Hyper IgE syndrom suspect - Case Report

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Abstract:

Introduction: Hyper IgE syndrome (HIES) is a rare condition of the immune system characterized by various types of infections throughout life. This syndrome can be divided into two types, dominant heterozygous related to STAT3 gene mutation and recessive homozygous, which can also be subdivided into two groups related to Tyk2 and DOCK8 gene mutations, each presenting variations in their clinical presentations. Diagnosis is based on genetic sequencing, although there are some symptoms, clinical factors, and hereditary factors that can assist in diagnosis. There is no specific treatment for this pathology, with the main focus being on controlling infections and infusing immunological therapies such as intravenous immunoglobulin G.

Case Report:

Young patient with suspected HIES and severe pulmonary complications. Initially diagnosed with Dengue and pneumonia, the individual developed dysphagia and dyspnea, requiring supplemental oxygen. In the intensive care unit, they experienced an anaphylaxis episode requiring orotracheal intubation. While hospitalized, several complications occurred. However, after administration of Xolair® (omalizumab) and medication adjustments, the patient showed progressive clinical improvement. After a 34-day period, the patient was discharged from the hospital and continues under continuous outpatient care.

Keywords:

- Hyper IgE Syndrome;
- Job Syndrome;
- Buckley Syndrome;
- Immunoglobulin E;
- Dermatitis;
- Recurrent infections;
- Genetic mutations (STAT3, Tyk2, DOCK8);
- Genetic diagnosis;

- Immunological treatment;

- Respiratory complications.

Introduction:

Hyper IgE Syndrome (HIES), also known as Job Syndrome or Buckley Syndrome, is a rare disease of the immune system characterized by recurrent infections, dermatitis, and persistently elevated serum levels of immunoglobulin E (IgE)^1,2. It was first described by Davis et al. in 1966 as Job Syndrome, due to its resemblance to the biblical texts ("Job covered with purulent sores")^4. HIES has garnered increasing interest due to its complex pathophysiology and clinical implications^1,4.

HIES is estimated to have an incidence of approximately 1 case per 1 million individuals^4. The syndrome affects both sexes equally and can manifest in any ethnic group. It is estimated that the oldest person diagnosed with this syndrome would be around 60 years old, with a long history of pulmonary infections, at least three decades^4. Autosomal dominant inheritance patterns have been identified in certain families, suggesting a genetic basis for the disease^2,11.

HIES can be classified into two types, autosomal dominant type 1 (HIES-AD) and autosomal recessive type 2 (HIES-AR)^2,6. Type 1 is characterized by a mutation in the STAT3 gene, while type 2 can be subdivided into 2 subtypes, the first of which presents a homozygous mutation in tyrosine kinase (Tyk2) and the second a mutation in the dedicator of cytokinesis 8 gene (DOCK8)^2,5,11.

The pathophysiology of HIES-AD is associated with defects in the regulation of innate and adaptive immune responses. STAT3 gene mutation is the most common cause of the syndrome, leading to functional deficiency in cytokine signaling, especially T-cell transcription factor (STAT3)^1.

STAT3 is a protein responsible for signal transduction in various intracellular pathways. This protein binds to another protein named Jaks, thus activating the JAK-STAT pathway that transmits the signal from receptors of various pro-inflammatory and anti-inflammatory cytokines, leading to genetic transcription and playing a fundamental role in angiogenesis, wound healing, immunity, and even neoplasia induction^1. This results

in dysfunction of neutrophils and Th17 cells, compromising the immune response against extracellular pathogens. Additionally, dysfunction of the skin barrier, due to deficiency in the expression of filaggrin and other structural skin proteins, contributes to the chronic dermatitis observed in HIES-AD. Characteristics of HIES-AD include alterations in dental arches, musculoskeletal, and vascular systems^2.

Patients with DOCK8 gene defects present with a decreased immune response^5. CD3+/CD4+ and CD3+/CD8+ T cells are decreased in these patients, consequently showing reduced production of antiviral cytokines, making them more prone to infections (mainly S. Aureus), higher risk of neoplasms, and autoimmune diseases^2,5.

Tyk2 gene deficiency tends to result in a less elevated IgE level and a more varied clinical picture than other types and subtypes^5. These patients have a failure in the body's immune response to exogenous or endogenous infections or tissue repair, as well as increased susceptibility to intracellular bacteria (Mycobacteria, Salmonella), fungi, and viruses^2,5.

This pathology, in general, is characterized by various infections throughout life, so newborns may present with eczematoid pustular rash on the face and scalp as early as the first month of life^1. Classic features of the disease include the presence of "cold" furuncles and abscesses (without inflammatory signs) despite being extremely pustular. In many cases, infections associated with mucocutaneous Candida (oral, vaginal, and nail) occur^11.

Diagnosis of HIES is based on genetic sequencing^1. As the cost of this test is extremely high and availability is relatively low, scores can be used to facilitate the diagnosis of this pathology^11:

- Possible: IgE >1000 IU/ml and a score higher than 30 based on clinical characteristics of recurrent pneumonia, neonatal rash, pathological fractures;

- Probable: These characteristics and absence of Th17 cells or defined family history of HIES;

- Definitive: These characteristics and a negative dominant heterozygous mutation of STAT3.

