Immunodeficiency

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Objectives
- Develop a basic understanding of immune deficiency
- Understand the different classes of deficiency
- Be familiar with the more common defects
- Know when to think about immunodeficiency
- To be able to begin the diagnostic process
- Know when consultation is needed.

Immunodeficiency States
- Primary
  - Congenital
  - Genetic
- Secondary – acquired
  - Infections, particularly viruses
  - Malnutrition or malabsorption
  - Medications – corticosteroids, chemotherapy
- Allergic vs. Non-allergic
- Respiratory tract is often involved, but other organ systems may also be affected.
- Otolaryngologists may be exposed to a higher incidence of these problems.

When to Consider Immunodeficiency
- Recurrent or chronic respiratory infections
- Unusual or disseminated infections
- Persistent or unusual organisms
- Immunosuppressive factors
- Other organ system infections
- Consistently poor response to antibiotics
- Recurring CRS post surgery
- Think about it at least once during an Allergy evaluation

Focused Differential Diagnosis for Immune Deficiency
- Cystic fibrosis
  - Autosomal recessive disorder
  - Mutation on CFTR gene on chromosome 7
  - 1:3000 live, white newborns
  - Recurring respiratory infections (Staphylococcus, Pseudomonas)
  - Diarrhea, malabsorption, failure to thrive
  - Spectrum of disease
  - Sweat chloride test
  - Genetic testing

Focused Differential Diagnosis for Immune Deficiency
- Primary ciliary dyskinesia (PCD)
  - Rare problem – 1:10,000 in general population
  - Autosomal recessive in most cases
  - Recurrent rhinosinusitis, OM, pneumonia and bronchiectasis beginning at a young age
  - 50% have laterality problem (ex. situs inversus)
  - 10% have congenital heart disease
  - Males may be infertile
  - Females have ectopic pregnancies
  - Defects may be from protein structure or from disordered orientation of the cilia on mucosal surfaces
### Primary Immunodeficiency Disorders

- **Humoral defects** – impaired antibody production
  - Molecular defect of B cells
  - Failure of interaction of T and B cells
  - Cellular immunity is usually intact
- **Cell-mediated defects**
- **Phagocytic defects**
- **Complement defects**
- **Combined humoral and cell-mediated defects**

### Humoral Defects

- **X-linked agammaglobulinemia**
- **Transient hypogammaglobulinemia of infancy**
- **Hyperimmunoglobulin M syndrome**
- **Common variable immunodeficiency**
- **Immunoglobulin A deficiency**
- **Immunoglobulin G subclass deficiency**
- **Hyperimmunoglobulin E**

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### X-Linked Agammaglobulinemia

- Burton’s agammaglobulinemia
- Low B cell and antibody production
- Onset 6-18 months
- Absence of tonsil and lymph tissue
- 25% have neutropenia as well
- Collagen vascular disease may develop later
- Spectrum of severity
- Rx with IV immune globulin q2-4 weeks
- Normal growth rate and life span

### Transient Hypogammaglobulinemia of Infancy

- Familial pattern
- Low total IgG and delay in T cell-mediated antibody production
- Generally resolves by age 3-4
- Normal immunization responses should occur. If not, consider other diagnosis
- Treatment is antibiotic prophylaxis
- IVIG if needed to prevent infection

### Immunoglobulin M Syndrome

- Rare condition
- Defect is T cell surface molecule for class switching from IgM to other classes
- X-linked and autosomal, some acquired forms seen after lymphoma, anemia and post-rubella
- Opportunistic infections in the first 2 years
- No IgG, occasional IgA or IgE. All IgM
- Normal B cell numbers, but no memory
- Rx is IVIG, steroids to prevent lymphoproliferative disease, plasmapheresis for hyperviscosity, BMT

### Common Variable Immunodeficiency

- CVID is a heterogenous disorder associated with infections, autoimmunity and malignancy
- Bimodal distribution: 5-15 yrs. and 25-45 yrs.
- Sporadic, but some familial cases reported
- Associated with Sarcoidosis and IgA deficiency
- Total IgG low, T cells may be decreased
- Treated with IVIG q2-4 weeks, most respond
Immunoglobulin A Deficiency

- Common: 1 in 700, Whites. 1 in 5000 Asians
- Familial clusters, but no genetic defect found
- Possible cytokine defect in plasma cells
- Links with CVID, IgG subclass deficiency
- One study linked IgA deficiency with atopy: Plebani et al. Comparison of the frequency of atopic disease in children with severe and partial IgA deficiency. Int Arch All Appl Immunol 1987;82:485
- Predisposed to sinopulmonary infections, autoimmune disorders (RA, lupus), malignancy

