SEVERE COMBINED IMMUNODEFICIENCY CLINICAL MANIFESTATIONS

SCID in-person meeting
July 30-31, 2015

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Disclosures

- Baxalta: PI in clinical trials, consultant
- CSL Behring: Advisory board
- NIH/CDC: Investigator on grant for NBS in GA
- Grifoils: PI in clinical trials
- Immune deficiency foundation: speaker

What is SCID?

David Vetter

- "Boy in the bubble" disease
- Congenital *combined* immune deficiency caused by more than 20 different *single* gene defects
  - Results in profound impairment of both cellular (T cell) and humoral (B cell) immunity
  - Some forms also impair innate immune responses (natural killer cells)
- *Estimated* prevalence: 1:58,000 births (U.S)*

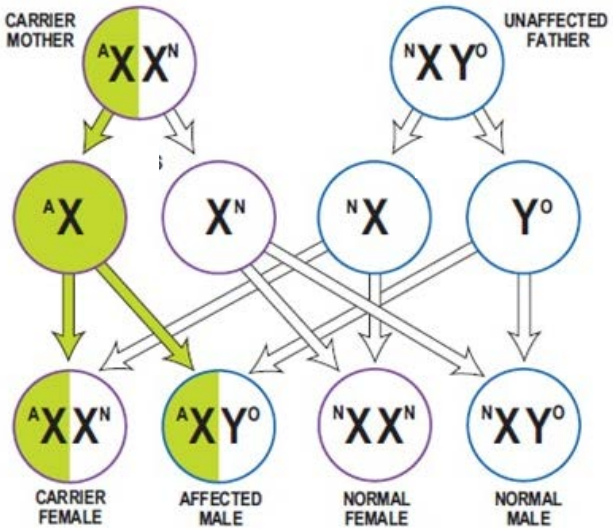
**Kwan JAMA 2014*

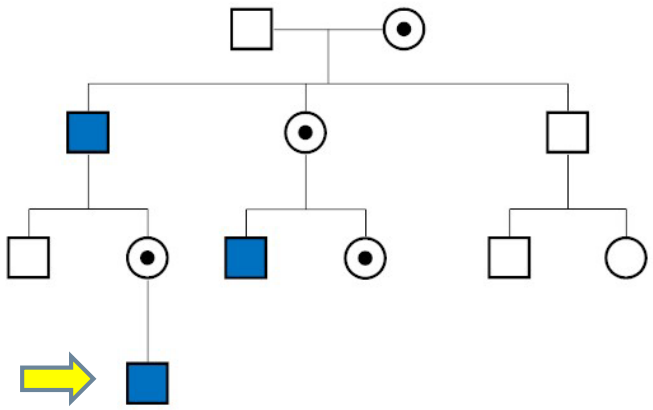
What is SCID?

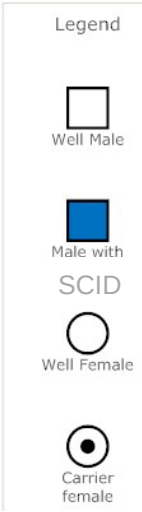
- Classical (typical) SCID = very low/no autologous T cells (< 300 cells/µL) and abnormal T cell proliferation (<10%)
- "Leaky" SCID = low T cells (300-1500 cells/µL), low naïve T cell proportion, no maternal T cells, poor T cell function (10-50% normal)
- Omenn syndrome = often low T cells, no maternal T cells, few naïve T cells, characteristic symptoms

How is SCID inherited?

- Affects both males and females
  - *X-linked or autosomal recessive inheritance*
  - *X-linked form is more common in this country*
  - *Slight increase in frequency in males* Kwan JAMA 2014
- Family history is present in approximately 20% *(in U.S.)** **Chan Clin Immunol 2011*





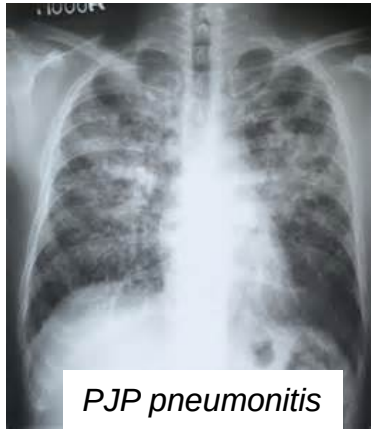


SCID: Clinical presentation

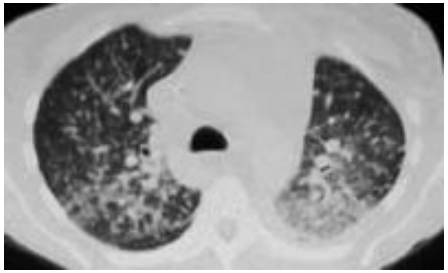
- Affected infants appear well at birth
- Hallmark of SCID is an increased frequency and severity of infection
- Infants with SCID are unable to clear viruses and fungal infections
- Infections can begin as soon as 4 weeks of age
- Without family history – mean age at diagnosis is 140 days (4.7 months)

