/post) (for ages 3 and up) • IgG subclass analysis
3	• Candida and Tetanus skin tests • Lymphocyte surface markers CD3/CD4/CD8/CD19/CD16/CD56 • Mononuclear lymphocyte proliferation studies (using mitogen and antigen stimulation) • Neutrophil oxidation burst (if indicated)
4	• Complement screening CH50, C3, C4 • Enzyme measurements (adenosine deaminase, purine nucleoside phosphorylase) • Phagocyte studies (surface glycoproteins, mobility, phagocytosis) • NK cytotoxicity studies • Further complement studies AH50 • Neo antigen to test antibody production • Other surface/cytoplasmic molecules • Cytokine receptor studies • Family/genetic studies

Laboratory Evaluation

- CBC with differential
  - Total WBC, ANC, ALC, AEC (age-appropriate values)
  - Lymphopenia = < 3,000 in infants, < 1500 in children and adults
  - Persistently high ANC occurs in LAD
  - Hemolytic anemia, thrombocytopenia, leukopenia occurs in some B-Cell deficiencies.

Laboratory Evaluation

- Quantification of serum immunoglobulins
  - IgG, IgA, IgM is the first-step in evaluation for humoral immunity.
  - IgG subclasses do not need to be ordered as screening.
  - IgE only if severe atopy, or chronic dermatitis

Laboratory Evaluation

- Qualitative Evaluation of Antibodies
  - Isohemagglutins – Antibodies to ABO blood-group determinants
  - Antibodies to tetanus and diptheria glycoproteins and pneumococcal polysaccharides.
    - If low titers, give booster, then repeat titers 4 weeks later.
    - Children younger than 2 can not be tested for polysaccharide antigen antibody.

Laboratory Evaluation

- T-Cell Immunity
  - Delayed-hypersensitivity skin tests
    - Intradermal injection of antigens; Candida, tetanus, trichophyton.
    - Should produce redness and induration of > 5mm by 48-72 hours.
    - Severe illness, or steroids can cause diminished responses. (anergy)
  - Mitogen testing
    - In vitro proliferative responses to concanvalin A, phytohemagglutinin
    - Fast Immune
    - Blastogensis

Laboratory Evaluation

- **Phagocytic Cell Function**
  - Adhesion antigens by flow cytometry (CD11/CD18) – checks for adhesion defects
  - Chemiluminescence – phagocytic killing power

Laboratory Evaluation

- Complement function
  - Total hemolytic complement (CH50) – tests functional integrity of classic complement pathway.
  - AH50 – tests the functional integrity of alternate pathway.
  - The most common reason for an abnormal CH50 is improper handling of specimen.

eatment for Primary mune Deficiencies

- Bone marrow transplantation
- Immunoglobulin replacement
- Enzyme replacement
- Gene therapy

Management Issues

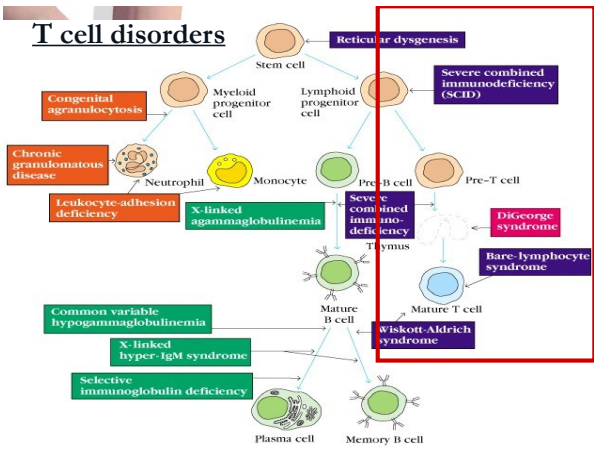
- Prompt recognition of infection and aggressive treatment
- Obtain cultures, and initiate early empiric therapy for suspected pathogens
- Prophylactic antibiotics for patients with significant T-cell defects. (trimethoprim-sulfamethoxazole)
- Live vaccines should not be given to children with T-cell defects
- Only irradiated, leukocyte reduced, virus-free blood products should be given.
- Monitor growth and weight gain diligently.

