

INHERITED IMMUNODEFICIENCIES (3/28 and 3/30)

Inherited immunodeficiencies:

- seen in clinic as recurrent or overwhelming infections in very young children
- primary immunodeficiencies: increased frequency, severity, or persistence of infections (attributable to opportunistic pathogens)
- many immunodeficiencies are found in males as X-linked (recessive) diseases
- can cause susceptibility to infection, autoimmunity, and increased risk of leukemias or lymphomas

I. Immunodeficiencies involving complement:

- **early complement proteins: C1 – C4**
- **late complement proteins: C5 – C9**
- patients with early complement deficiency can have rheumatic problems (glomerulonephritis and systemic lupus erythematosus)
- present as unusual autoimmune disorders, recurrent infections, or disseminated Neisserial infections
- **Total hemolytic complement (CH50) test:** measures fxn of direct complement cascade; single best test when complement deficiency is considered
- AH50 test: measures the fxn of the alternative pathway

A. Deficiency of late complement components (Case 14):

- specifically exhibit an increase in susceptibility to Neisseria infection (*N. gonorrhoea* and/or *N. meningitidis*), occurs in young adults
- 1 in 40 Japanese people are heterozygous for C9 deficiency
- Neisseria are susceptible to complement mediated lysis ONLY when they divide

B. Deficiency of early complement components (Case 13):

- results in increase of rheumatic disorders, pyogenic (pus forming) infections, or both (includes species of *Staphylococcus*, *Streptococcus*, *Pseudomonas*, and *Haemophilus*)
- lack of production of C3b results in defective opsonization of bacteria (no phagocytosis)
- activation of C3 is also required to form MAC, so patients also susceptible to *Neisseria* infections (as in late complement deficiencies)
- Factor I: ensures C3 supplies do not become depleted by inhibiting the C3 convertase of the C3b complex; acts as a serine protease eventually cleaving C3b to iC3b which activates neutrophils and macrophages

C. Hereditary angioneurotic edema (HANE) (Case 12):

- **C1INH** is a complement regulatory protein that prevents adverse consequences from the activation of complement by C1 (occurs spontaneously in plasma)
- HANE is chronic spontaneous complement activation
- C1INH inhibits four serine proteases (which produce C2 kinin and bradykinin, which increase the permeability of postcapillary venules)
- HANE is characterized by recurrent episodes of painless swelling
- swelling in the larynx is the most dangerous symptom (cuts off air supply)

- Tx: significant attacks are treated with C1INH intravenously, long term with anabolic androgens (suppress the symptoms)

D. Paroxysmal nocturnal hemoglobinuria (PNH)

- deficiency of **Decay Accelerating Factor (DAF/CD55)** and **Membrane Inhibitor of Cell Lysis (MIRL/CD59)**
- DAF and MIRL are cell surface proteins expressed on erythrocytes that inhibit complement-mediated cell lysis
- DAF and MIRL are modified by addition of a GPI (glycosyl phosphatidylinositol) that anchors these two components into the cell membrane
- PNH cells are defective in GPI anchor synthesis, the **PIG-A (phosphatidylinositol glycan A)** gene
- causes an increased fragility of erythrocytes, leading to hemolytic anemia, pancytopenia, deficient hematopoiesis, and venous thrombosis
- no Tx, mean survival time is 10-15 years
- always acquired, not inherited

II. Immunodeficiencies involving antibody

- antibodies are critical in the control of extracellular bacteria
- first step in evaluating humoral immunocompetence is quantifying **serum immunoglobulins** (measures total immunoglobulin levels, classes, and IgG subclasses)
- in most cases of B cell deficiency, all lymphoid tissues (except thymus) are hypoplastic, lack a defined germinal center, and are deficient of plasma cells

A. X-linked agammaglobulinaemia (XLA) (Case 2):

- deficiency in ***btk* (Bruton's tyrosine kinase)**
- *btk* mediates the survival and development of pre-B cells into mature B cells
- characterized by no serum immunoglobulins, low numbers of B cells, small tonsils, lymph nodes are rarely palpable
- recurrent pyogenic infections such as otitis media, sinusitis, conjunctivitis, pneumonia, and pyoderma (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Pseudomonas* spp.)
- boys are at risk of acquiring paralytic poliomyelitis from live-virus vaccines
- recurrent infections lead to anatomical destruction, particularly of the lungs
- Tx: monthly intravenous gamma globulin
- other cause have been seen with deletions of μ heavy chain gene and $\lambda 5$ surrogate light chain gene

