26th Annual General Pediatric Review & Self-Assessment

Nicklaus Children's Hospital

IMMUNOLOGY

Vivian Hernandez-Trujillo, MD

Allergy & Immunology Care Center of South Florida
Miami Lakes, Florida
Medical Director, Division of Allergy-Immunology
Fellowship Training Program Director
Nicklaus Children's Hospital
Miami, Florida

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Disclosure of Relevant Relationship

Dr. Hernandez-Trujillo disclosed relevant conflicts of interests (COIs) and/or financial relationships in the past 24 months with the following ineligible companies:

Ineligible Company(ies)	Topic	Role/ Type of Relationship
DBV	Food Allergy	Independent Contractor (Speaker Bureau)
US World Meds & Kaleo	Anaphylaxis	Independent Contractor (Speaker Bureau)
Covis	Asthma	Independent Contractor (Speaker Bureau)
Takeda & CSL	Immunodeficiency	Independent Contractor (Speaker Bureau)

All COIs have been mitigated prior to this activity

Dr. Hernandez-Trujillo will support this presentation and clinical recommendations with the "best available evidence" from medical literature.

Dr. Hernandez-Trujillo does not intend to discuss an unapproved/investigative use of a commercial product/device in this presentation.

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Immunodeficiency (ID)

- Definition: ID is the result of a diverse group of abnormalities of the immune system resulting primarily in an increased incidence of infection
- Primary: Congenital and hereditary
- Secondary: Acquired on a transient or permanent basis

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PRIMARY ID

COMMON:
- Selective IgA deficiency (1:500)
- Selective antibody deficiency
- DiGeorge anomaly
- Transient hypogammaglobulinemia of infancy

UNCOMMON:
-B-cell disorders: XLA 1-4:1,000,000,
CVID 1:75,000
-T-cell disorders: SCID 1:100,000
-Phagocytic disorders: CGD 1:500,000
-Complement disorders

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Primary ID General Considerations

- 58% of cases diagnosed in children less than 15 years old
- 83% of these are male
- Mode of transmission:
  - X-linked
  - Autosomal dominant
  - Autosomal recessive
  - Sporadic inheritance patterns observed

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Importance of Early Detection

- Prevention of life-threatening infection
- Avoidance of non-irradiated blood transfusions
- Avoidance of live viral vaccines
- Genetic Counseling
- Earlier diagnosis and improve therapeutic interventions allowing more children to survive in adulthood

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Development of the Immune System

- B and T Cell Function begin in the late first Trimester
- Lymphocyte counts in neonates and infants > 3000***
- Only maternal IgG present at birth**
- Even premature infants capable of synthesizing antibody at birth

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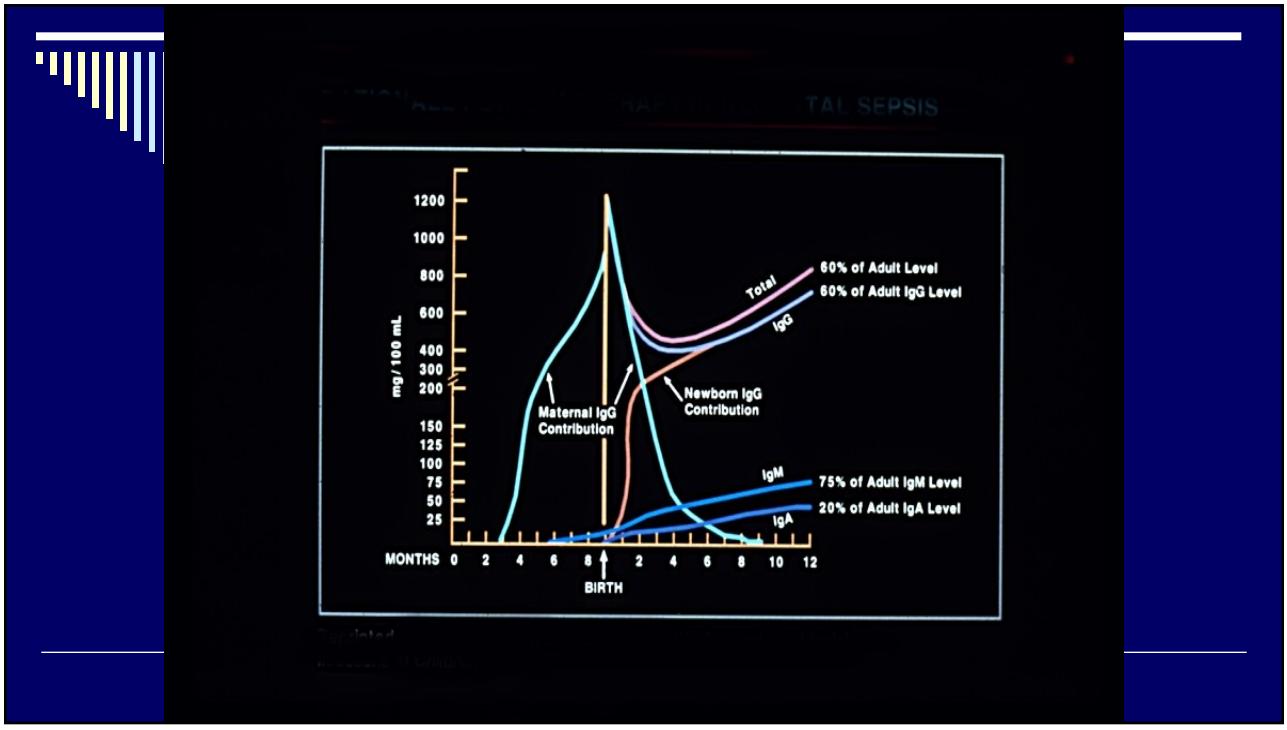

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Development of Immune System

- Immunoglobulin Production:
  - IgM > IgG > IgA
- Response to protein antigens present at birth
- Response to unmodified carbohydrate (polysaccharide) antigens develops after 2 years of age
- Response to polysaccharide antigens not fully mature until 7-10 years of age

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Clinical Features of Primary ID

- Increased frequency, severity and duration of infection
- Unexpected complications or unusual manifestations of infections
- Infections with organisms normally considered of low pathogenicity
- Noninfectious manifestations in gastrointestinal, endocrinologic and hematologic systems

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Common Clinical Findings in Primary ID

- Recurrent respiratory infections
- Persistent sinus infection
- Paucity of lymphoid tissue**
- Failure to thrive (FTT) in infants**
- Skin lesions (rash, pyoderma, eczema)
- Oral & perianal candidiasis
- Diarrhea and malabsorption**

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Indications to Evaluate Humoral Immune System

Recurrent Sinopulmonary Infections
Recurrent Meningitis, Sepsis
Chronic Diarrhea
Infections with Unusual organisms

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Indications to Evaluate Cellular Immune System

- Persistent Fungal Infection
- Viral Infections (HSV, VZ, CMV, EBV, enterovirus)
  - Protozoa (Cryptosporidium, toxoplasmosis)
  - Mycobacteria
  - Fungal (Candida, PCP)
  - Bacteria, gram negative enteric
- Persistent Diarrhea
- Failure to thrive
- Lymphocytopenia**- Risk for GVHD

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Case study

- 11 year old male with recurrent sinus infections. Also, history of “reaction” with blood transfusion in past. Otherwise, growing well. Active. Good appetite.

