Primary Immunodeficiencies

Elsa Sotelo

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Primary Immunodeficiencies

- Humoral immunity defects (affecting B-cell differentiation or antibody production)
- T-cell defects and combined B- and T-cell defects
- Phagocytic disorders
- Complement deficiencies
- Miscellaneous

Disorders of Humoral Immunity

- Make up 50% of primary immunodeficiencies
- Patients present after 6 months when maternal antibodies are lost
- Recurrent bacterial sinus and pulmonary infections are the hallmark
- Intact cellular immune system are able to handle most viral and fungal pathogens

Subgroups

- Common Variable Immunodeficiency
- Selective IgA deficiency
- Bruton's or X-linked agammaglobulinemia
- Selective antibody deficiency

Common Variable Immunodeficiency

- Most frequently diagnosed
- Encompasses a heterogenous group of disorders that cause hypogammaglobulinemia (gamma-globulins 200-300 mg/dL)
- Defective antibody formation with normal number of B and T-cells
- Decrease in IgG and IgA are more common
- 50% will also have an IgM deficiency

Presentation

- Presents at different ages but most commonly occurs in late childhood or early adulthood
- Patients present with giardiasis and bronchiectasis
- Increased risk of malignancies such as gastric cancer and lymphoma, amyloidosis, autoimmune disorders and IgA deficiency
- Poor response to vaccination

Selective IgA Deficiency

- May have highest incidence but often undiagnosed
- B-lymphocytes are unable to mature to IgA producing plasma cells
- Caused by deletions of IgA1 and 2 on chromosome 14 and partial deletion of the long arm of chromosome 18
- Serum IgA levels are usually less than 5 mg/dL
- IgG and IgM levels are normal

Presentation

- Patients often have sinusitis and respiratory tract infections along with GI involvement
- Common organisms are pyogenic bacteria
- Increased risk of allergies, autoimmune disorders and lupus-like syndromes

X-linked Agammaglobulinemia/Bruton's

- Caused by a mutation or absence of the Bruton's tyrosine kinase gene (BTK) which is responsible for maturation
- Early B-cell development is arrested and serum immunoglobulins are markedly deficient or absent (less than 100 mg/dL)
- T-cells are normal in number
- Lymph nodes show hypoplasia, absence of germinal centers and decreased plasma cells
- Different BTK mutations give rise to different phenotypes

Presentation

- May not present until 3-5 years old
- Patients present with recurrent respiratory tract, joint, CNS and systemic infections
- Most common bacteria are S. pneumonia, H. influenza and streptococcus
- Susceptible to viral hepatitis
- Reports of paralysis following live polio vaccinations

Selective Antibody (class and subclass) deficiency

- Many individuals harbor subclass (IgG1-4) deficiencies
- Total serum IgG concentration may be normal or abnormal depending on the subclass
- 70% of IgG is IgG1 and 1-2% is IgG4
- IgA and IgM levels are normal
- 1/5 of IgA deficient patients have a concomitant IgG subclass deficiency

T-cell and Combined B and T-cell Defects

- Make up about 30% of the primary immunodeficiencies
- Present before 6 months
- Severe infections with viruses, fungi and mycobacterium
- Failure to thrive

Subgroups

- DiGeorge Syndrome
- Severe Combined Immunodeficiency
- Wiskott-Aldrich Syndrome
- Ataxia-telangiectasia
- Hyper-IgM
- Major Histocompatibility Complex Deficiency

DiGeorge Syndrome

- Caused by a deletion in chromosome 22q11
- Results from an abnormal migration of the third and fourth branchial pouches during embryogenesis
- Hypoplasia to aplasia of the thymus and parathyroids
- Hypocalcemic tetany
- Associated defects include Truncus Arteriosis, Tetralogy of Fallot, esophageal atresia and dysmorphic facial features

Presentation

- Presents within the first few months
- Characterized by viral, fungal and protozoal infections
- Dissemination is common
- CD 3 T-cell count is usually less than 500 per mL
- Normal immunoglobulin concentrations
- Some may have decreased IgA and increased IgE

Severe Combined Immunodeficiency

- Presents in the first few months of life
- Characterized by severe opportunistic infections such as Candida, measles, varicella, CMV and Pneumocystis
- Patients also present with chronic diarrhea, failure to thrive and an increased risk of graft vs host disease