B. X-linked hyper IgM syndrome (XHIGM) (Case 3):

- T cells are deficient in **CD40L**
- the interaction between CD40/CD40L is the second signal required for Ig isotype switching, it is also important for the production of hematopoietic factors that cause maturation of macrophages
- pts are capable of generating antibodies of IgM isotype which do not require T cell help (such as blood group antigens)

- pts susceptible to pyogenic infections, opportunistic infections (*P. carinii*), autoimmune diseases (autoimmune hemolytic anemia, thrombocytopenic purpura, and neutropenia)
- Tx: monthly intravenous gamma globulin

C. Other hyper IgM syndromes (Case 4)

- possess intrinsic B Cell defects that prevent class switch recombination
- DNA modification enzymes that initiate the DNA repair process leading to class switch recombination are defective
- **activation-induced deaminase (AID)** and **uracil-DNA-glycosylase (UNG)** are two enzymes that, when defective, can cause a HIGM syndrome
- AID is also required for somatic hypermutation (the process that underlies the production of antibodies of increasingly higher affinity for an antigen)
- pts have increased susceptibility to pyogenic infections but they do NOT possess defect in macrophage activation

D. Common variable immunodeficiency

- denotes a group of undifferentiated syndromes
- ALL have defective antibody formation
- for populations of European descent, it is the most common of the primary specific immunodeficiency diseases
- pts have recurrent pyogenic sinopulmonary infections
- decreased serum IgG concentrations (usually decreased serum IgA and IgM, as well)
- appears to be an insufficient in vivo stimulus for B-cell activation
- relatives of these pts have a high incidence of **IgA deficiency** (most common form of immunoglobulin deficiency among Caucasians) and increased incidence of autoimmune disorders manifested as autoantibodies

III. Defects of phagocyte function

- mutation that affects the innate immune system
- pts susceptible to normally nonpathogenic bacteria or fungi
- catalase positive microorganisms and *aspergillus* spp. are characteristic of chronic granulomatous disease
- atypical mycobacteria suggest a defect in the interferon- γ -interleukin-12 axis
- recurrent infections of the lungs, liver, and bone; aphthous ulcers; severe gingivitis; periodontitis; lymphadenopathy (chronic enlargement of lymph nodes) and hepatosplenomegaly (enlargement of liver/spleen) are common

A. Leukocyte adhesion deficiency (LAD) (Case 18)

- LAD-1:
 - Lack of **CD18, a leukocyte integrin**
 - Neutrophils are defective in cell adhesion, migration across blood vessel walls, and ingestion of opsonized bacteria
 - White cells in the bloodstream are very high
 - Infecting pathogens include Gm- enteric bacteria, *S. aureus*, candida spp., and aspergillus spp.
- LAD-2:

- **Absence of sialyl-Lewis X**, which acts as the ligand on neutrophils for endothelial cell E-selectin and perhaps P-selectin (interactions required for leukocyte rolling and eventual extravasion)
 - Thought to be because of a loss of a variety of fucose groups due to either the generation or transport of metabolic precursors of fucose
 - Tx with oral fucose reduces the frequency of infections and fevers
- LAD can be diagnosed through a procedure known as a rebuck skin window: skin is abraded with a scalpel and a cover slip is placed over the abrasion, the cover slip is replaced every few hours and examined for presence of monocytes and neutrophils (LAD patients have no leukocytes present)