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Question: What diagnosis does this patient have?

A. No Primary Immunodeficiency
B. Selective Antibody Deficiency
C. Selective IgA deficiency
D. X linked Agammaglobulinemia

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Selective IgA deficiency

- **Most frequently occurring ID**
- **Serum IgA < 10mg/dL**
- **Most patients are asymptomatic**
- **Assoc. with recurrent sinopulmonary infection, autoimmune, GI & endocrine disorders**
- **Development of anti-IgA Ab may lead to severe anaphylactic reactions with blood transfusions- need IgA depleted blood products*****
- **Treatment – Observation; prophylactic antibiotics**

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Case study

- 8 month old child with frequent upper respiratory infections (URI). One episode of otitis media. Otherwise, good appetite and growing well.
- Labs reveal IgG of 180 (low for age) Normal IgA and IgM

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Question: What diagnosis does this patient have?

A. Selective Antibody Deficiency
B. Transient Hypogammaglobulinemia of Infancy
C. Selective IgA deficiency
D. X linked Agammaglobulinemia

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Transient Hypogammaglobulinemia of Infancy

- Begins in infants below the age of one year. IgG typically within normal limits by the age of 5 years.
- Usually children grow well
- Frequent URI
- Laboratory evaluation reveals decreased IgG, normal IgM and IgA. Normal specific antibody responses.
- Treatment: Observation for most; in the case of severe infections requiring hospitalization, consider IVIG/SCIG

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Case study

- 30 month old male with recurrent sinusitis. As a 9 month old infant, episode of Hemophilus Influenza type B meningitis despite routine immunizations. Growing well. Development milestones normal.
- Poor response to pneumococcal vaccines.

23

Question: What diagnosis does this patient have?

A. Selective Antibody Deficiency
B. Transient Hypogammaglobulinemia of Infancy
C. Selective IgA deficiency
D. X linked Agammaglobulinemia

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Specific Antibody Deficiency

- **Present with recurrent infections with Otitis Media, Sinusitis and Pneumonia.**
- **Grow well.**
- **Patients unable to respond to polysaccharide antigens, specifically pneumococcus and Hemophilus influenza type B. Less than fourfold increase in titers post-vaccine.**
- **Treatment: Require close monitoring. If recurrent infections, likely need IVIG/SCIG.**

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IgG subclass Deficiency

- Deficiency in IgG subclasses has been reported in some individuals
- Recurrent pyogenic infection has been assoc. with some individuals
- ***Most individuals with IgG subclass deficiency are asymptomatic***
- Relationship of IgG2 deficiency to IgA deficiency
- ***Clinical significance of IgG subclass deficiency is variable- controversial****
- If assoc with specific antibody deficiency, may treat with IVIG

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Case Study

- 18 year old female presents with history of recurrent sinus infections and "bronchitis." Chronic cough. Responds well to antibiotics. Otherwise unremarkable medical history as young child.

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Question: What diagnosis does this patient have?

A. Selective Antibody Deficiency
B. Common Variable Immunodeficiency
C. Selective IgA deficiency
D. X linked Agammaglobulinemia

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Common Variable ID (CVID)

- **Onset usually in 2nd or 3rd decade of life****
- **Slow decline in all classes of immunoglobulin (IgG,A,M,E)**
- **Recurrent sinopulmonary infections (usually bacterial in origin)**
- **May follow Epstein-Barr infection**
- **Can be assoc. with GI (sprue & colitis), endocrine (hypothyroidism) & hematologic disorders (lymphoma)**

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CVID (cont)

- Increased Incidence of Autoimmune Disease
- High Incidence of Chronic Diarrhea and Malabsorption
- May be Associated with Lymphadenopathy, Hepatosplenomegaly, Interstitial Pneumonia
- Treatment- IVIG/SCIG, prophylactic antibiotics

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Case study

- 7 month old male with history of failure to thrive beginning at 4 months of age. Chronic diarrhea. Hypoproteinemia. Losing milestones- no longer rolls, smiles.
- Family history of two unexplained infant male deaths.

33

Question: What diagnosis does this patient have?

A. Autosomal recessive Agammaglobulinemia
B. Transient Hypogammaglobulinemia of Infancy
C. Selective IgA deficiency
D. X linked Agammaglobulinemia

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X-Linked Agammaglobulinemia (XLA or Bruton's)

- **Gene defect chromosome on Xq21.3-22; B-cell tyrosine kinase deficiency**
- **Infections begin 6 weeks to 6 months**
- **Absent circulating mature B-cells <1% (Block from Pro B cell to Pre B Cell stage, some patients block after Pre B cell)**
- **All major classes of immunoglobulin affected (IgG, IgM, IgA, IgE)**
- **To diagnose an infant, obtain lymph subsets- maternal Ab production will obscure immunoglobulins****

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XLA

- Pyogenic infections, Giardia,*** Enteroviral –red flag if loss of milestones- R/O meningitis***
- PCP
- May Have Family History of Males with Infections or Death in Infancy
- Paucity of Lymphoid Tissue on Exam- absent tonsils and lymph nodes***
- Treatment- Lifelong IVIG/SCIG, prophylactic antibiotics

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Case study

- 5 year old male with history of recurrent infections. Recurrent lymphadenopathy. Has had "enlarged liver." Also, developed autoimmune hemolytic anemia and thrombocytopenia at 2 years old.

38

Question: What diagnosis does this patient have?

A. Chronic Granulomatous Disease
B. Hyper IgE syndrome
C. Hyper IgM syndrome
D. Wiskott Aldrich

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Hyper IgM Syndrome

- **Multiple causes- CD40 (B cells) deficiency, CD40 ligand (T cells) deficiency, Activation Induced Deaminase (AID) deficiency, Uracil DNA Glycosylase (UNG), NF kappa beta essential modulator (NEMO); no isotype switching occurs**
- **Polyclonal normal to increased IgM**, lack IgG,A,E**
- **Infection from encapsulated bacteria**
- **Autoantibody production (hemolytic anemia, thrombocytopenia, neutropenia)**
- **Lack of immune surveillance: hepatocellular carcinoma****
- **Treatment- BMT- haplo-identical sibling, IVIG/SCIG, prophylactic antibiotics**

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Case study

- 8 year old male with recurrent “abscesses” of the skin. “Problems” with lung infections. Face looks “coarse.” Had history of “eczema” since infancy. Retained primary teeth.

