STAT MUTATIONS

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Disclosure Information
I have no financial relationships to disclose

Objectives
1. Discuss the importance and function of the STAT mechanism.
2. Recognize the clinical manifestations of STAT mutations.
3. Diagnose, manage and appropriately refer patients with STAT mutations.
Discuss the importance and function of the STAT mechanism.

### STAT Definition

- Signal transducer and activator of transcription
- These latent transcription factors are activated via interaction of cytokines with their receptors
- STAT proteins then mediate aspects of:
  - Cellular Immunity
  - Proliferation
  - Apoptosis
  - Differentiation

### Translational Genotype

- STAT Family
  - The first two STAT proteins were identified in the interferon system
  - The seven mammalian STAT family members identified are: STAT1, STAT2, STAT3, STAT4, STAT5 (STAT5A and STAT5B), and STAT6.
**Translational Genotype**

**STAT Function**
- STAT proteins were originally described as latent cytoplasmic transcription factors that require phosphorylation for nuclear retention.
- The unphosphorylated STAT proteins shuttle between cytosol and the nucleus waiting for its activation signal.
- Once the activated transcription factor reaches the nucleus it binds to consensus DNA-recognition motif called gamma activated sites (GAS) in the promoter region of cytokine inducible genes and activates transcription of these genes.

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**STAT Gene**

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Recognize the clinical manifestations of STAT mutations.

- STAT 3
- STAT 1
- STAT 5

STAT 3 Mutation is also known as:

- Job Syndrome
- Buckley Syndrome
- Hyper-IgE
- HIES (hyper-IgE syndrome)
- AD-HIES (autosomal dominant hyper-IgE syndrome)

Historical Significance
STAT 3 is critical in signaling pathways of:

- IL-6 (pyrogen and acute phase response)
- IL-10 (anti-inflammatory)
- Differentiation pathways of IL-17 producing CD4+ T cells (helps defend against extracellular pathogens)
- IL-22 (stimulates β-defensin in skin and lungs)
- Down-regulation of osteoclasts

STAT 3 deletions have shown higher levels of TNFα and INFγ

Translational Genotype

Classification

- Autosomal dominant type- includes both sporadic (>90% of cases) and familial autosomal dominant inheritance

- Caused by STAT3 mutation on chromosome 17q21

- Autosomal recessive type- caused by homozygous or compound heterozygous loss of function mutations in dedicator of cytokinesis 8 (DOCK8 deficiency)

- Sporadic Mutations
Historical Significance

- Job syndrome received its name from the description of the biblical figure Job
- First identified by Davis et al. in 1966 in two unrelated red hairred girls with recurrent 'cold' staphylococcal abscesses

Original Phenotype

- Job syndrome is a very rare immune deficiency characterized by the triad
  - Eczema
  - Recurrent sinopulmonary and pulmonary infections
  - Eosinophilia
- Worldwide, at least 250 cases have been reported
Diffuse Eczema

Recurrent “Cold Abscesses”

- The syndrome was redefined by Buckley et al. in 1972 when hyper eosinophilia was recognized as a cardinal feature of this syndrome and the term HIES was introduced

- Buckley et al. noted recurrent pyogenic abscesses in two adolescent boys

Abscesses
Findings expanded beyond the classic triad include:

- Recurrent cutaneous, pulmonary, and joint abscesses
- Growth retardation
- Coarse facies
- Chronic dermatitis
- Exquisite immediate hypersensitivity associated with exceptionally high serum IgE levels and eosinophilia
- Depressed in vivo cellular immunity and antibody formation

Establishment of Multi-System Disorder

- In 1999, Grimbacher et al. established HIES as a multisystem disorder with variable expressivity

- The following characteristics were added to the spectrum:
  - Hyper extensible joints
  - Joint deformities
  - Scoliosis
  - Retention of primary dentition

Systemic Features
Hyper IgE Scoring System

- Grimbacher et al. devised a scoring system using both clinical and laboratory test criteria to aid in the diagnosis of HIES

- 30 patients with HIES and 70 of their relatives were analyzed and given points based on the most common findings specific for HIES

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**Scoring System Summary:**

- ≥15 points: patient likely to carry HIES genotype
- 10-14 points: presence of HIES genotype is indeterminate
- < 10 points: unlikely to have HIES genotype
Until 2007, HIES remained one of the last major immune deficiencies with unknown genetic etiology and lack of comprehensive understanding of the immune dysfunction.

**HIES Classifications**

The HIES syndrome is classified in two types based on clinical and etiological data:

**Clinical abnormalities:**

- Autosomal dominant: dental, skeletal, and pulmonary cysts
- Autosomal recessive type: viral infections predominate (herpes simplex, molluscum contagiosum) with neurological complications
Revised Scoring System

- In 2010 Woellner et al. revised the original scoring system by Grimbacher et al.

- The score sheet was devised to determine whether there is a correlation between the genotype and the phenotype of patients with HIES and to establish diagnostic criteria to distinguish between STAT3 mutated and STAT3 wild-type patients

Revised Scoring System

- The following diagnostic guidelines were included for STAT 3 deficient HIES:

  - Possible: IgE > 1000 IU/mL plus weighted score of clinical features > 30 based on recurrent pneumonia, newborn rash, pathologic bone fractures, characteristic facies, and high palate
  - Probable: Above characteristics plus lack of TH7 cells or family history for definitive HIES
  - Definitive: Above characteristics plus a dominant-negative heterozygous mutation in STAT3
Skin Manifestations-Eczema