SCID

- Clinical and laboratory evaluation reveals absence of cellular immune function manifested by lymphopenia, cutaneous anergy and absence of lymphocyte proliferation response
- Serum immunoglobulin concentrations are depressed and antibody response to immunization is difficult to detect
- T-cells have an immature phenotype resembling Stage I or Stage II thymocytes
- Subclassified into T-B- and T-B+

T-B-

- RAG1 and RAG2 deficiencies (recombinant activating genes)
- Omenn syndrome: erythroderma, eosinophilia, increased IgE and hepatosplenomegaly
- Reticular dysgenesis: failure of bone marrow stem cell production; patients are lymphopenic and granulocytopenic

T-B+

- Autosomal recessive harboring JAK 3 mutations (tyrosine kinase that transduces the interleukin gamma chain receptors)
- X-linked caused by mutations in the gene that codes the common gamma chain of IL-2, 4, 7, 9 and 15 receptors

Abnormal Purine Metabolism

- Dysfunction of adenosine deaminase (ADA) and purine nucleoside phosphorylase (PNP) enzymes can lead to accumulation of toxic intermediates that cause loss of lymphocytes
- Both B and T-cells are decreased
- ADA deficient patients have skeletal abnormalities
- PNP deficiencies are associated with neurologic abnormalities and autoimmune disorders

Hyper IgM

- Caused by a mutation in CD 40L gene which prevents immunoglobulin production
- Can be X-linked, AD, AR or acquired
- Exhibit low concentrations of IgG, IgA and IgE and a polyclonal increase in IgM
- Patients present in infancy with pneumonia, sinusitis, otitis media and tonsillitis
- Have pronounced lymphadenopathy
- May have autoimmune hemolytic anemia and thrombocytopenia

Major Histocompatibility Complex Deficiencies

- Divided into type I and type II
- Type I is associated with low levels of HLA class I molecules and chronic infections of the respiratory tract and vasculitis
- Type II results in a profound combined immunodeficiency with fungal and protozoal infections of the respiratory and GI tract
- Type II is AR and is caused by mutations in at least three different transcription factors (RFX5, RFXAP, and MHC2TA)
- B and T-cells are present in normal number but HLA-DR is absent

Wiskott-Aldrich

- The gene is X-linked and encodes the Wiskott-Aldrich syndrome (WAS) protein responsible for actin filaments in the cytoskeleton
- T-cells are decreased due to decreased or absent CD 43 (glycoprotein for T-cell activation and proliferation)
- Decreased IgM, low or normal IgG and increased IgA and IgE

Presentation

- Characterized by eczema, thrombocytopenia, small platelets and platelet dysfunction with a normal amount of megakaryocytes in the bone marrow
- Patients exhibit impaired humoral response to encapsulated and high-grade bacterial pathogens resulting in otitis media, pneumonia, meningitis and sepsis
- Later patients suffer from Herpes and Pneumocystis infection
- Increased risk of autoimmune disease and cancer

Ataxia-telangiectasia (Louis-Bar's syndrome)

- Progressive neurologic disorder associated with cerebellar ataxia, oculocutaneous telangiectasias, chronic respiratory infections, a high incidence of malignancy
- Variable humoral and cellular immunodeficiency
- B cell numbers and IgM concentrations are normal to low
- IgG is often reduced and IgA is considerably reduced (in 70% of the cases)
- Occurs in childhood
- Defects arise from a breakage in chromosome 14 at the site of TCR and Ig heavy chain genes
- Disorder of DNA repair

Phagocytic Disorders

- Chronic granulomatous disease (CGD)
- Leukocyte Adhesion Deficiency
- Chediak-Higashi syndrome

CGD

- Most frequently diagnosed phagocytic primary immunodeficiency
- Characterized by marked lymphadenopathy, hepato-splenomegaly and chronic draining lymph nodes
- 70 % are X-linked and 22% are AR
- Leukocytes have poor intracellular killing and low respiratory burst
- Deficiency is due to a defect in NADPH oxidase that participates in phagocytic respiratory burst
- Patients are susceptible to catalase + organisms (Staph)
- Aspergillus is the most common cause of death

Leukocyte Adhesion Deficiency

- Leukocytes lack the complement receptor CR3 due to a defect in CD11 or CD18 peptides and consequently they cannot respond to C3b opsonin.
- Alternatively there may a defect in integrin molecules, LFA-1 or mac-1 arising from defective CD11a or CD11b peptides
- These molecules are involved in diapedesis and hence defective neutrophils cannot respond effectively to chemotactic signals
- Patients suffer from recurrent bacterial infections without much pus, periodontitis, delayed wound healing, elevated leukocyte counts and a history of delayed shedding of the umbilical cord stump
- Soft tissue infections are common and severe mainly with S. aureus, Pseudomonas and enterobacteraceae