  Bony abnormalities and pneumatoceles on chest film.

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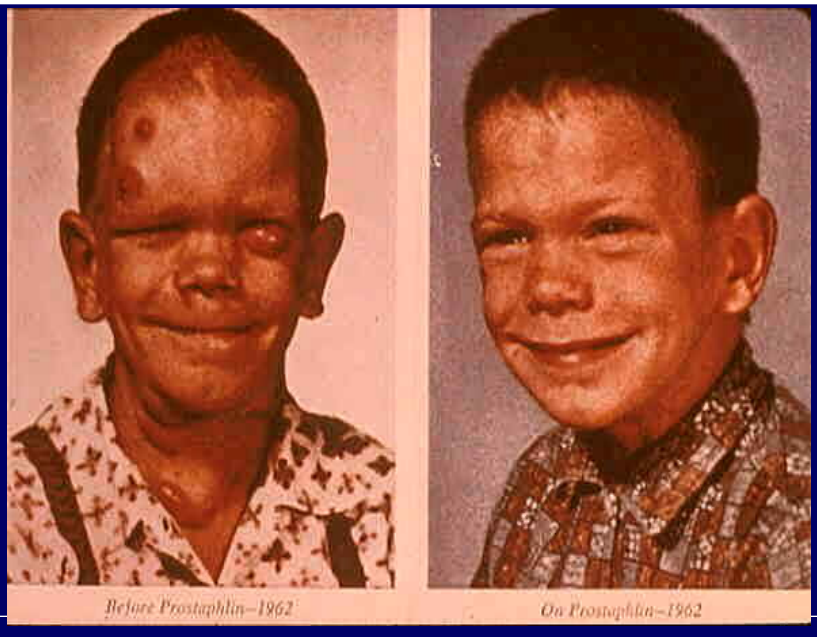

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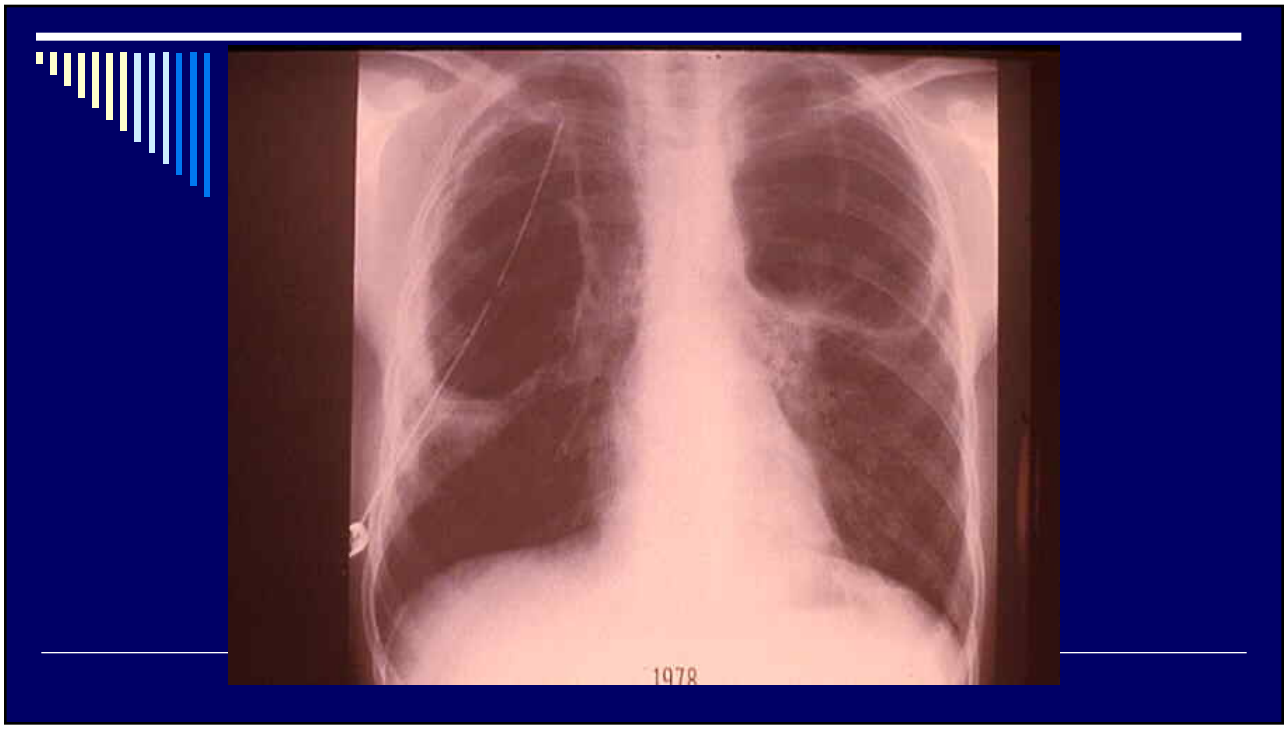

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Question: What diagnosis does this patient have?

A. Chronic Granulomatous Disease
B. Hyper IgE syndrome
C. Chronic Mucocutaneous Candidiasis
D. Wiskott Aldrich

45

Hyper IgE Syndrome (Job Syndrome)

- Most sporadic, AD (STAT 3) and AR (DOCK8) forms exist
- Severe recurrent abscesses (Staph) in skin, lungs, viscera**
- Increased IgE; Low to normal IgG, A, M
- Increased blood and sputum eosinophilia
- Pruritic Dermatitis-face, scalp, neck**
- Coarse facial features**
- Delayed or lack of shedding primary teeth
- Chronic lung disease and lymphoreticular malignancy
- Treatment- prophylactic antibiotics- Anti-Staph