Specific Diseases

History Our Guide

PREDOMINANT T-CELL DEFECTS

- Early onset, usually 2-6 mos
- Bacteria, mycobacteria, viruses: CMV, EBV, varicella; fungi, parasites, PCP, mycobacterium avium-intracellulare



- FTT, protracted diarrhea, extensive
- Mucocutaneous candidiasis
- GVHD caused by maternal engrafment, nonirradiated blood
- Hypocalcemic tetany in infancy

Severe Combined Immunodeficiency

- Recurrent infections by three months. Can be life-threatening.
- Candida, PCP, cryptosporidiosis, HSV, RSV, rotavirus, adeno, entero, EBV, CMV.
- Absence of lyphoid tissue, lymphopenia, no thymic shadow.
- Anergy, abnormal T-Cell proliferation, +/- B-Cell dysfunction.
- Absence of adaptive immunity.

DiGeorge Anomaly

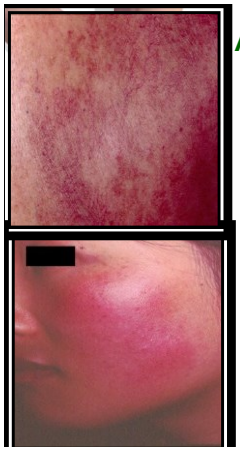
Variable hypoplasia of thymus and parathyroid.

Hypocalcemia → seizures

- Susceptability to fungi, viruses, PCP.
- T-Cells variable in number, abnormal mitogen studies
- Normal to increased B-Cells, normal antibody levels.
- Microdeletion of 22q11.2
- Associated heart defects, facial anomalies, esophageal atresia.

"CATCH-22

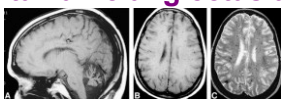
Cardiac malf.
Abnormal face
Thymic hypopl.
Cleft palate
Hypo-Ca-emia

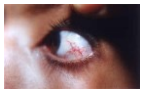


Ataxia-Telangiectasia

- Recurrent sinopulmonary disease.
- Telangiectasias between 3-6 years.
- Ataxia soon after learning to walk, in wheelchair by 10-12 years.
- Often low or absent IgA. Varaible depressions of other immunoglobulins.
- Anergy and depressed mitogen studies.
- Risk for lymphoreticular malignancy.

Ataxia-Telangiectasia





- **AR, chromosome 11**
- 1 case in 100,000 births
- Single gene mutation results in impaired repair of DNA damage = cancer in1/4 (lymphoma)
- Usually presents in the 2-d year of life as a lack of balance and slurred speech.
- Ocular telactasia before age of 6. Mild MR in 1/3
-

Hyper-IgE Syndrome

- Chronic pruritic dermatitis.
- Recurrent staph infections of skin, lungs, joints, and dental infections.
- Course facial features.
- Markedly elevated IgE and eosinophilia.

Hyper-E syndrome

Pruritic dermatitis (eczema) –

Recurrent staphylococcal – abscesses of skin, lung, joints, etc.

Eosinophilia of blood and sputum –

Ig G, M, A usually normal –

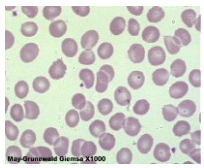
Extremely high Ig E > 1000 , high Ig D –

