Lunch & Learn: Hyper IgE/Job Syndrome

October 19th, 2022
IDF MISSION

Improving the diagnosis, treatment, and quality of life of people affected by primary immunodeficiency through fostering a community empowered by advocacy, education, and research.

Immune Deficiency Foundation
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- Attendees will not have access to their microphone or webcam throughout the event.
- To see the full slides, you can adjust the settings on the speaker view panel on the top of the Zoom screen and select "side-by-side" in the dropdown option.
- Please submit all questions for the presenter via the Q&A box
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Chapter 20

Hyper IgE Syndromes (HIES): STAT3 Loss of Function, DOCK8 Deficiency and Others

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Hyper IgE Syndromes (HIES) are rare forms of primary immunodeficiency diseases (PI) characterized by recurrent eczema, skin abscesses, fungal infections, eosinophilia (high numbers of eosinophils in the blood), and high serum levels of immunoglobulin E (IgE). Although initially described as two forms, with autosomal dominant (AD) and autosomal recessive (AR) inheritance, we now recognize that these are two distinct diseases caused by different genetic causes, with the two most common being from harmful mutations in STAT3 causing loss of function (STAT3-LOF) and DOCK8. These diseases share overlapping clinical and laboratory features; however, they also exhibit distinct clinical symptoms, disease courses, and outcomes. In addition, several other genetic variants have since been described to present with similar symptoms.

History
STAT3-LOF was described first as Job Syndrome in 1966 in two girls with many episodes of pneumonia, eczema-like lesions, and recurrent skin abscesses. These were remarkable for their lack of surrounding warmth, redness or tenderness, and were referred to as cold abscesses. In 1972, the syndrome was refined and clarified upon. A similar infectious problem in two boys who also had a distinctive facial appearance and extremely elevated IgE levels. Following this report, elevated IgE was found in the two girls from the initial report, showing that Job Syndrome and Buckley Syndrome represented the same condition. In 2007, a heterozygous mutation in the gene encoding the transcription factor STAT3 was found in under one-third of patients with AD-IgE. In 2009, mutations and deletions in the DOCK8 gene were found in under one-third of patients with AD-IgE. Additional findings include connective tissue and skeletal abnormalities, such as a typical facial appearance, hyper-extendibility of joints, retained primary teeth, recurrent bone fractures with minimal trauma, and...
To view all Hyper IgE Resources and Materials, visit: https://primaryimmune.org/about-primary-immunodeficiencies/specific-disease-types/hyper-ige-syndrome
PI COMMUNITY SERVICES

- Monthly Lunch & Learns: medical experts present on various diagnosis-specific topics
- Get Connected Groups: share experiences, receive information, and gain support
- IDF Forums
- Ask IDF
- Annual PI Conference

To view a list of all upcoming IDF events, visit: https://community.primaryimmune.org/s/events?language=en_US
WELCOME!

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The Hyper IgE Syndromes

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Hyper IgE syndromes: Each distinct disease

- High IgE, eczema, recurrent infections
- Connective tissue abnormalities
- Remodeling abnormalities
- Persistent, recurrent viral infections
- Neurologic defects, autoimmunity

Genes involved:

- STAT3 (Job’s syndrome)
- ERBIN
- CARD11
- CARD14
- DOCK8
- PGM3
- ZNF341
- IL6ST
- Prolidase Deficiency
Hyper IgE syndromes: Each distinct disease
STAT3 deficient Hyper IgE Syndrome (Autosomal dominant HIES; Job’s syndrome)

“So Satan went forth from the presence of the Lord, and smote Job with sore boils from the sole of his foot unto his crown.”
*Staphylococcus aureus* and *Candida* epithelial infections in STAT3 DN
Skeletal, joint, dental, vascular abnormalities
Characteristic facial appearance
Percentage of HIES Patients with Esophageal Symptoms

- 37% Dysphagia
- 21% GERD
- 23% Both
- 19% Neither

- Tortuous esophagus with dysmotility
- Colon and cecum perforations
- Diverticulitis
STAT3 Mutations in the Hyper-IgE Syndrome

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Adeline R. Whitney, B.A., Jovanka M. Voyich, Ph.D., James M. Musser, M.D., Ph.D.,
Cristina Woellner, M.Sc., Alejandro A. Schäffer, Ph.D., Jennifer M. Puck, M.D.,
and Bodo Grimbacher, M.D.

Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome

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Nobuaki Kawamura⁵, Tadashi Ariga⁶, Srdjan Pasic⁶, Oliver Stojkovic⁷, Ayse Metin⁸ & Hajime Karasuyama¹
Key mediator for many pathways including those of the immune system, cancer, wound healing, vascular remodeling. Expressed widely in most tissue types.
Epithelial/mucosal infection susceptibility: Lack of Th17 cells

Decreased memory T and B Cells
Zoster reactivation is increased in HIES patients and occurs at young ages

![Graph showing minimum lifetime prevalence of shingles](image)

Minimum lifetime prevalence $\frac{19}{60}=31.7\%$

Siegel et al, Immunity 2011
AD-HIES with less food allergy and anaphylaxis

Similar levels of IgE

Less mast cell reactivity
STAT3 is expressed widely and involved in many pathways making understanding the diverse clinical features difficult.
AD-HIES abnormal tissue remodeling