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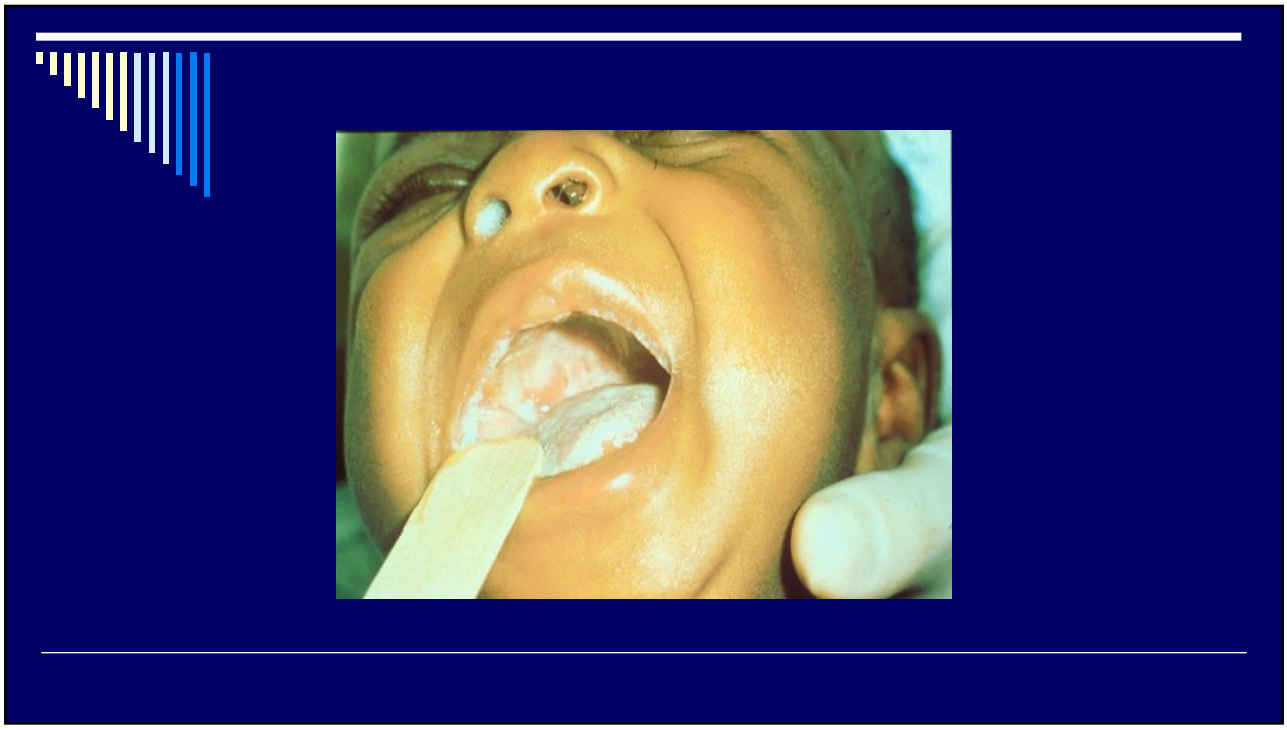
Case study

- 10 day old male with history of seizures 3 days after birth. Congenital heart disease diagnosed prenatally, requiring surgical repair. Fish-shaped mouth with posteriorly rotated ears. Chest films shows absent sail sign (no thymus).

48



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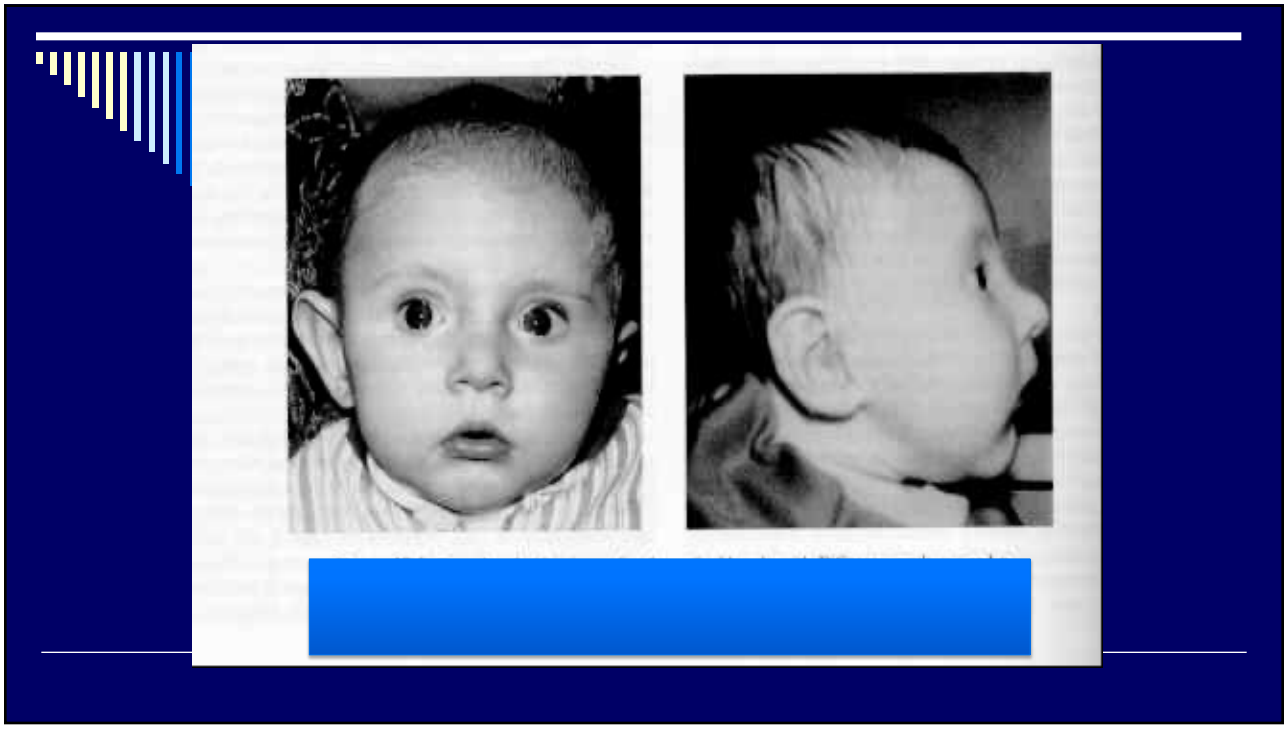

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Question: What diagnosis does this patient have?

A. Chronic Granulomatous Disease
B. DiGeorge Syndrome
C. Chronic Mucocutaneous Candidiasis
D. Wiskott Aldrich

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DiGeorge Syndrome (DGS)

- Defect in embryogenesis, 3rd & 4th pharyngeal pouches
- Chromosomal abnormality: 22q11.2
- Presents in first few days of life (tetany)**
- CXR, absence of thymic shadow
- Clinical features:
  - Dysmorphic facies (micrognathia)
  - Hypocalcemia (lack of parathyroid glands)**
  - Depressed T-cell immunity- T cell numbers and lymphocyte function decreased**
  - Congenital heart disease- most common Tet of Fallot, interrupted aortic arch, VSD***

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DGS (cont)

- Treatment- Prophylactic antibiotics (Septra), Thymic implantation, Observation for most

54

Case study

- Infant born at 10 lbs. Now, 3 month old with chronic diarrhea. Weighs 6 lbs. Poor appetite. Not smiling or cooing. Frog leg position. Weak.

