Longitudinal Observation of Pediatric Dermatology Patients

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To my wife, Aimée, whose love, brilliance, and calm guidance leads me through all of life's amazing adventures.

– TAS

Introduction from the Senior Author (TAS)

Pediatric dermatology has been my life and passion for more than thirty years. Seems like a long time looking forward, but it has gone by quickly. This book was the brainchild of my (then) fellow Dr. Devika Patel Icecreamwala who recognized in my vast library of images (many thousands) the kernel of a book to pass the accumulated knowledge onto future generations. We have tended to illustrate the unusual cases rather than the mundane. My thanks to Drs. Sam Schneider and Marla Jahnke for their dogged contributions and editorial additions.

Contents

Part X Collagen Vascular Disorders

Part I
Eczematous Eruption of Childhood

Chapter 1
Hyper IgE Syndrome

Hyper-immunoglobulin E (IgE) syndrome (HIES) is a rare clinical entity that was first recognized by Davis in 1966 that affects 1:100,000 patients annually [1]. HIES is a primary immunodeficiency, previously called Job syndrome. It is equally prevalent in men and women (Table 1.1).

HIES is characterized by eosinophilia, eczema, elevated IgE levels, and recurrent cutaneous and pulmonary infections. Early cutaneous manifestations of HIES include eczematous eruptions, recurrent abscesses, and chronic mucocutaneous candidiasis. The abscesses are referred to as "cold abscesses" because they are non-inflammatory and are typically caused by *Staphylococcus aureus* [2]. Diagnostically, patients have eosinophilia and elevated IgE levels. Pulmonary findings mainly consist of recurrent sinopulmonary infections with various bacterial, viral, and fungal pathogens ultimately leading to the formation of bronchiectasis, pneumatoceles, and parenchymal lung damage. Patients can present with abnormal craniofacial features (i.e. characteristic facies, craniosynostosis, retained childhood dentition, and high-arched palate), musculoskeletal abnormalities (i.e. hyperextensibility, scoliosis, and osteoporosis), vascular abnormalities (coronary artery dilatation, aneurysms, and hypertension) as well as parenchymal brain lesions. Patients with HIES are at increased risk of developing certain malignancies such as non-Hodgkin lymphoma [2].

The pathogenesis involves the JAK/STAT pathway, which is critical in mediating the inflammatory cascade. Mutations in the *STAT3* locus on chromosome 17 have been identified in patients with HIES. Other mutations include *DOCK8* and *Tyk2* mutations.

The differential diagnosis of elevated serum IgE includes Wiscott-Aldrich, Omenn, atypical complete DiGeorge, Netherton and polyendocrinopathy enteropathy X-linked (IPEX) syndromes as well as immune dysregulation syndromes.

Prevention of skin and pulmonary infections is with prophylactic antibiotics and antifungals. Eczema and skin abscesses can be mitigated with bleach baths and chlorhexidine washes. Topical calcineurin inhibitors and topical corticosteroids

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Table 1.1 Scoring system for Hyper IgE Syndrome (Job syndrome)

Clinical findings	0	1	2	3	4	5	6	7	8	10
Highest IgE (IU/mL)	<200	200–500			501–1000				1001–2000	>2000
Total skin abscesses/boils	None		1–2		3–4				>4	
Total pneumonias	None		1		2		3		>3	
Parenchymal lung abnormalities	None						Bronchiectasis		Pneumatocele	
Other serious infection	None				Present					
Fatal infection	None				Present					
Highest eosinophils/uL	<700			701–800			>800			
Newborn rash	None				Present					
Eczema (worst stage)	None	Mild	Moderate		Severe					
Sinusitis/otitis (in worst year)	1–2	3	4–6		>6					
Candidiasis	None	Oral, vaginal	Fingernail		Systemic					
Retained primary teeth	None	1	2		3				>3	
Scoliosis (maximum curvature)	<10		10-14		15–20				>20	
Minimal trauma fractures	None				1–2				>2	
Hyperextensibility	None				Present					
Characteristic face	None		Mild			Present				
Increased interalar distance	<1 SD	1–2 SD		>2 SD						
High palate	None		Present							
Congenital anomaly	None					Present				
Lymphoma	None				Present					

may help with the eczematous dermatitis. Certain patients with HIES may benefit from immunoglobulin substitution therapy (i.e. IV IgG). Bone marrow transplantation has been attempted in several patients with mixed results making the utility of this treatment less clear.