SCID: Clinical presentation

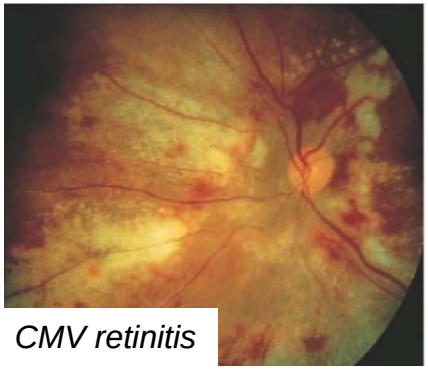
- Recurring/persistent viral infections
  - Respiratory: respiratory syncytial virus (RSV), parainfluenza, adenovirus
  - Gastrointestinal: rotavirus, enterovirus
- Opportunistic infections
  - *pneumocystis jirovecii* pneumonia
  - cytomegalovirus pneumonia/disseminated
  - disseminated mycobacteria



PJP pneumonitis



MAI pneumonia

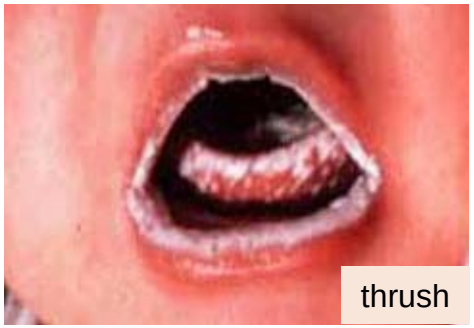


CMV retinitis

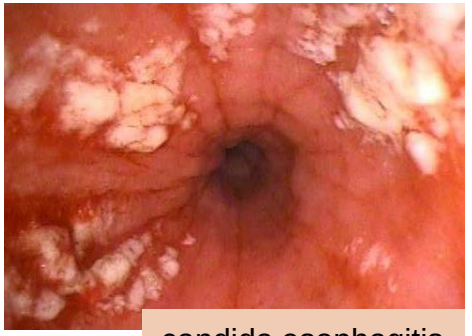
Emedicine.medscape

SCID: Clinical presentation

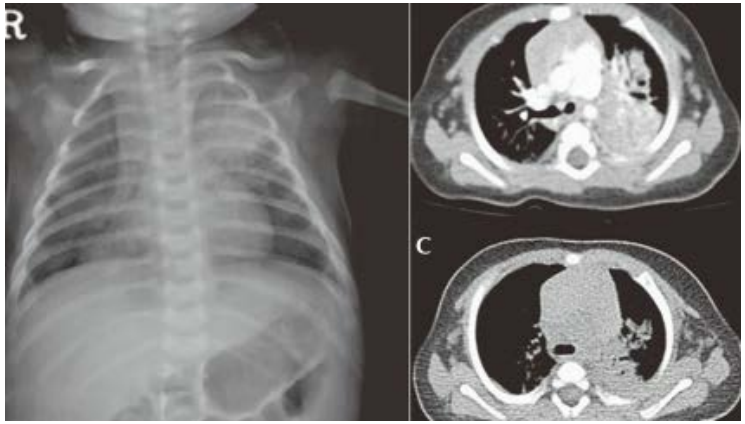
- Fungal infections
  - Persistent thrush (candida)
  - Candida esophagitis
  - Aspergillus
- Sepsis/meningitis
  - bacterial, fungal