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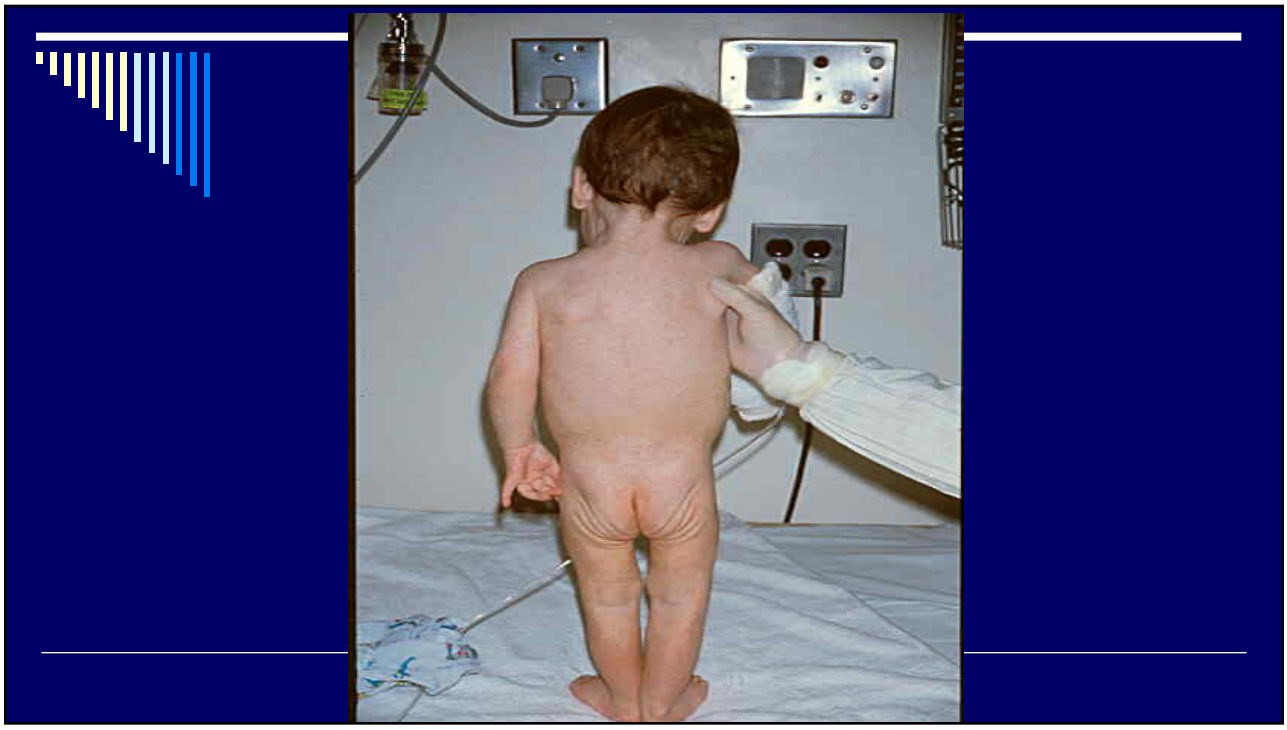

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Question: What diagnosis does this patient have?

A. Chronic Granulomatous Disease
B. Wiskott Aldrich
C. Chronic Mucocutaneous Candidiasis
D. Severe Combined Immunodeficiency

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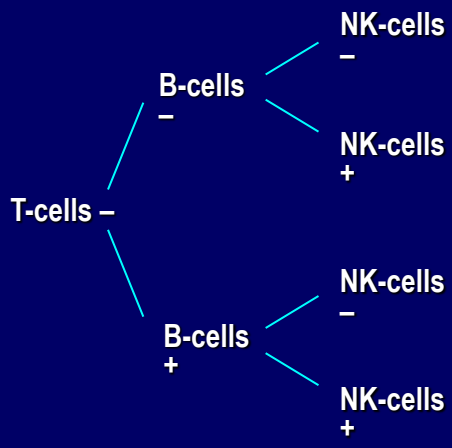
Severe Combined ID (SCID)



T-cells + (clonal) B-cells low NK-cells +

Adapted from AAAAI Primary ID Presentation www.AAAAI.org

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SCID

- Usually present with failure to thrive, persistent diarrhea
- Respiratory symptoms +/- thrush between 2-7 months of age
- Recurrent infections, severe infections (ie: meningitis)
- Infections due to opportunistic organisms- Commonly, Pneumocystis jirovecii
- Absent thymic shadow on chest X-ray-infants
- **Absent tonsils/ lymph nodes**

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SCID (cont)

- Important to remember that normal absolute lymphocyte numbers in infants are higher than in other age groups (3,000 though 11,000)
- Calculate absolute lymphocyte number (total white blood cell count multiplied by the percentage of lymphocytes)
- Absent or nonfunctional lymphocytic cells
- Decreased IgG, IgA and IgM
- Absent antibody responses to specific antigens

- **If lymphopenic on CBC, obtain lymphocyte subsets (T, B, NK cell numbers)**

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SCID (cont)

- Treatment- Aggressive feeding, prophylactic antibiotics, Gamma globulin replacement, leading to BMT- haplo-identical sibling or parental transplant as earlier as possible- prior to infections

62

Case Report

- 5 year old began with difficulty walking as young child.

  Eye blood vessels are prominent. Recurrent upper respiratory infections.

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Question: What diagnosis does this patient have?

A. X-linked Lymphoproliferative Disease
B. Chediak Higashi
C. X linked Agammaglobulinemia
D. Ataxia Telangiectasia

65

Ataxia Telangiectasia/ Louis- Bar syndrome

- **Progressive neurologic disorder: cerebellar ataxia, oculocutaneous telangiectasia, chronic respiratory infections, a high incidence of malignancy, and variable humoral and cellular immunodeficiency**
- **Cerebellar ataxia starts usually in childhood, telangiectasias appear later**
- **Recurrent sinopulmonary infections**
- **Serum IgM, IgA, IgE levels are diminished in some patients**
- **Treatment- Observation; Prophylactic antibiotics**

67

Case study

- 3 year old female with multiple episodes of liver abscesses, requiring drainage. Culture +Staph. Also, history of multiple draining abscesses of the skin. History of lymphadenopathy.

68

Question: What diagnosis does this patient have?