B. Immunodeficiencies of the IL-12-IFN- γ axis (Case 40)

- recall the **IL-12-IFN- γ axis**: the presence of a pathogen triggers IL-12 production by dendritic cells and macrophages, this induces the secretion of IFN- γ by T cells and NK cells, IFN- γ activates macrophages and neutrophils which produce TNF- α and activate NADPH oxidase – this promotes killing of the pathogen
- this type of defense is critical against intracellular microbes
- defects in type-1 cytokine (IL-12) or more frequently **type-1 cytokine receptor (IFN- γ R1, IFN- γ R2, IL-12R β 1)** can give rise to infection by poorly pathogenic microorganisms (*Mycobacterium* or *Salmonella* spp.)
- pts exhibit disseminated infections as a result of severely reduced granuloma formation that normally serve to wall off the infection
- a lack of macrophage response to IFN- γ is diagnostic

C. Chronic granulomatous disease (Case 21)

- caused by a genetic defect in any of the four constituent proteins of the **NADPH oxidase system**
- defective intracellular killing of bacteria, phagocytes fail to produce the superoxide radical
- pts have recurrent infections of catalase-positive microorganisms (*S. aureus*, *Burkholderia cepacia*, aspergillus spp., nocardia spp., and *Serratia marcescens*)
- recurrent infections of the soft tissues, lungs, and other organs despite antibiotic therapy
- severe, resistant acne and painful inflammation of the nares (nostrils) are common
- extensive formation of granulomas in all tissues are seen
- most prevalent and severe form is X-linked
- diagnosed by nitroblue tetrazolium test or by flow cytometry with dihydrorhodamine dye; both dyes undergo a color change as a result of reduction by hydrogen peroxide produced by NADPH oxidase
- daily Tx with one single-strength tablet of trimethoprim-sulfamethoxazole reduces frequency of life-threatening bacterial infections (from 1/year to 1/4 years)
- Tx with IFN- γ also improves resistance to infection
- Tx for granulomas with short courses of corticosteroids

IV. Severe combined immunodeficiency (SCID)

- due to an absence of functional T cells (B cells can not function without help from T cells), thus it is fatal

- has many genetic causes, but a uniform phenotype
- affected infants become ill around 3 mos. with persistent thrush or rash in diaper area
- growth and weight gain drop off, infants FAIL TO THRIVE
- persistent infections include *Candida albicans*, *P. carinii*, varicella, adenovirus, respiratory syncytial virus, para-influenza virus type 3, cytomegalovirus, Epstein-Barr virus (EBV), and bacilli Calmette-Guérin (ALL are fatal)
- defects that affect T cell number or activity also affect the humoral immune system because of the T helper cell requirement to activate B cells
- early diagnosis is made possible by lymphopenia (low numbers of white blood cells)
- *in vitro*, these lymphocytes do not proliferate in the presence of nonspecific mitogens (e.g. phytohemagglutinin) or allogeneic stimuli/specific antigens (e.g. tetanus toxoid)
- immunoglobulins in the pt serum are low/undetectable and lymph nodes and tonsils are absent
- Tx: bone marrow transplant
- bone marrow transplant also puts the patient at risk for graft-versus-host disease

A. X-linked SCID (Case 6)

- due to a mutation in the **gamma chain** of the IL-2 receptor
- 3X more likely to occur in ♂, most common form of SCID (55% of total cases)
- the gamma chain is part of several interleukin receptors (IL-4, IL-7, IL-9, IL-15)
- pts have normal numbers of B cells, but they are immature and nonfunctional

B. Adenosine deaminase (ADA) deficiency (Case 7)

- due to deficient **adenosine deaminase (ADA)**
- represents the remainder of SCID cases, autosomally inherited
- lack of ADA creates a build up of nucleotide metabolites that are toxic to developing T and B lymphocytes
- Tx: regular injections of ADA conjugated to polyethylene glycol
- Tx: gene therapy (this was the first problem corrected with gene therapy), but has to be repeated every few months

C. Omenn's syndrome (Case 11)

- caused by a mutation in either **RAG1 or RAG2**
- a mutation in either gene reduces recombination efficiency without entirely abrogating the capacity for rearrangement of both T and B cell antigen specific receptors
- pts have variable numbers of T cells with restricted receptor rearrangement heterogeneity and B cells are virtually absent
- pts have lymphadenopathy, hepatosplenomegaly, erythrodermia (abnormal redness of the skin due to capillary congestion), eosinophilia, and increased levels of IL-4, IL-5, and IL-10, there are elevated levels of IgE in the serum
- Tx: bone marrow transplant (the disease is rapidly fatal otherwise)

