2021-2022

Immunodeficiency

(1 of 2)

Primary immunodeficiency diseases

- Innate or adaptive
- Most are detected in infancy (6 months – 2 years)
- Rare…but some mild genetic forms exist in many individuals

Defects in Innate Immunity

- ***Defects in Leukocyte Function:***

-adhesion

-phagolysosome function

-microbicidal activity

-TLR signaling

- ***Deficiencies Affecting the Complement System:***

-C2

-components of the alternative pathway (properdin and factor D)

-C3

-terminal components of complement C5, 6, 7, 8, and 9

Defects in leukocyte adhesion

- ***Leukocyte adhesion deficiency type 1***

⬇ β2 chain…shared by the LFA-1 and Mac-1 integrins

- ***Leukocyte adhesion deficiency type 2***

⬇ sialyl-Lewis X, the fucose-containing ligand for E- and P-selectins

…defect in a fucosyl transferase

Both will cause recurrent bacterial infections due to inadequate granulocyte function

Defects in phagolysosome function

- ***Chédiak-Higashi syndrome:***

- autosomal recessive
- defective fusion of phagosomes and lysosomes
- -neutropenia
  -defective degranulation
  -delayed microbial killing
- Leukocytes contain giant granules
- Abnormalities in melanocytes (leading to albinism), cells of the nervous system (associated with nerve defects), and platelets (causing bleeding disorders)
- The gene encodes a large cytosolic protein called LYST, which is believed to regulate lysosomal trafficking

Defects in microbicidal activity

- ***Chronic granulomatous disease***

…recurrent bacterial infections

…defects in the genes encoding components of *phagocyte oxidase*

…X-linked ➡ membrane-bound component (gp91phox)

…AR ➡ cytoplasmic components (p47phox and p67phox)

Defects in TLR signaling

- **Defects in TLR3**…recurrent herpes simplex encephalitis

- **Defects in MyD88**…bacterial pneumonias

C2 deficiency

- The most common complement protein deficiency
- Increased bacterial or viral infections…also if C4 is deficient
- Many patients have no clinical manifestations
- In some of these patients, as well as in patients with C1q deficiency, the dominant manifestation is SLE-like autoimmune disease!!

Deficiency of components of the alternative pathway (properdin and factor D)

- Rare
- Recurrent pyogenic infections

C3 deficiency

- Serious and recurrent pyogenic infections
- Increased incidence of immune complex-mediated glomerulonephritis

Defects in adaptive immunity

- Lymphocyte maturation
- Lymphocyte activation and function
- Deficiencies associated with systemic disorders

SCID

Defects in lymphocyte maturation

- Affected infants:

-oral candidiasis
-extensive diaper rash
-failure to thrive

- Some patients: morbilliform rash…maternal T cells attack the fetus…GVHD
- Without HSC transplantation…death in the first year
- The genetic lesion is not known in many cases
- Often…T-cell problem…secondary humoral problem

X-linked SCID

Defects in lymphocyte maturation

- The most common form of SCID…50% to 60% of cases
- Mutation: γ-chain (γc) subunit of cytokine receptors
  …receptors for IL-2, IL-4, IL-7, IL-9, IL-11, IL-15, and IL-21
- IL-7…survival and proliferation of lymphoid progenitors, esp. T-lineage
- T-cell numbers are greatly reduced
- IL-15…maturation and proliferation of NK cells…also deficiency of NK cells

Autosomal recessive SCID

- **Deficiency of adenosine deaminase (ADA)**

...accumulation of deoxyadenosine and its derivatives (e.g., deoxy-ATP)

toxic to rapidly dividing immature lymphocytes

Defects in lymphocyte maturation

Several other less common causes of autosomal recessive SCID have been identified:

- RAG mutations

  …blocks the development of T and B cells.

