Hyper IgE Syndromes

From Job Syndrome
To Netherton Syndrome

Kuala Lumpur, October 2016
Hyper IgE ("Job") Syndrome – A Story that begins with 2 redheaded girls

JOB’S SYNDROME
Recurrent, "Cold", Staphylococcal Abscesses

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"So went Satan forth from the presence of the Lord, and smote Job with sore boils from the sole of his foot unto his crown."—Job, II, 7.

We have examined two girls who have had recurrent, "cold", staphylococcal abscesses since birth. The staphylococci do not seem to be unusually virulent, and neither child has diabetes or any other condition known to predispose to infection. Since we are not aware that any similar cases have been described previously, we report these cases in detail.
Red Hair and more

- 2 unrelated infant girls with sores, “cold” abscesses without inflammation
- eczema
- fungal infection
  - (thrush, hyperkeratotic finger and toe nails)
- one developed scoliosis
- the other had unexplained bone fractures

Davis SD, Schaller J, Wedgwood RJ: Job syndrome, Lancet, 1966
Hyper IgE - Job Syndrome

- Eczema
- Abscesses ("cold"), skin and subcutaneous
- Lung abscesses -> pneumatoceles
- Staph, fungal (candida) infections
- Coarse facial features, broad based nose
- Scoliosis, fractures, overextended joints
- Retention of primary teeth
- Aneurisms (CNS, coronary arteries)
- No allergies!
The Girls grow up, become a syndrome

More of the same:
recurrent skin-, lymphnode-, joint-abscesses
recurrent staph pneumonia, pneumatoceles
eczema, thrush, hyperkeratotic finger nails
coarse facial features,
hyper-extensible joints, fractures, scoliosis
persistent baby teeth
High IgE, eosinophilia
One dies age 19 y, one has children......
Job Syndrome
K.F. age 6 Y
Job Syndrome

K.F. age 17 y
Job Syndrome, R.B.
Lung abscess, Scoliosis
Job Syndrome, R.B.: “cold” Staph abscess
Job Syndrome
D.V. age 2 mo
Job syndrome, D.V. age 6 months
Job Syndrome: AD-HIES

D.V.
Age 4 y
Original Job syndrome patient (case 1)
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Percentage of patients with symptoms present:
- 100% 92% 92% 72% 81% 89%
Hyper IgE – Job Syndrome
Laboratory abnormalities

• Very high IgE serum level
• Eosinophilia
• Allergy testing usually negative
• Chemotactic defect (secondary, inconsistent)
• Immature B cells
• Abnormal antibody responses
• Abnormal cytokine production
• Lack of Th17 cells, low IL-17
STAT3 mutation in the Original Patient with Job Syndrome

**JOB’S SYNDROME**

**Recurrent, “Cold”, Staphylococcal Abscesses**

*Starkey D. Davis*  
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Assistant Professor

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M.D. Harvard  
Instructor

*Ralph J. Wedgewood*  
M.D. Harvard  
Professor and Chairman, Department of Pediatrics, University of Washington School of Medicine

“So went Susan forth from the presence of the Lord, and smote Job with sore boils from the sole of his foot unto his crown” — Job, iii. 7.

We have examined two girls who have had recurrent, “cold”, staphylococcal abscesses since birth. The staphylococci do not seem to be unusually virulent, and neither child has diabetes or any other condition known to predispose to infection. Since we are not aware that any similar cases have been described previously, we report these cases in detail.

**1144 C>T/C R382W**

*Renner and Torgerson et al., NEJM*
Dominant Negative STAT3 Mutations Cause Autosomal Dominant Hyper IgE Syndrome
4 Decades of Observation

- 1966: Job Syndrome described
- 1972: elevated IgE recognized
- 1980: AD-inheritance
- 2005: Abnormal cytokines
- 2006: homozygous Tyk2 mutation – 1 patient
- 2007: heterozygous STAT3 mutations in AD-HIES affecting the DNA binding and SH2 domains
- 2008: mutations affecting the transactivation (TA) domain, low number of Th17 cells abnormal phosphorylation (SH2, TA domain)
- 2009 AR-HIES due to DOCK8 mutations
Hyper IgE Syndromes (HIES)

AR-HIES – DOCK8, Tyk2 mutations
AD-HIES - heterozygous STAT3 mutations
Others: Netherton, WAS, IPEX, Omenn Syndrome
Comel-Netherton Syndrome

- Congenital Ichthyosis, bamboo hair
- Atopic diathesis: eczema, asthma, food allergies, angioedema
- Enteropathy, failure to thrive.
- Mutated SPINK5, (serine protease inhibitor)
- Lack of LEKTI, expressed by epithelial cells, including in Thymus and tonsils
- Antibody def, abnormal cytokines, NK
- Response to IVIG
Figure 2: Toddler (patient #5) with Comèl-Netherton Syndrome before, and three months after, IVIG treatment in addition to hydrating skin lotions.
Omenn Syndrome

• SCID with restricted T cell function (self)
• Normal # of T cells, restricted repertoire
• Low B cell numbers
• Hypogammaglobulinemia, with high IgE and Eosinophils
• Increased IL-4, IL-5
• Eczema, infections (SCID), failure to thrive
• Mutations of Rag1,2, Artemis, IL-7R, ADA
• Tx: HSCT with conditioning
IPEX - Immunedysregulation, Polyendocrinopathy, endocrinopathy, X-L

- Villous atrophy, malabsorption
- Multiple autoimmune disorders
- Eczema, psoriasiform, alopecia
- Infections
- High IgE and IgA
- Mutations in FOXP3
- Lack of regulatory T cells
Wiskott-Aldrich Syndrome

- ** X-linked recessive disorder
- ** Thrombocytopenia/small platelets
- * Eczema; Elevated IgE
- Recurrent infections
- Abnormal B and T cell functions
- Autoimmune diseases
- Malignancies
Genetics beyond Gregor Mendel

- X-linked, loss of function (LOF) (mostly)
  - IPEX, WAS, XLA
- Autosomal recessive:
  - LOF: DOCK 8, Rag 1,2
  - hypomorphemic: Omenn (Rag missense)
- Autosomal dominant:
  - dominant negative (25%): STAT3 in JOB
  - haploinsufficiency (50%): CTLA4 deficiency
  - gain of function (GOF): STAT1, STAT3
Dominant Negative STAT3 Mutations Cause Autosomal Dominant Hyper IgE Syndrome