V. Other SCID-like immunodeficiencies:

A. Wiskott-Aldrich syndrome (WAS) (Case 19)

- due to a defective **WASP** gene (role as a key regulator of lymphocyte and platelet fxn)

- inherited as an X-linked disease
- profound thrombocytopenia (abnormal decrease in the number of platelets in circulatory blood) with small platelets is diagnostic
- serum IgM is low, IgA and IgE are elevated, total IgG concentrations are normal
- pts are susceptible to pyogenic and opportunistic infections such as chickenpox, herpes simplex, and molluscum contagiosum
- pts do not make antibodies to polysaccharide antigens and have a poor response to protein antigens
- T cells exhibit disorganization of the **actin cytoskeleton** and loss of microvilli
- platelets in circulation become spontaneously activated
- T cells are unable to form immunologic synapses (between APCs and T cells) or emigrate from the thymus – both processes that require actin rearrangement
- CD8+ T cells have impaired cytotoxic fxn and impaired secondary responses (increased affinity and class switching) to protein and polysaccharide antigens – this reflects the defect in interactions between the T and B cells
- the disease is managed with splenectomy and intravenous immune globulin therapy
- bone marrow transplants have also been successful

B. MHC class I and class II deficiencies (Bare Lymphocyte Syndromes) (Cases 5 and 25)

- SCID-like symptoms due to deficiencies in MHC expression; antigens can not be presented to T cells
- this is NOT an intrinsic T cell defect (pts have T cells that respond to nonspecific T cell mitogens)
- **type 1 BLS:**
 - Deficiency in class I MHC expression
 - Due to mutations in **TAP1 or TAP2** genes
 - TAP proteins are required for loading peptides onto MHC class I molecules
 - Pts have repeated infections of the sinuses, middle ears, and lungs
 - Pts have normal humoral immunity (high levels of serum IgG)
 - Pts have skin lesions because killer inhibitory receptors (KIRs) on NK cells are not engaged by contact with self MHC class I leading to excessive activation of NK cells
- type 2 BLS:
 - Deficiency in class II MHC expression
 - Due to mutation in **CIITA**, which functions as a transactivator of MHC class II genes
 - Pts have severe, protracted diarrhea associated with candidiasis, cryptosporidiosis, and failure to thrive
 - Pts have insufficient numbers of CD4+ T cells because CD4+ T cells can not be selected positively in the thymus
 - Without MHC II molecules, antigen can not be presented to CD4+ T cells (the few that exist) and pts have low levels of gamma globulins

VI. Clinical assessment of lymphocyte function:

- immunodeficiencies can be narrowed down through a **battery of tests**
- first step is a CBC (complete blood count) and a differential (assess the lymphocyte and other blood cell numbers)

- the presence of various blood cell types is determined by hematology followed by Fluorescence Activated Cell Sorting (FACS) which gives a profile of relative lymphocyte populations
- fluorescently labeled monoclonal antibodies can be used to assess the proportion of major cell subsets in peripheral blood; α -CD3 (total T cells), α -CD4 (CD4+ T cells), α -CD8 (CD8+ T cells), α -CD19 (total B cells), and α -CD16/CD56 (total NK cells)
- delayed-type hypersensitivity skin tests can screen for defects in cell-mediated immunity
- lymphocyte function can be measured in vitro by culturing lymphocytes with mitogenic agents and then measuring proliferation; antigens can be tested in pts who have previously been exposed (e.g. tetanus toxoid)
- cytokine levels can be assessed by using ELISA or flow cytometry

VII. Transplantation or gene therapy may be useful to correct inherited immunodeficiencies:

- currently BMT (bone marrow transplantation) is the best available treatment for SCID patients (pts)
- GVH (graft-versus-host) disease is the greatest danger in immunologic reconstitution using bone marrow cells
- the danger of GVH disease can be lessened by depleting mature T cells from the donor bone marrow
- hematopoietic stem-cell transplantation offers pts up to a 95% chance of survival if transplanted within the first 3 months of life
- the ultimate cure is inserting correct copies of the defective gene into bone marrow pluripotent stem cells

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