- Jak3 (an intracellular kinase)…signal transduction through the common cytokine receptor γ chain

Clinical manifestations & treatment of SCID

- In the two most common forms (γc mutation and ADA deficiency):
  - -the thymus: small and devoid of lymphoid cells
  - -other lymphoid tissues: hypoplastic
    - …marked depletion of T-cell areas
    - …in some cases both T-cell and B-cell zones

- X-linked SCID is the first human disease in which gene therapy has been successful

  …20% of these patients have developed T-cell lymphoblastic leukemia

X-Linked agammaglobulinemia (Bruton agammaglobulinemia)

- Failure of B-cell precursors (pro-B cells and pre-B cells) to develop into mature B cells

- Mutation: *Bruton tyrosine kinase (Btk)*…the gene is on the long arm of the X chromosome at Xq21.22…associated with Ig receptor complex

- Because light chains are not produced, the complete antigen receptor molecule (which contains Ig heavy and light chains) cannot be assembled and transported to the cell membrane

Bruton agammaglobulinemia, clinical notes

- Not apparent until 6 months of age

- Recurrent bacterial infections of the respiratory tract
  …pharyngitis, sinusitis, otitis media, bronchitis, and pneumonia

- Almost always: the infections are by Haemophilus influenzae, Streptococcus pneumoniae, or Staphylococcus aureus…need to be opsonized by antibodies
  …also: viruses in the bloodstream or mucosal secretions or being passed from cell to cell…especially enteroviruses, such as echovirus, poliovirus, and coxsackievirus
  …can disseminate to the nervous system via the blood
  …also: persistent *Giardia lamblia* infections

Most intracellular viral, fungal, and protozoal infections are handled quite well by the intact T cell–mediated immunity

Bruton agammaglobulinemia, cont'd

The classic form of this disease has the following characteristics:

- B cells are absent or markedly decreased in the circulation, and the serum levels of all classes of immunoglobulins are depressed. Pre-B cells, which express the B-lineage marker CD19 but not membrane Ig, are found in normal numbers in the bone marrow.
- Germinal centers of lymph nodes, Peyer's patches, the appendix, and tonsils are underdeveloped.
- Plasma cells are absent throughout the body.
- T cell–mediated reactions are normal.

Robbins and Cotran pathologic basis of disease 9th edition

Bruton agammaglobulinemia, cont'd

- Autoimmune arthritis and dermatomyositis…35%

  … induced by chronic infections associated with the immune deficiency

- Prophylactic intravenous Ig therapy allows most individuals to reach adulthood

DiGeorge syndrome (Thymic hypoplasia)

- A T-cell deficiency

- Failure of development of the third and fourth pharyngeal pouches

- -hypoplasia or lack of the thymus
  -tetany
  -congenital defects of the heart and great vessels
  -abnormal appearance of the mouth, ears, and facies
  -low numbers of T lymphocytes in the blood and lymphoid tissues
  -poor defense against certain fungal and viral infections
  -Ig levels may be normal or reduced, depending on the severity of the T-cell deficiency

DiGeorge syndrome, cont'd

- In many cases, DiGeorge syndrome is not a familial disorder

- Deletion 22q11…in more than 50% of patients

  …*TBX1* gene

- DiGeorge syndrome is a component of the *22q11 deletion syndrome*

Defects in lymphocyte activation and function

Hyper-IgM syndrome

- IgM antibodies are produced but…

  deficiency in IgG, IgA, and IgE antibodies

- Inability of helper T cells to deliver activating signals to B cells and macrophages

- CD40 on B cells, macrophages and dendritic cells interact with CD40L (also called CD154) on antigen-activated T cells

  ⇒ Ig class switching and affinity maturation in B cells

  ⇒ ⇧microbicidal functions of macrophages

Hyper-IgM syndrome, cont'd

- 70%:

  …X-linked

  …mutations in CD40L located on Xq26

- The remainder are autosomal recessive

  … -mutations of CD40

  -mutations of activation-induced cytidine deaminase (AID)…

  required for Ig class switching and affinity maturation

Hyper-IgM syndrome, clinical notes

- Normal or elevated levels of IgM
- No IgA or IgE
- Extremely low levels of IgG
- The number of B and T cells is normal
- Recurrent pyogenic infections…↓ opsonization by IgG
- Also Pneumocystis Jiroveci…defective CD40L mediated macrophage activation
- Occasionally:

  -autoimmune hemolytic anemia, thrombocytopenia, and neutropenia

  -proliferation of IgM-producing plasma cells that infiltrates the mucosa of the gastrointestinal tract…in older patients

Defects in lymphocyte activation and function

Common variable immunodeficiency

- Relatively frequent
- Affects both sexes equally
- Poorly defined entity
- Heterogeneous group of disorders
- The common feature is hypogammaglobulinemia
  …of all classes but sometimes only IgG
- Sporadic and inherited forms
- Relatives of such patients have a high incidence of selective IgA deficiency
- Normal or near-normal numbers of B cells in the blood and lymphoid tissues. These B cells, however, are not able to differentiate into plasma cells

In contrast to x-linked agammaglobulinemia

Common variable immunodeficiency, cont'd

- Abnormalities in B cells and helper T cell-mediated activation of B cells

- Reported to be abnormal here: receptor for a cytokine called BAFF

…also reported in these cases: abnormalities in ICOS (inducible costimulator)…homologous to CD28

Common variable immunodeficiency, clinical notes

- Resembles X-linked agammaglobulinemia
  - …recurrent sinopulmonary pyogenic infections
  - …20%: recurrent herpesvirus infections
  - …Serious enterovirus infections causing meningoencephalitis may also occur
  - …prone to the development of persistent diarrhea caused by *G. lamblia*
  - …the onset of symptoms is later than X-liked agammaglobulinemia

- Lymphoid follicles in nodes, spleen, and gut are hyperplastic → due to incomplete B cell activation

Common variable immunodeficiency, clinical notes…cont'd

- As in X-linked agammaglobulinemia…20% have autoimmune diseases including RA
- The risk of lymphoid malignancy is also increased
- Increase in gastric cancer…reported

Defects in lymphocyte activation and function

Isolated IgA Deficiency

- Common
- Less common in blacks and Asians
- Extremely low levels of both serum and secretory IgA
- Familial or acquired

  ⇓

  toxoplasmosis, measles, or some other viral infections
- Most are asymptomatic
- Mucosal defenses are weakened
- Symptomatic patients commonly present with recurrent sinopulmonary infections and diarrhea

Isolated IgA Deficiency

- Some individuals: also deficient in the IgG2 and IgG4 subclasses of IgG…particularly prone to infections
- High frequency of respiratory tract allergy and a variety of autoimmune diseases, particularly SLE and rheumatoid arthritis
- When transfused with blood containing normal IgA, some of these patients develop severe, even fatal, anaphylactic reactions, because the IgA behaves like a foreign antigen

Isolated IgA Deficiency

- The defect in IgA deficiency is impaired differentiation of naive B lymphocytes to IgA-producing plasma cells
- BAFF receptor defects have been reported

X-Linked Lymphoproliferative Syndrome

- Inability to eliminate Epstein-Barr virus (EBV)

  → -Fulminant infectious mononucleosis
  -Increased risk of tumors

- In about 80% of cases:

  mutation: adaptor molecule called *SLAM-associated protein* (*SAP*)

  …for activation of NK cells and T and B lymphocytes

Immunodeficiencies Associated with Systemic Diseases

- ***Wiskott-Aldrich Syndrome***

…X-linked disease characterized by thrombocytopenia, eczema, and a marked vulnerability to recurrent infection, resulting in early death

- ***Ataxia Telangiectasia***

…autosomal-recessive disorder characterized by abnormal gait (ataxia), vascular malformations (telangiectases), neurologic deficits, increased incidence of tumors, and immunodeficiency

Thank You