Inherited Immunodeficiency Disorders

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Objectives
- Formulate a diagnostic evaluation for a child with recurrent infections.
- Distinguish clinical characteristics of patients with humoral immunodeficiency from those with cellular immunodeficiency.

Components of Normal Immunity

Adaptive (Antigen-specific)
- B lymphocytes
- T lymphocytes

Innate (Non-specific)
- Phagocytes
- Complement proteins
B Lymphocytes and Immunoglobulin

- Neutralization
- Opsonization
- Complement activation
- Antibody directing killing

Immunoglobulin Classes

- IgG - major Ig in blood stream, crosses placenta, activates complement, 4 subs
- IgM - primary responder (less efficient) activates complement
- IgA - major secretory antibody, 2 subs
- IgE - immediate hypersensitivity
- IgD - transitional form

Immunoglobulin Deficiencies

- Most common - esp IgA deficiency
- Recurrent sinopulmonary infections
- Extracellular pathogens - primarily encapsulated bacteria
- Few problems with viruses or fungi
- Relatively good outcomes if recognized early
Immunoglobulin Deficiencies

**X-Linked Agammaglobulinemia**
- Lack of all Ig types
- Recurrent bacterial infections at 4 to 6 months when maternal IgG wanes
- Paucity of lymphoid tissue
- Risk of meningoencephalitis with enteroviral infections
- Treated with IVIG
- Due to defect in Btk

**Common Variable Immunodeficiency**
- Recurrent bacterial infections
- Variable presentation with later onset
- Probably autosomal recessive inheritance
- Some autoimmune disease may be present
- Risk of reaction to IVIG if anti-IgA antibodies are present

**Selective IgA Deficiency**
- Most common - (approx 1:1000)
- Most patients are asymptomatic, esp if concentration >10 mg/dl
- Recurrent bacterial infections, esp if concentration <10 mg/dl
- Risk of anti-IgA antibodies
- Some have IgG2 and IgG4 deficiency
Immunoglobulin Deficiencies

IgG Subclass Deficiency
- IgG1 and IgG3 respond best to protein antigens
- IgG2 and IgG4 respond best to polysaccharide antigens
- Isolated low concentrations are not necessarily associated with poor antibody function
- Recurrent infections present if poor antibody production to immunogens

Hyper IgM Syndrome
- X-linked inheritance
- Lack of isotype switch from inefficient IgM to other types
- Recurrent bacterial infections, some opportunistic infections
- Elevated IgM other types low
- Lack of CD40 Ligand (CD154) molecule on helper T cells

Cellular Immunodeficiency
- Recurrent infections with intracellular, often opportunistic infections
- Diarrhea, wasting, growth failure
- Risks with live virus vaccines
- Risk of GVHD and malignancy
- Risk of early death
Cell Mediated Immunity: Functions
- T cell help for Ig production
- Killing of infected cells
- Rejection of incompatible tissue
- Surveillance against malignant transformation
- Cytokine production - directing phagocytes and other cells

Cellular Immunodeficiency
DiGeorge Syndrome
- Defect in embryogenesis in 3rd and 4th branchial pouches
- Causes hypocalcemia, congenital heart disease and immunodeficiency
- Lack of thymus results in low or absent T cell numbers
- Early infections and mucocutaneous Candidiasis
- Some dysmorphic facies
- Defect on chromosome 22 is most common
- Severe form requires immune reconstitution

Combined Immune Deficiencies
Severe Combined Immune Deficiency
- Most severe immune deficiency - early problems with infections
- No immunoglobulin or cell mediated immunity
- Several forms - x-linked, autosomal recessive, adenosine deaminase deficiency, RAG1/RAG2 deficiency
- Early death without immune reconstitution
Combined Immune Deficiencies

- Wiskott-Aldrich syndrome - x-linked, eczema, thrombocytopenia, recurrent infections
- Ataxia telangiectasia - cerebellar ataxia, oculocutaneous telangiectasias, immune deficiency
- Hyper IgE syndrome - recurrent abscesses, high IgE levels, dental anomalies