Chediak-Higashi syndrome

- AR caused by a mutation in the CHS1 gene that encodes a protein involved in organelle trafficking
- Marked by reduced (slower rate) intracellular killing and chemotactic movement accompanied by inability of phagosome and lysosome fusion and proteinase deficiency
- Respiratory burst is normal
- Accompanying NK cell defect and platelet and neurological disorders are noted

Complement Disorders

- Account for less than 1% of immunodeficiencies
- Most are autosomal recessive (except for C1 esterase inhibitor)
- Result in recurrent infections, SLE, lupus-like disorders, autoimmune disorders or glomerulonephritis
- Majority are asymptomatic
- Patient with defects in the lytic pathway (C5, C6, C7 or C8) have infections with Neisseria
- Angioedema is associated with a C1 esterase inhibitor deficiency
- C3 deficiency leads to reduced serum opsonization and an increased incidence of severe infections due to encapsulated organisms
- C5 and C9 (Japan) have reduced hemolytic complement activity

Hyper-IgE Syndrome (Job's Syndrome)

- Autosomal dominant disorder of unknown cause
- Patients suffer from recurrent staphylococcal abscesses involving the skin, lungs, joints, and soft tissues
- May suffer from generalized dermatitis
- Job's syndrome is associated with a neutrophil motility defect attributed to defective production of interferon-gamma
- The poor production of interferon-gamma in response to IL-12 results in the marked elevation of IgE levels (by means of unopposed IL-4 action).
- IgE levels are increased in excess of 2000IU/Ml
- Peripheral eosinophilia is characteristic

Chronic Mucocutaneous Candidiasis

- Syndrome marked by chronic candidal infections of the skin and mucous membranes
- Not fatal
- Cause is unknown
- Have accompanying endocrinopathies
- Treatment is ketoconazole

X-linked Lymphoproliferative Syndrome (Duncan disease)

- Defects in the XLP (LYP) gene located at Xq25
- Abnormal response to EBV infections
- 70% die as a result of an intense lymphocyte proliferation that occurs during mononucleosis
- Often accompanying depression of T-cell immunity if survival is achieved
- Some patient's have normal B and T-cells with an elevated percentage of CD 8+ cells

Diagnosis

- Immunodeficiencies should be suspected when recurrent infections are severe, complicated, resistant to treatment or caused by unusual organisms
- Should also be suspected with chronic diarrhea, failure to thrive, skin lesions, oral or esophogeal thrush, oral ulcers and periodontitis
- Onset of infections before 12 months of age suggest combined B and T-cell or B-cell defects
- In general, the earlier the age, the more severe the immunodeficiency

Diagnosis

- Initial screening tests include:
  - CBC with diff to look for WBC and platelet count
  - Quantitative Ig measurements
  - Antibody titers
  - Skin testing for delayed hypersensitivity
  - Antibody response to vaccination

Diagnosis

- If initial tests are abnormal then:
  - Flow cytometry
  - In vitro mitogen stimulation
  - Serologic HLA typing for MHC deficiency
  - Flow cytometric respiratory burst assay to detect whether oxygen radicals are produced during phagocytosis
  - Nitroblue tetrazolium (NBT) test
  - Complement assay (CH50) test
  - DNA tests

Prenatal Diagnosis

- Can be done using chorionic villus sampling, cultured amniotic cells or fetal blood sampling
- Only done when a mutation in family members is identified

Treatment

- IVIG is standard therapy
- Bone marrow transplant for cellular deficiencies (SCID, Wiskott-Aldrich and DiGeorge) and may be beneficial in chronic granulomatous disease
- Patients with T-cell deficiencies require chemotherapy prior to transplantation
- Some reported benefit from thymus transplantation for DiGeorge
- Prophylactic antibodies
- Enzyme replacement in ADA deficiency
- Interferon-γ therapy for chronic granulomatous disease
- Gene therapy

Prognosis

- Ig or complement deficiencies have a near normal life expectancy if diagnosed early and treated appropriately
- Phagocytic and combined deficiencies have a guarded prognosis
- Combined B and T-cell and T-cell deficiencies have a poor prognosis
- SCID will die during infancy unless immunity can be restored through transplant before 3 months of age

References

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