Diminished response to immunization –

Poor cellular and humoral response to neoantigens –

Tx: IVIG BMT –

Wiskott-Aldrich Syndrome



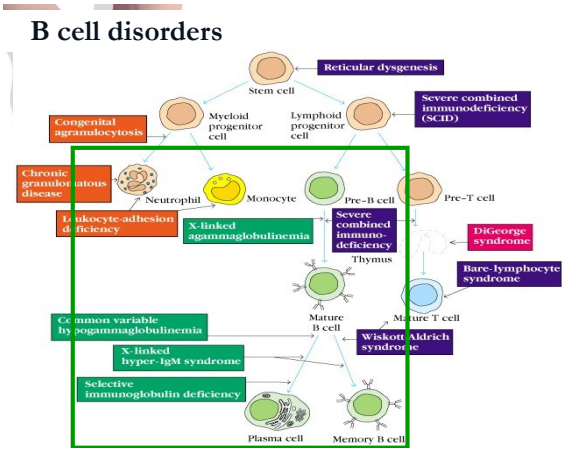
- Atopic dermatitis
- Microcytic thrombocytopenia → bleeding
- Recurrent infections with encapsulated bacteria: pneumococcus esp.
- Variable antibody levels. Often low IgM, high IgA and IgE. Poor antibody finction.
- Low to low-normal T-Cells.
- WASPy boys.

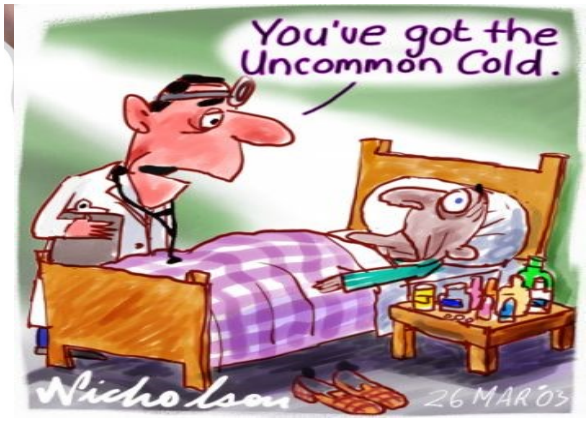
History Our Guide

B-Cell defects

-

– Onset after maternal antibodies diminish, usually after 5-7 months, later childhood to adulthood.





X-linked Agammaglobulinemia
Bruton's X-linked

- Well for first 6-9 months
- Recurrent infections with pneumococcus, H.Flu, Giardia.
- Minimal tonsillar tissue, and no palpable lymph nodes.
- <2SD below normal levels of IgG, IgA, IgM, IgE
- Defect in Btk gene (Bruton tyrosine kinase) → abnormal B-Cells

- Recurrent sinopulmonary infections,
- Chronic GI symptoms, malabsorption,
- Arthritis,
- Viral meningoencephalitis
- Autoimmunity,
- lymphoreticular malignancy; thymoma,
- lymphoma

- Bacteria: strep, staph, H.flu; Campylobacter, enteroviruses, giardia, cryptosporidia

IgA Deficiency

- 1:400 to 1:800
- Symptoms: GI, GU, RTI infections. Many asymptomatic patients.
- Normal IgG and IgM response to pathogens and vaccines.
- Role in diagnosis of Celiac disease.
- May evolve into CVID.
- Be very careful if pt. develops Kawasaki…

Transient Hypogammaglobulinemia of Infancy

- Decreased IgG beyond 6 months.
- Normal IgA, and variable IgM.
- Able to synthesize antibodies to blood type, diptheria, and tetanus antigens normally.
- May have increase otitis and sinusitis.
- Usually resolves by 4 years of age.

Common Variable Immunodeficiency

- Recurrent sinopulmonary infections with usual pathogens.
- Age of onset 15-35 years. Equal male:female.
- Low IgG and poor antibody responses to immunizations.
- Variable levels of IgM and IgA.
- Increased risk for autoimmune diseases and malignancy.
- B-Cells phenotypically normal.

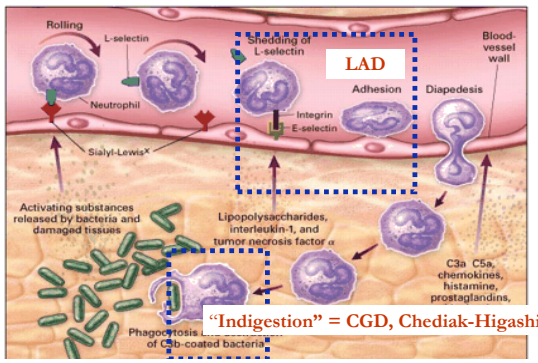
Selective IgG Subclass Deficiencies

- Unsure of clinical relevance.
- May be evolving form of CVID.
- May be normal variation.
- Does not need treatment or evaluation unless there is an impaired ability to form antibodies to protein and polysaccharide antigens.