Many many patients with atopic dermatitis have high levels of IgE. The query "is this Job's Syndrome" comes up quite frequently. Now that we have genetic testing for DOCK8 and *STAT3* a firm diagnosis can be made. To my surprise my last two patients did not have the long list of facial, brain, and bone problems usually associated with HIES, rather they had persistent pustules, hard to control eczema, and multiple staph infections. A nice check list for HIES is:

- 8 or more ear infections in the past 12 months:
- 2 or more sinus infections in the past 12 months:
- Two or more months or antibiotics with little relief:
- Two or more pneumonias within 1 year:
- Failure of infant to gain weight or grow normally:
- Recurrent, deep skin or organ abscesses:
- Persistent thrush in mouth or elsewhere on skin, after age 1:
- Need IV antibiotics to clear infections:
- Two or more deep seated infections:
- Family history of immunodeficiency:
- Consanguineous parents:
- Dental abnormalities or missing teeth:
- Alopecia: Sparse hair on head or eyebrows:
- Does patient sweat or history of febrile seizures:
- Normal nail development:
- Any history of unexplained childhood deaths:

This is a shorthand from a very nice graph published by Rebecca Buckley MD. This chart is helpful for *STAT3* deficiency type IgE.

When I ask the above questions, I am tallying up the points from Table 1.1 for total of:

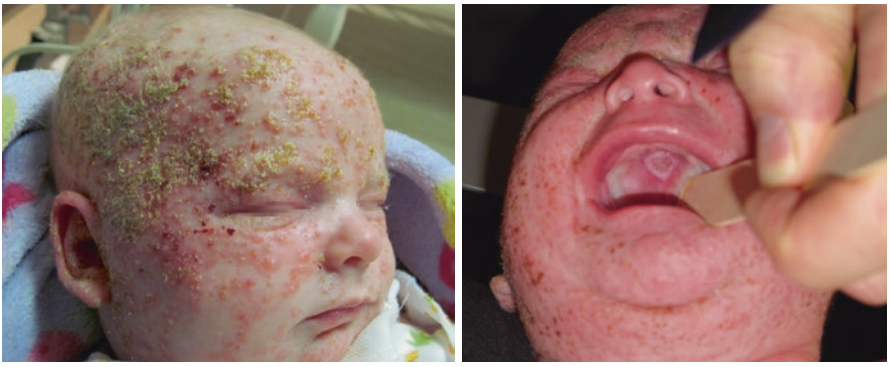
- >40 points likely
- 20–40 points uncertain
- <20 points unlikely HyperIgE syndrome.

If I see a female patient with bad atopic dermatitis and recurrent skin viral issues or any history of invasive viral infection or cervical cancer then I think of *DOC8* or *TYK* (tyrosine kinase) deficiencies.

All three deficiencies have elevated IgE levels and bad atopic dermatitis but a "weird" infection history.

I usually end up ordering all of the other immunoglobulin levels and HIV to make sure I'm not missing anything else.

Sometimes, I will also order flow cytometry to make sure they have functioning NK/T/B cell lines as well.



Patient presented at 5 weeks of age for pustules and crusting on her scalp. Genetic testing revealed a positive *STAT-3* mutation, which confirmed her diagnosis of Hyper IgE Syndrome. She was initially treated with IV IgG infusions once a month and daily trimethoprim-sulfamethoxizole as prophylaxis.