A. Chronic Granulomatous Disease
B. Wiskott Aldrich
C. STAT 3 Deficiency
D. WHIM syndrome

69

Chronic Granulomatous Disease (CGD)

- Recurrent bacterial infections
- Granulomas of skin, lungs, LN and liver- Staph Aspergillus and Nocardia**
- Phagocytic cells ingest but not kill bacteria due to failure to form oxygen radicals
- 1:500,000, 65% X-linked
- Gene defect chromosome location:
  - gp91 phox (X-linked)
  - P22 phox (AR)
  - P47 phox (AR)
  - P67 phox (AR)

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CGD (cont)

- Diagnosis- NBT, Oxidative burst, 1,2,3, dihydrorhodamine***
- Treatment- Prophylactic antibiotics, antifungals; some patients may be treated with Interferon gamma; BMT- if HLA-identical sibling

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Case Study

- 5 year old patient with recurrent candidal infections of extremities. Also, recently developed hypothyroidism. Otherwise, well. No hospitalizations.

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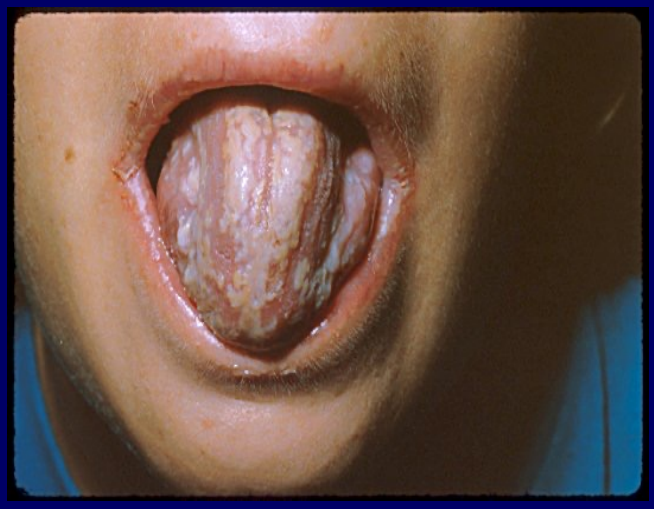

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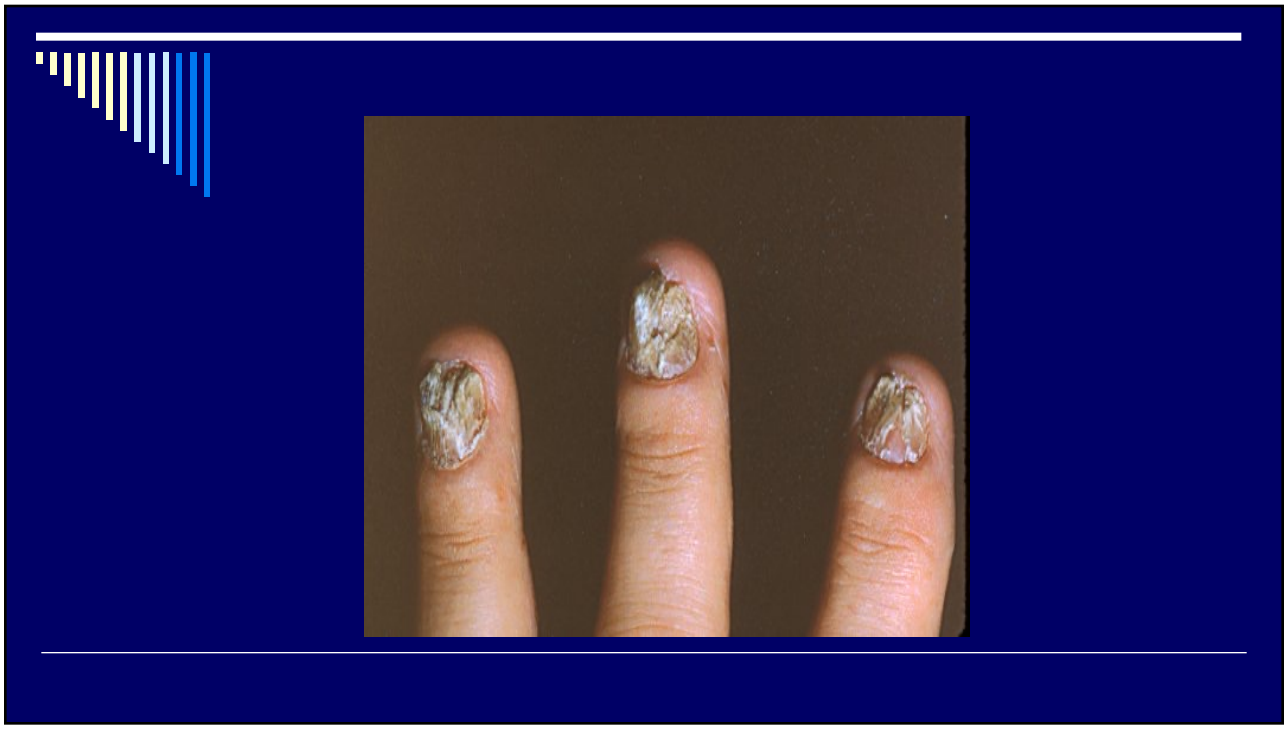