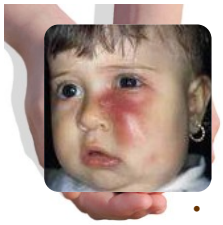
X-linked Lymphoproliferative Syndrome

- Initially asymptomatic.
- Defective response to EBV.
- Fulminant often fatal mono, lymphomas, acquired hypogammalobulinemia.
- 70% of boys die by 10.
- Impairment of antibody to EBNA
- Viral capsid antigen antibody titers may be absent to exaggerated.

Phagocytic disorders

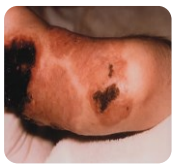


"Indigestion" = CGD, Chediak-Higashi



History Our Guide

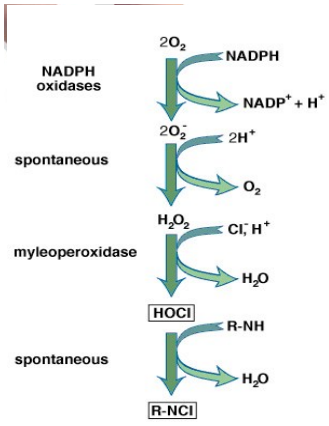
GRANULOCYTE DEFECTS



– Early onset, delayed separation of cord (>8 weeks), poor wound healing

Chronic Granulomatous Disease

- Recurrent abscesses, lymphadenitis, or osteomyelitis at multiple sites.
- Unusual infections with catalase positive organisms: Staph, Serratia, Aspergillus, Candida, Salmonella, gram - enterics.
- Defect in NADPH oxidase enzyme → leading to the inability to produce H2O2.
- No problem with streprococci.
- Chemiluminescence (DHR test)

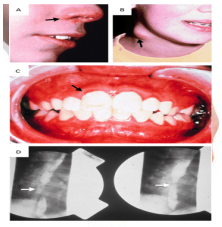


Phagocytic disorders

. NADPH oxidase catalyzesreduction of O_2 to superoxide anion ($O_{-\bullet 2}$)

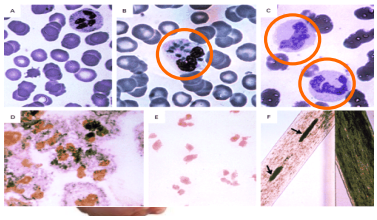
2. Superoxide dismutase convert it to H_2O_2

3. Neutrophil-derived myeloperoxidase (MPO) converts H_2O_2 into a HOCl–bleach Cl_2



- Staph, Pseudomonas, Serratia,
- Klebsiella;
- Fungi: Candida,
- Nocardia,
- Aspergillus

- Dermatitis, impetigo, cellulitis,
- abscesses,
- supparativelymp hadenitis,
- periodontitis,
- osteomyelits



Phagocytic disoders

A. Normal peripheral blood smear

B. Peripheral blood smear from a patient with the Chédiak–Higashi syndrome: large perinuclear granules.

C. Peripheral-blood smear from a patient with agranulocytosis: the cytoplasm is pale, no granules are present, and nuclei are notched and hyposegmented.

D. Nitroblue tetrazolium test (NBT) in normal neutrophils: phagocytosis results in dark-blue staining of the cytoplasm

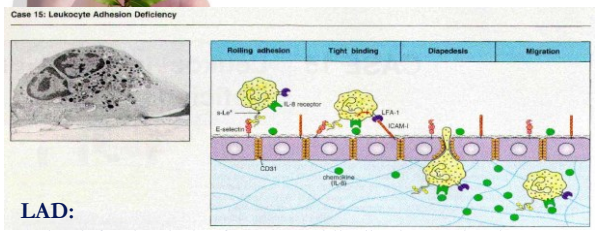
E. NBT in neutrophils from a patient with CGD: there is no phagocytosis = no dark-blue cytoplasmic staining.