thrush



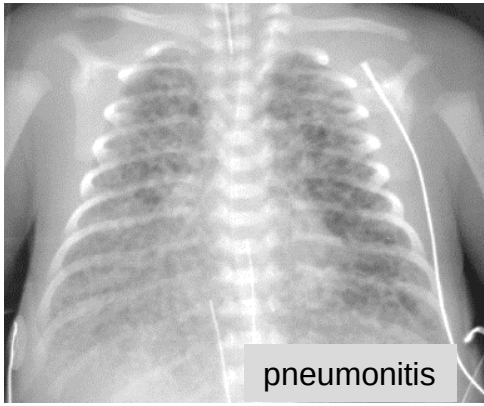
candida esophagitis



aspergillus pneumonia

SCID: Clinical presentation

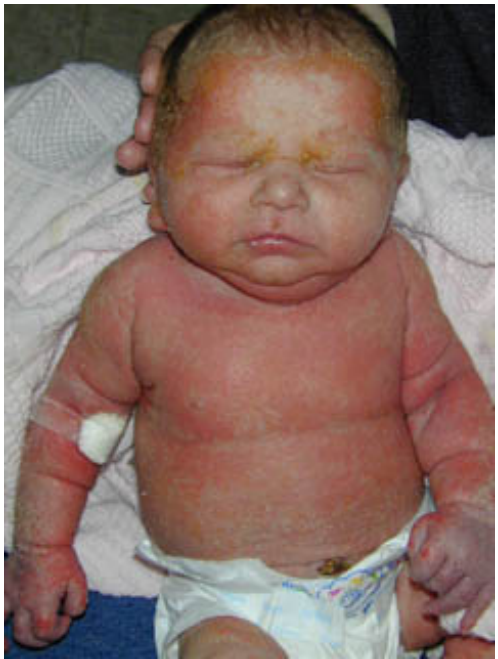
- Sequelae
  - Chronic diarrhea – rotavirus, giardiasis
  - Interstitial pneumonia
  - Failure to thrive
- Other symptoms
  - Absence of lymphoid tissue
  - Erythematous skin rash
    - Due maternal T cells
    - Bacterial superinfection
  - Neurologic – ADA-SCID
  - Skeletal abnormalities (ribs in ADA-SCID)


pneumonitis


GvHD like skin rash

Omenn syndrome

- Refers to SCID with a distinct phenotype
- Features of Omenn syndrome
  - Severe erythematous, scaly skin rash
  - Alopecia
  - Enlarged lymph nodes
  - Enlarged liver and spleen
  - Increased eosinophils in the blood
  - Respiratory distress
  - Diffuse edema (swelling)



SCID genotypes

TYPE	GENE	CD4	CD8	B	NK	Igs
IL2R gamma c	X-linked	↓	↓	NL/↑	↓	Low
JAK3	19p13.1	↓	↓	NL	↓	Low
ADA	20q13.2	↓	↓	↓	+/-	Low
RAG 1/2	11p13	↓	↓	↓	NL	Low
IL7R alpha	5p13	↓	↓	NL	NL	Low
CD3ε	11q23	↓	↓	NL	NL	Low/nl
CD3delta	11q23	↓	↓	NL/↑	NL/↑	Low/nl
Artemis	10p	↓	↓	NL	NL	Low
AR - others		↓*	↓†	NL	NL	Low*

*Except ZAP70 def – 2q12
†except MHC II def- 16p13, 1q21

Reduce infection risks

Measure	Rationale
Avoid crowded areas/daycare	Reduce exposures to respiratory illnesses, other viral infections
Avoidance of pets (including reptiles)	Reduce risk of infection from bacteria carried by animals
Careful/regular handwashing	Reduce spread of respiratory and GI infections
Avoid live viral vaccines (rotavirus)	Reduce risk of prolonged diarrhea following rotavirus (live viral) vaccine
Use only irradiated (leukodepleted) blood and platelets	Reduce risk of developing graft versus host disease after transfusion

Non-SCID conditions with lymphopenia: Primary causes

Condition	Features
DiGeorge syndrome (22q11.2 deletion syndrome)	Heart defects, low calcium, small/absent thymus gland, cleft palate, multiple other anomalies
Trisomy 21	Congenital heart defects, facial features, intestinal defects, developmental delay, low tone
Trisomy 18	IUGR/low birth weight, heart defects, abnormal facial features, developmental delay
Jacobsen syndrome	Developmental delay, characteristic facial features, bleeding, heart defects, decreased CD4 lymphocytes
CHARGE syndrome	Coloboma, Heart defects, Atresia choanae, Retarded growth/development, Genital, Ear abnormality
Ataxia-telangiectasia	Abnormal repair of DNA breaks, ataxia (age 2-3 yrs), telangiectasia of skin, eye, defect in cellular and humoral immunity
CLOVES	Congenital Lipomatous Overgrowth, Vascular malformation, Epidermal nevi, Skeletal anomalies
Noonan syndrome	Congenital heart defect, skeletal defects, webb neck, mental retardation, dysmorphic

Non-SCID conditions with lymphopenia

Secondary causes

Disorder	Effect
Congenital heart defects	Loss of lymphocytes after heart surgery
Chylothorax	Disruption of thoracic duct causes loss of lymphatic fluid
Gastroschisis/omphalocoele	Defect in abdominal wall with intestines outside the abdomen leaking lymph
Intestinal lymphangiectasia	Defect in lymphoid vessels of the gut leaking of lymph
ABO incompatibility/hydrops	Severe edema with loss of fluid into tissue space

SCID

- Multiple different genetic defects that cause an inability to fight infections from viruses, fungi and bacteria
- Symptoms of infection develop early
- Affected infants die due to infection at a young age unless treated by hematopoietic cell transplantation, gene therapy or enzyme replacement

Newborn Screening Saves Lives!!!