Pneumatocoele with aspergilloma

Bronchopleural fistulae

Freeman et al, J of Clin Immunology 2013
Middle sized arterial aneurysm

Left anterior descending artery dilation and aneurysm, and RCA Tortuosity

We screen coronary and brain middle size arteries by MRA or CT to try and prevent complications.
Disordered Tissue Remodeling
Collaboration with Manfred Boehm NHLBI and lab, and Ian Myles, NIAID

• STAT3 important for angiogenesis (new blood vessel growth) and tissue remodeling
Evolving Prognosis

Improving long term survival
Early diagnosis changing natural history
But need to figure out the vascular and orthopedic issues

Hip Replacement in a 55 year old
Diagnosis of HIES

• Genetic testing with compatible symptoms
  – STAT3- BOTH infections/eczema plus connective tissue (such as flexible joints) or bone issues
• HIES scoring system - was used more before STAT3 testing was widely available
• Whole exome sequencing or panel can identify the other Hyper IgE syndromes as well.
Approach to Care

• Supportive with suppressive antimicrobials
  – TMP/SMX (Bactrim) typically, antifungals
  – Travel plans- antifungals if going to Southwest US!
• Antiseptics (i.e. dilute bleach baths, chlorhexidine, swimming in chlorinated water) to control eczema, reduce *S. aureus* colonization
• Consideration of dupilumab for eczema
• Consideration of IgG supplementation: IVIG or SCIG
• Bone and dental health: Vitamin D levels
• Low suspicion of infection
• Consideration of bone marrow transplant
Dupilumab

• Monoclonal antibody approved for use in eczema (above 6 months), moderate to severe asthma (6 years and up), eosinophilic esophagitis (12 years and up), sinusitis with polyps
  – Mostly used in HIES for eczema
• Injection (comes as pre-filled injection with pen) that is given subcutaneously every 2 weeks. Can be given at home- let warm to room temp before giving.
• Side effects- main one are injection site pain and conjunctivitis (pink eye)
• Can cause transient increase in eosinophils in the blood, and decreases IgE.
What is the role for HSCT?

Case report

Bone marrow transplantation does not correct the hyper IgE syndrome

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Department of Paediatric Immunology, Newcastle General Hospital, Newcastle upon Tyne, UK

Successful long-term immunologic reconstitution by allogeneic hematopoietic stem cell transplantation cures patients with autosomal dominant hyper-IgE syndrome.

General Approach to Transplant

• Choose who is the best donor
  – HLA (white blood cell typing) matched sibling, matched unrelated donor, haplo-identical donor
• General tune up to be in best health possible
• Typically about one week of chemotherapy to clear out one’s own bone marrow from progenitors of white blood cells, red blood cells, platelets.
• Infusion of bone marrow or stem cells from donor
• Wait with lots of supportive care for the new cells to grow
HSCT Pros/Cons

• Pro: Eczema and infection susceptibility should be cured or close to cured
  – Exception- if bronchiectasis or pneumatocele is present, the lung disease will hopefully stabilize and improve but infections may occur still.

• Cons: Increased infection risk around HSCT (closely monitored)
  – Graft versus host disease
  – Potential infertility (discuss possible options in advance)
What is the role for HSCT in STAT3 HIES?

• Seems to make sense in some cases
  – four pediatric patients transplanted at NIH- all at worse end of spectrum
  – About 25 patients transplanted worldwide?
  – Some great outcomes being reported

• But for HIES from STAT3, not everything will be corrected
  – Will the infection phenotype be improved? Probably
  – Will the bone phenotype be improved? Maybe
  – Will the vascular phenotype be improved? Maybe not
  – Lung healing if there a post- transplant pneumonia? Unknown
COVID-19 in STAT3 HIES

Pre-or no Vaccination: at least 13 COVID-19 Infections
- 5 hospitalized
  - All significant parenchymal lung disease (one full pneumonectomy)
  - Two with obesity, at least 4 with hypertension
  - One fatality (and only one to ICU)- 41 year old Hispanic male, obesity, bronchiectasis with MRSA and Pseudomonas, Hypertension, Prior MI with coronary artery aneurysm, busy hospital with many COVID cases.

Post- vaccination: > 26 COVID-19 infections
One hospitalization: secondary bacterial pneumonia.
No fatalities yet

Baseline CTs of patients who got COVID-19 post vaccination and did fine, no hospitalizations (but I worried); two got antivirals
Some Ongoing Projects

- COVID vaccine responses (Good! Important to get!)
- International collaboration (many sites around the world) to study quality of life for those with HIES and therapies or diseases processes that affect QOL
  - Transplant, dupilumab, etc
- Studies of the lung pathology for HIES
  - Germany, NIH/University of North Carolina
- Gene Editing
  - Trying to “fix” the mutation
THANKS!!

QUESTIONS?
Additional Resources

• IDF Resource Center: https://primaryimmune.org/resource-center

• IDF Support Services: https://primaryimmune.org/support-services

• IDF’s YouTube Channel (recordings of all IDF education sessions available): https://www.youtube.com/user/IDFvideos
Have more Questions?

www.Primaryimmune.org/ask-idf
800-296-4433
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Upcoming Events

IDF Lunch & Learn: NEMO
Wednesday, 11/9/22
Kelly Walkovich, MD

SCID Compass Lunch & Learn:
Organ Function and Long-term Follow-up outcomes
Wednesday, 11/16/22
Ami Shah, MD

For a list of all upcoming IDF Events, visit:
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THANK YOU!

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