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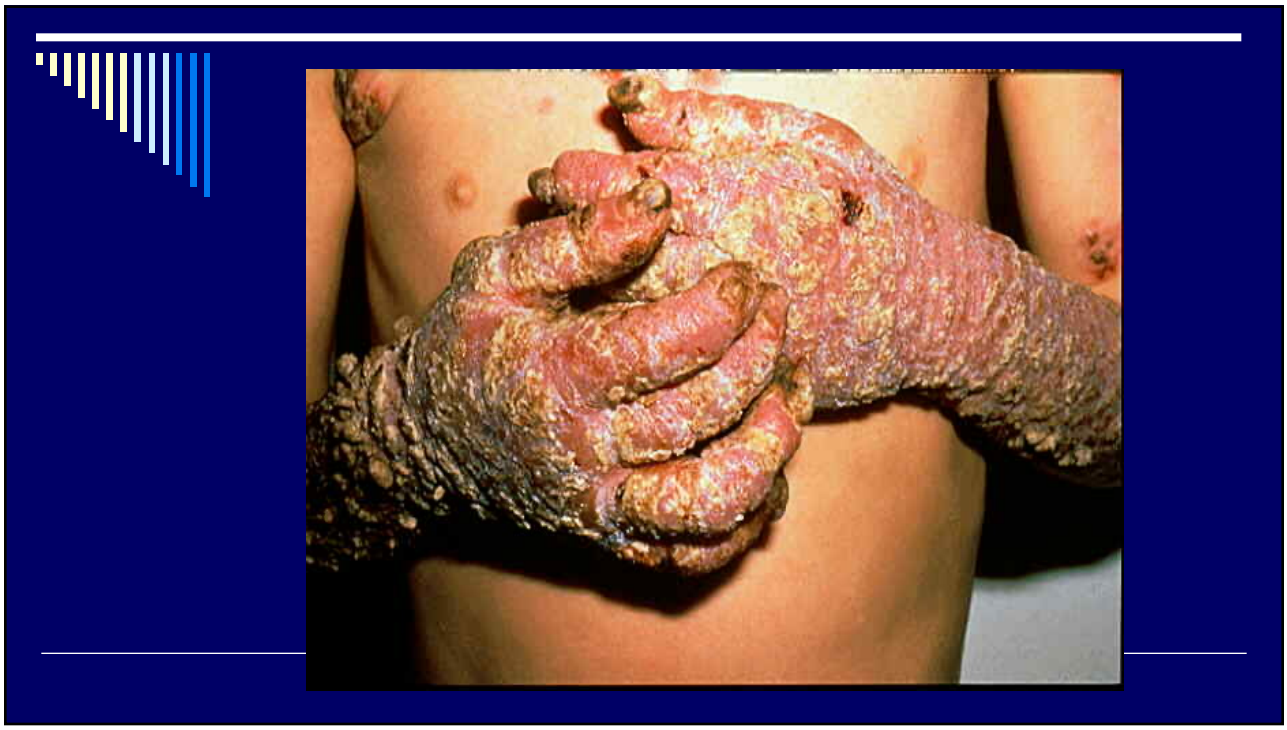

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Question: What diagnosis does this patient have?

A. Chronic Granulomatous Disease
B. Wiskott Aldrich
C. Chronic Mucocutaneous Candidiasis
D. Severe Combined Immunodeficiency

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Chronic Mucocutaneous Candidiasis

- **Chronic and Recurrent Candida Infections**
- **Fungemia Rare*****
- **High incidence of endocrinopathies**
  - **More common in familial cases**
  - **If associated with polyendocrinopathy, look for AIRE mutation**
- **Cellular immune studies usually normal**
- **Many children have non-Candidal infections**
- **Treatment- Antifungal treatment**

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Case study

- 8 week old male infant with “umbilical cord that won’t come off.” Had surgical repair of inguinal hernia- poor wound healing. No pus. No family history of immune deficiency.
- CBC revealed WBC 25k.

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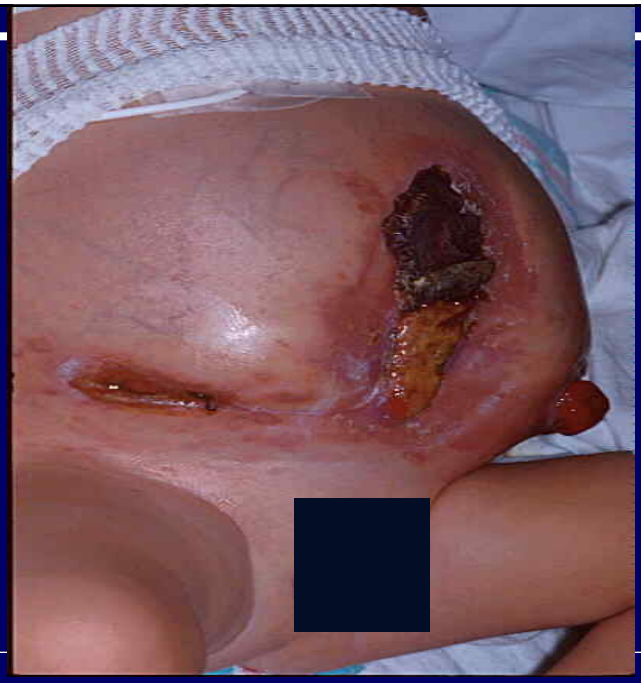

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Question: What diagnosis does this patient have?

A. Interferon Gamma Receptor Deficiency
B. Wiskott Aldrich
C. WHIM syndrome
D. Leukocyte Adhesion Defect

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Leukocyte Adhesion Defect (LAD)

- **Absent beta subunit (CD18) on cell surface glycoproteins (CD11 family)**
- **Neutrophils cannot migrate toward inflammatory stimuli or adhere to vascular endothelium**
- **Clinically:**
  - **Recurrent soft tissue infections**
  - **Delayed umbilical separation****
  - **Severe peridontal disease****
  - **No pus formation despite high WBC counts****

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LAD (cont)

Diagnosis- Obtain lymphocyte subsets with CD11/ CD18 numbers

Treatment- BMT

85

Case study

- **3 year old male with pale skin and silvery hair. Has had recurrent lung infections. He also has a history of nystagmus.**
- **On blood smear, large granules are seen.**

86

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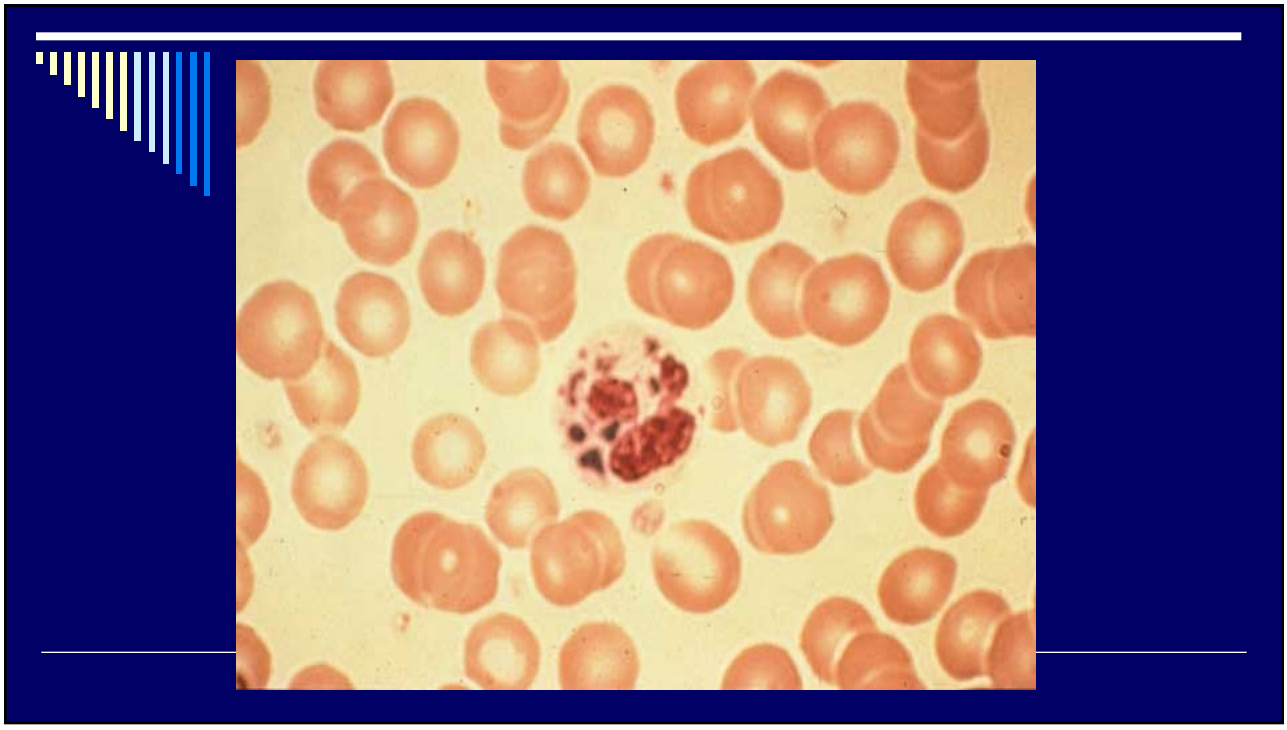