- Newborn rash
- First manifestation of STAT 3 deficiency
- In 43 babies with STAT 3 deficiency, Grimbacher et al found 8 babies were born with the rash and 23 acquired it within the first week of life
- Characterized as eczematous and pustular
- Biopsy reveals eosinophilic infiltrates
- Culture shows *Staphylococcal aureus*
- Control with antibiotics, topical antiseptics

Eczema of HIES

Skin Manifestations-Abscesses

- Abscesses are characteristic of the diagnosis
- Variable erythema and tenderness ('cold')
- Frank pus on aspiration which grows *S. aureus*
- Decrease occurrence with prophylactic antibiotics
- Intertriginous areas may be difficult to treat
**Lung Manifestations**

- Recurrent pyogenic pneumonias begin in childhood
- *S. aureus, Streptococcus pneumoniae, and Haemophilus influenzae*
- Pus present on sputum culture and bronchoscopy
- May become complicated by pneumatoceles
- Possible secondary infections
- Treat underlying cause

**Large Pneumatoceles**

**Digital Clubbing**
Other infections of HIES

- Mucocutaneous candidiasis
- Disseminated Cryptococcus and Histoplasma infections (histoplasmosis of the tongue, intestinal cryptococcal infection)
- Pneumocystis jiroveci pneumonia (rare)

Musculoskeletal Abnormalities

- Scoliosis
- Osteopenia
- Minimal trauma fractures (long bones, ribs, and pelvis)
- Degenerative joint disease
- Muscular infections

Myositis
### Cranial and Dental Abnormalities
- Craniosynostosis
- Chiari I malformations
- Failure of primary teeth to exfoliate (leads to retention)
- High arched palate

### Vascular Abnormalities
- Arterial aneurysms – bilateral berry aneurysms of internal carotid artery and mycotic aneurysms reported
- Arterial tortuosity and dilation
- Lacunar infarcts reported at younger age

### Facial Characteristics
- Facial asymmetry
- Broad nose
- Deep set eyes
- Prominent forehead
- Patients with STAT3 deficiency appear more similar to one another than their own families
Summary of Clinical Characteristics

Table 1
Clinical Characteristics of STAT3 Deficiency

<table>
<thead>
<tr>
<th>Immunologic Characteristics (% Frequency)</th>
<th>Non-Immunologic Characteristics (% Frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn rash (81%)</td>
<td>Characteristic face (83%)</td>
</tr>
<tr>
<td>Bools (87%)</td>
<td>Retained primary teeth (72%)</td>
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<tr>
<td>Recurrent pneumonias (87%)</td>
<td>Minimal trauma fractures (71%)</td>
</tr>
<tr>
<td>Pneumatoceles (77%)</td>
<td>Scoliosis &gt;10 degrees (83%)</td>
</tr>
<tr>
<td>Eczema (100%)</td>
<td>Hyperextensibility (89%)</td>
</tr>
<tr>
<td>Mucocutaneous candidiasis (83%)</td>
<td>Focal Brain Hyperintensities (70%)</td>
</tr>
<tr>
<td>Peak Serum IgE &gt;2000 U/l/m (97%)</td>
<td>Chiari 1 Malformations (18%)</td>
</tr>
<tr>
<td>Eosinophilia (93%)</td>
<td>Craniosynostosis (unknown)</td>
</tr>
<tr>
<td>Increased incidence of Lymphoma</td>
<td>Arterial Aneurysms (unknown)</td>
</tr>
</tbody>
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Newly Generated Phenotypes

- Children may go through life without classic phenotypic manifestations
- Hence we’re now discovering survivors in the genotyping age that are presenting with milder and varied phenotypes

STAT1 Mutations

- Mutations in the coiled coil and DNA binding domains of STAT1 have been observed
- These mutations specifically affect the Th1 and Th17 responses
- Fungal and Mycobacterial Infections seen
- Many reported terminal cases of Progressive multifocal leukoencephalopathy triggered by JC Virus
STAT1 Mutations

- Nearly all cases of STAT 1 mutations have been de novo mutations
- One case of Autosomal Dominant Transmission of STAT 1 has been documented

STAT5 Mutations

- STAT5b mutations: autosomal recessive
- Homozygous mutation
- Severe post natal growth failure
- Growth hormone insensitivity syndrome
- Marked IGF-I deficiency
- Chronic pulmonary disease
- No current treatment available

Management of STAT3 Patients

- Management and Prognosis vary depending on the specific phenotype
- Frequent Treatment course of antibiotics and antifungal will be necessary
- Prophylactic antibiotics decrease frequency of serious infections
Antimicrobial Prophylaxis
- Trimethoprim-Sulfamethoxazole Divided BID
- General dosing is 5-8 mg/kg/day
- >12 years old recommended dosing of 960 mg/day

Intravenous Immunoglobulin
- Benefits of IVIG

Infectious Treatment
- Manage bacterial infection aggressively with systemic antibiotics
- Have a high clinical suspicion for deep seeded infections such as osteomyelitis or myositis
**Skin Care**
- Goals of controlling pruritus and eczema
- Prevent severe systemic infection
- Look to maintain hydration
- Dilute bleach or chlorhexidine baths can decrease *Staph aureus* colonization

**Referrals in STAT 3 Mutations**
- Immunologist
- Pulmonologist
- Infectious Disease
- Neurologist

**STAT 1 Treatment**
- Antifungal treatment and or prophylaxis
- Skin Care
- Consult immunology, dermatology, endocrinology
STAT 5b Treatment

- Antimicrobial treatment
- IVIG
- Referral to immunology, endocrine, dermatology

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References 1

References 2


2. Autosomal Dominant Transmission of Signal Transduction and Activator of Transcription 1 (STAT1) Mutation (Thr385 Met) and Extended Lifespan. Ruda-Wessell K, Hostoffer R. Lymphosign-2015-001