F. A hair from a patient with the Chédiak–Higashi syndrome in which giant granules are present, (normal hair on thr right).

Leukocyte Adhesion Defect

- 1:10 million
- Striking neutrophilia.
- Recurrent bacterial and fungal infections without pus.
- Severe gingivitis, periodontitis, alveolar bone loss.
- Decreased or absent CD18/CD11 by flow.
- Delayed separation of umbilical cord.

Phagocytic Disorders: 1. "commuting"

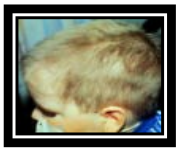


LAD:

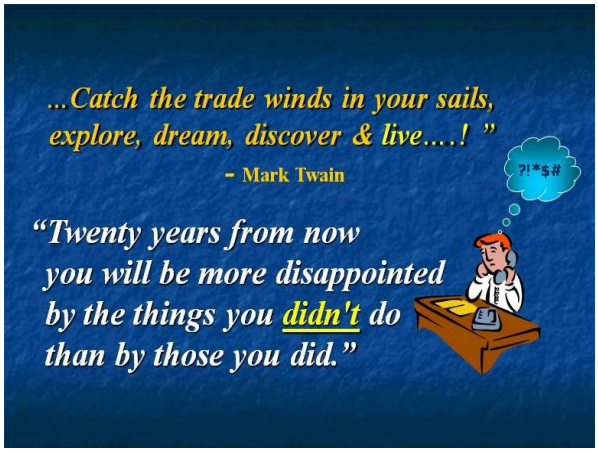
- the defect is a lack of a neutrophil adhesion molecule = no emigration into tissues.
- presents with delayed separation of the umbilical cord, recurrent SBIs, leukemoid reactions

Chediak-Higashi Syndrome

- Partial oculocutaneous albinism.
- Frequent infections of skin, mucous membranes, respiratory tract. Gram -, Gram +, and fungi.
- Large inclusions in all nucleated blood cells.



- Accelerated lymphoma-like syndrome; non-neoplastic infiltration of liver, spleen, and lymph nodes associated with recurrent infections and death.



History Our Guide

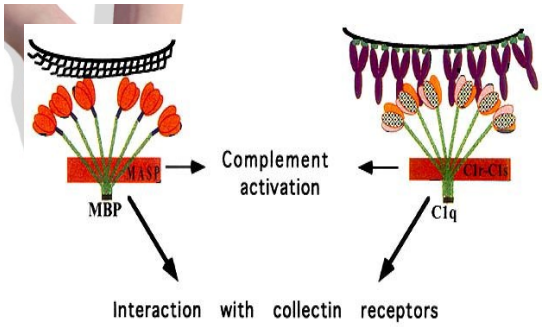
Complement Defects

– Late (C5-C9) –
– Neisserial infections:
– *meningitidis*, septic arthritis from *gonorrhoeae.*

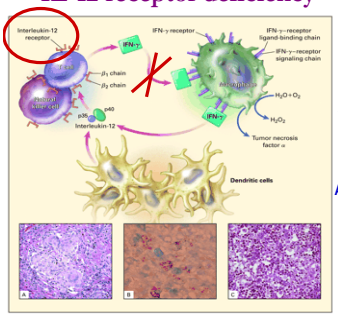
Complement Defects

– Early (C1, C4, and C2) – autoimmune disease

– C3 deficiency – overwhelming sepsis, especially with gram negative organisms



IL-12 receptor deficiency



Monocytes and macrophages bind

IFN- γ ⟹ activation:

1. production of hydrogen peroxide (H2O2)
2. **synthesis & release of IL-12**
   & tumor necrosis factor (TNF)

A. Resolving mycobacterial infection with normal granuloma formation

B. An **AR** mutation of the IFN-γ receptor : mycobacteria survive in macrophages

C. Same patient: no granuloma

IL-12 produced by macrophages and dendritic cells in the presence of a pathogen,

binds to its receptors on T cells and NK cells ↘

inducing the release of IFN-γ