- Drug induced (reversible) from penicillamine, sulfasalazine, captopril, phenytoin, thyroxine, valproic acid
- Diagnosis made in child over 4 yrs with IgA levels less than 7 mg/dl, normal IgG, IgM
- Most patients are asymptomatic. Children with levels 5 mg/dl usually recover
- Associated with anaphylaxis during blood transfusion (1/3 of patients have anti-IgA)
- Rx: prophylaxis and treatment of infections
- IVIG for failures and if IgG is also low

Immunoglobulin G Subclass Deficiency

- Four subclasses:
  - IgG1 (67%) – soluble protein antigens
  - IgG2 (23%) – pneumococcal polysaccharide, deficiency is more common in children and males
  - IgG3 (7%) – deficiency is more common in women
  - IgG4 (3%) – considered the “blocking antibody” for IT
- Dx: low in one or more subclass + nl total IgG
- Assess child’s response to tetanus and H. flu vaccination for help in making diagnosis
- Most patients are asymptomatic, but associated with recurrent bacterial infections with common pathogens, frequent URI, diarrhea, allergies, asthma, vasculitis or other autoimmune disease

- Recurrent infections
- Job’s syndrome
  - Very elevated IgE and eosinophilia
  - Skin and respiratory tract (usually lower) infections
  - Anti-staph IgE is specific for Job’s syndrome
  - Failure of primary dental exfoliation, scoliosis, hypertelorism, protruding mandible, broad bulbous nose, skin abscesses and positive family history
- Differential diagnosis for elevated IgE
  - Allergy – Atopy
  - Parasitic disease, other infections
  - Malignancy
  - Skin disease, smoking, drugs, RA, burns

William Blake: Satan afflicts Job with boils

Cellular Immunodeficiency

- Congenital T cell defects
  - Presents within the first few months of life
  - Severe mucocutaneous candidiasis
  - Constant URI, diarrhea, failure to thrive
  - Infection following vaccination
- B and T cell defects
  - Severe combined immunodeficiency
  - Bacterial infections after maternal antibodies wane
  - Low immunoglobulin levels, lymphopenia
- Normal lymphocyte counts (50% are T cells)
- 7000 microliter/l in infants
- 4000 in children, 2000 from adolescence on.
- Lymphopenia and other minor cellular defects seen with AIDS
- DTH test (candida, trichophyton, tetanus, streptococcal antigens)
Phagocyte Defects

- Neutrophil disorders characterized by gingivitis, oral ulcers, skin or visceral infections with staph – delayed presentation
- Myeloperoxidase deficiency
  - Most common neutrophil disorder – 1/2000
  - Defective fungi killing (Aspergillus), worse with DM
- Chediak-Higashi S. – lysosomal transport protein defect
- Leukocyte adhesion defect
- Nitroblue tetratolium dye test (NBT) is used to study the metabolism of neutrophils

Cellular Immunodeficiency

- DiGeorge Syndrome
  - Third and fourth pharyngeal pouch anomaly (Chr 21)
  - Agenesis of the thymus and parathyroids
  - Immune deficiency, hypocalcemia, neonatal tetany
- Ataxia-Telangectasia
  - Low IgA, CD3+ and CD4+ T cells
  - Progressive ataxia and ocuculocutaneous telangectasias
  - Increased bacterial respiratory infections and malignancy
- Wiskott-Aldrich Syndrome
  - Combined defect
  - Eczema, thrombocytopenia, repeat opportunistic infections

Phagocyte Defects

- Recurrent systemic bacterial infections
- Best screen is total hemolytic complement (CH50 assay)
- Pneumonia is common with early defects in the classic and alternate pathways
- Recurrent Neisseria bacteremia and meningitis with late component defects (C5-9)
- Early complement defects are associated with collagen vascular disease and lupus
- Other components such as C3 or C4 can be studied

Initial Laboratory Workup

- CBC with differential and platelet count
  - Manual smear for morphology
  - ESR
  - T and B cell counts
- Immunoglobulins
  - IgG, IgA, IgM, IgE
  - IgG subclasses
  - Isohemagglutinins
  - Antibody titers for tetanus, pneumococcus, etc.
- CH50
- Delayed hypersensitivity skin testing
- Chemistry profile

Complement Defects

- Recurrent systemic bacterial infections
- Best screen is total hemolytic complement (CH50 assay)
- Pneumonia is common with early defects in the classic and alternate pathways
- Recurrent Neisseria bacteremia and meningitis with late component defects (C5-9)
- Early complement defects are associated with collagen vascular disease and lupus
- Other components such as C3 or C4 can be studied

Conclusions

- The Rhinologist / Allergist will contact many patients with underlying immunodeficiencies
- Diagnosis requires a high index of suspicion
- Directed screening is easily accomplished
- Recognition will enhance the management of the patient
- Consultation with Immunology should be obtained to follow these patients or to assist in diagnosis.