Phagocytes

- Neutrophils
- Macrophages
- Tissue specific macrophages

Phagocyte Functions

- Chemotaxis
- Adherence
- Enzymatic digestion
- Oxidative degradation
Phagocyte Deficiencies

- Abnormal neutrophil counts
- Adenopathy often present
- Recurrent infections - skin, lungs, lymphoid tissues, deep tissues, oral and anal ulcers
- Staphylococci most common, also unusual organisms

Phagocyte Deficiencies

Chronic Granulomatous Disease

- Unable to produce oxidative "respiratory burst" in phagococytes due to defect in CytP450/NADPH oxidase system
- Catalase producers are organisms involved, esp Staph aureus
- Recurrent skin and deep tissue infections
- Enlarged nodes, liver, spleen
- Abnormal NBT test
- Responds to interferon gamma
- X-linked and AR forms

Phagocyte Deficiencies

Chediak-Higashi syndrome - recurrent Staph infections, large granules in WBCs
- Leukocyte adhesion deficiency - recurrent infections without pus formation, lack of neutrophil adhesion molecules, delayed umbilical cord separation in Type 1
- Cyclic neutropenia - cycles of neutropenia approx every 3 to 4 weeks with infections at nadirs
Complement

- A series of serum proteins that aid in immune function
- C3b is potent opsonin
- C5a is potent chemotactic agent for PMNs
- Bacterial killing through cytolysis
- Immune complex processing

Complement Cascade

C1 (qrs) → C1

C4 + C2 → C42

C3 → C3b

P → C3bBb

D → C3b+B

Immune complex disease

C5 + C6 + C7 + C8 + C9 Neisseria infections

Recurrent bacterial infections

Complement Deficiencies

- Relatively rare
- Classical pathway defects (C1, C2, C4) give lupus-like diseases
- Alternative pathway defects (C3, B.D,P.H,I) give recurrent sinopulmonary infections
- Membrane attack complex defects (C5, C6, C7, C8, C9) give recurrent Neisseria infections
- C1 inhibitor deficiency causes hereditary angioedema (autosomal dominant)
Immunodeficiency: Diagnosis and Treatment

- History
- Physical exam
- Family history
- Laboratory tests
- HIV screening

Ten Warning Signs of Primary Immunodeficiency

- 8 or more new ear infections within 1 year
- 2 or more serious sinus infections within 1 year
- 2 or more months on antibiotics with little effect
- 2 or more pneumonias within 1 year
- Failure of an infant to gain weight or grow normally

* Jeffrey Modell Foundation
Laboratory Tests
Immunoglobulin Deficiency
- Quantitative IgG, IgA, IgM, IgE
- Antibody titers to specific antigens - Tetanus, Diphtheria, ABO blood groups, Pneumococcus
- Post-immunization antibody titers
- IgG subclasses

Laboratory Tests
Cell Mediated Immunity
- Delayed hypersensitivity skin tests (over age 2)
- Lymphocyte count
- T cell enumerations and subsets
- Proliferative responses to mitogens and antigens
- HIV screening

Laboratory Tests
Phagocytes
- Neutrophil counts
- Neutrophil chemotaxis
- NBT test or superoxide generation for oxidative metabolism
- Measurement of adhesion molecules
Laboratory Tests
Complement
- CH50
- Alternative pathway assays
- C3, C4, commonly performed
- Specific complement components
- C4, C1 INH functions for hereditary angioedema

Inherited Immunodeficiency: Treatment
- IVIG for B cell disorders, combined immune deficiencies
- Aggressive antibiotic therapy after determining responsible organism
- Avoidance of live virus vaccines for T cell and combined deficiencies
- Irradiate blood products for severe T cell or combined deficiencies
- May need to go for tissue diagnosis with infections in CGD and cellular defects

Inherited Immunodeficiency: Treatment
- Immune reconstitution for T cell and combined deficiencies
- Interferon gamma for CGD
- Screen for associated conditions and autoimmune disease
- Screen for HIV
- Antibiotic prophylaxis for PCP in cellular defects, TMP-SMX and itraconazole for CGD
- Careful monitoring for malignancies in cellular defects