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Question: What diagnosis does this patient have?

A. Chediak Higashi
B. Wiskott Aldrich
C. STAT 3 Deficiency
D. WHIM syndrome

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Chediak Higashi Syndrome

- **Autosomal recessive disease.**
- **Disease of hematologic, immune and neurological systems. Platelet dysfunction leads to bleeding. Defect in leukocytes, neutropenia and decreased NK cell numbers. Patients have oculocutaneous albinism. Hair appears silvery. As adults, develop ataxia and peripheral neuropathy. EBV can lead to fatal lymphoma.**
- **Treatment: Prophylactic antibiotics; BMT**

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Case study

- **4 year old with history of two Neisseria meningitis infections. Otherwise healthy. Growing well. Active.**

92

Question: What diagnosis does this patient have?

A. Wiskott Aldrich
B. Complement Deficiency
C. STAT 3 Deficiency
D. WHIM syndrome

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Complement Deficiency

- Reported deficiency of all complement components, still uncommon ID
- Associated with recurrent pyogenic infections and CT diseases (esp. C2 & C4)
- Deficiency of C5-8 associate with recurrent Neisseria species infection- meningitis (C6)**
- Deficiency of C1 esterase inhibitor assoc. with angioedema (hereditary- HAE)
- Treatment- Late components C5-C9- Penicillin
  - HAE-Fresh Frozen Plasma, Danazol/Stanazol, C1 Esterase Inhibitor- prophylaxis or treatment

95

Case study

- 2 year old male with eczema, recurrent infections and easy bruising. As an infant, bloody diarrhea and "pink tears."
- Other male infants in family with similar presentation.

96

Question: What diagnosis does this patient have?

A. Chediak Higashi
B. WHIM syndrome
C. STAT 3 Deficiency
D. Wiskott Aldrich

97

Wiskott Aldrich Syndrome (WAS)

- **X-linked recessive X 11.22-11.23; lack WASP – important in cell signaling in lymphoid and megakaryocytic cells**
- **Triad: Eczema, thrombocytopenia (<20,000 & small)**, increased susceptibility to infections**
- **Presentation: bloody diarrhea/bloody tears, prolonged bleeding from circumcision, excessive bruising; later P. jirovecii, herpes virus, autoimmune cytopenias, vasculitis**
- **Treatment: BMT**
- **Cause of death: infection, bleeding, EBV induced lymphoreticular malignancy**

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When to think about ID diagnosis?

- Family history positive for ID
- 8 new ear infections/year
- 3 *serious* sinus infection/year
- 2 months of PO antibiotics without improvement
- 2 pneumonias/year (esp. if needed hosp.)
- 2 deep-seated infections (meningitis, sepsis, osteomyelitis)

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When to think about ID diagnosis?

- Need for IV antibiotics to clear infections
- Recurrent deep skin or organ abscesses
- FTT/chronic diarrhea
- Persistent thrush

  - 10 warning signs Jeffrey Modell Foundation

101

Physical Exam

- Growth measurements***
- Inspection of tonsils-if absent, Ask about history of tonsillectomy****
- Palpation of LN****
- Organomegaly
- Skin lesions

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Laboratory Testing

- Antibody mediated immunity
  - Quantitative serum immunoglobulins
  - Iso-hemagglutinins (Anti A, Anti B)
  - Antibodies to Tetanus and Diphtheria (protein antigens)
  - Antibodies to H influenza B and Pneumococcal (polysaccharide antigens)

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Laboratory Testing

T-cell immunity

CBC with differential- calculate ALC

- **Cell surface markers/ subsets**
- **Mitogen proliferation studies**
- **Delayed hypersensitivity skin tests-candida, tetanus (individuals > 2 y/o)**

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Laboratory Testing

- **Neutrophil function:**
  - **Nitroblue tetrazolium dye test (NBT)**
  - **Oxidative burst assay**
  - **1,2,3 Dihydrorrhodamine**
- **Complement function:**
  - **Total hemolytic complement test, C3, C4**
  - **Quantitative measurements of components**
  - **Functional assays for components**

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Treatment

- Antibody deficiency (XLA, Hyper IgM, Hyper IgE)
  - IVIG (400mg/kg/dose every 4 weeks) or SCIG (100-150 mg/kg weekly, every other week or more often)
  - Prophylactic antibiotics (not universal)
  - Bone marrow transplantation in some patients- Hyper IgM
  - Frequent follow-up q 4-6 months

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Treatment

- T cell disorders/ Combined Immunodeficiency (SCID, WAS, DGA, XLP)
  - Stem cell transplantation/BMT
  - Enzyme replacement (ADA)
  - Thymic implant (Di George)
  - IVIG (400mg/kg/dose every 4 weeks) or SCIG (100-150 mg/kg weekly, every other week or more often)
  - Prophylactic po antibiotics
  - Avoidance of live viral vaccines
  - Irradiation and leuko-depleted blood products
  - Frequent follow-up

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Treatment

- **Phagocytic cell deficiency:**
  - **Prophylactic antimicrobials-Bactrim/Itraconazole**
  - **Gamma interferon in CGD**
  - **Avoidance of live viral vaccines**
  - **Bone marrow transplantation in some patients**
  - **Frequent follow-up**

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Treatment

- **Complement deficiency:**
  - **Prophylactic antibiotics-Penicillin**
  - **Immunizations with bacterial polysaccharide vaccines**
  - **Frequent use of IV antibiotics**
  - **Frequent follow-up**

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110