Currently, there is no specific treatment for HIES, as the condition of these patients is related to a greater susceptibility to infectious diseases, and the preferred therapy is to treat the most frequent bacterial infections and use prophylaxis for common pathogens^11. Another therapy that has been used with some success in some patients is regular use of intravenous immunoglobulin G, although data are still scarce, it has been shown to be effective in cases of patients with specific antibody synthesis deficits^11.

Table 1

Scoring System with Clinical and Laboratory Tests for Individuals in Kindreds with HIES

	Points[a]									
Clinical Findings	0	1	2	3	4	5	6	7	8	10
Highest serum-IgE level (IU/ml)[b]	<200	200–500			501–1,000				1,001–2,000	>2,000
Skin abscesses	None		1–2		3–4				>4	
Pneumonia (episodes over lifetime)	None		1		2		3		>3	
Parenchymal lung anomalies	Absent						Bronchiectasis		Pneumatocele	
Retained primary teeth	None	1	2		3				>3	
Scoliosis, maximum curvature	<10°		10–14°		15°–20°				>20°	
Fractures with minor trauma	None				1-2				>2	
Highest eosinophil count (cells/μl)[c]	<700			700–800			>800			
Characteristic face	Absent		Mildly present			Present				
Midline anomaly[d]	Absent					Present				
Newborn rash	Absent				Present					
Eczema (worst stage)	Absent	Mild	Moderate		Severe					
Upper respiratory infections per year	1-2	3	4–6		>6					
Candidiasis	None	Oral	Fingernails		Systemic					
Other serious infections	None				Severe					
Fatal infection	Absent				Present					
Hyperextensibility	Absent				Present					
Lymphoma	Absent				Present					
Increased nasal width[e]	<1 SD	1–2 SD		>2 SD						
High palate	Absent		Present							
Young-age correction	>5 years			2–5 years		1–2 years		≤1 year		

[a] The entry in the furthest-right column is assigned the maximum points allowed for each finding.
[b] Normal <130 IU/ml.
[c] 700/μl = 1SD, 800/μl = 2 SD above the mean value for normal individuals.
[d] For example, cleft palate, cleft tongue, hemivertebrae, other vertebral anomaly, etc. (see Grimbacher et al. 1999*a*).
[e] Compared with age- and sex-matched controls (see Farkas et al. 1994).

Table 1 from:

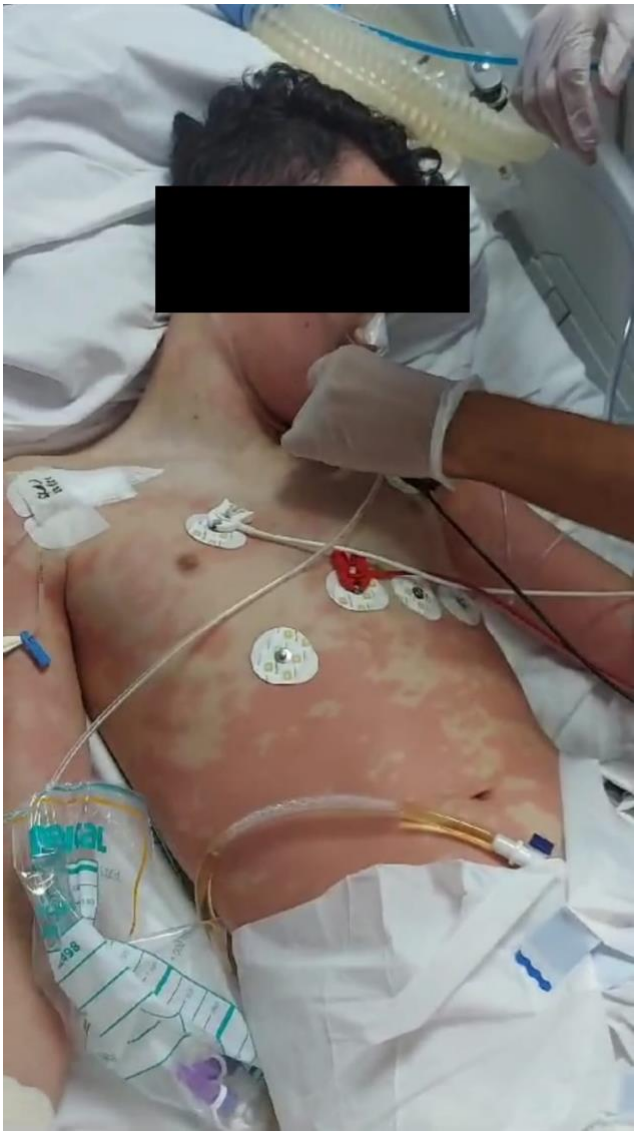
Freitas, Sara et al. “Hyper-IgE syndrome: a review article.” Journal of Clinical & Diagnostic Research : JCDR vol. 8,2 (2014): 199-202.

Case Report: Patient with Suspected Hyper IgE Syndrome and Respiratory Complications

Patient EAM, male, 14 years old, was admitted to the emergency room due to a dengue episode with significant thrombocytopenia associated with pneumonia. He was on the first day of Ceftriaxone use. During hospitalization, he presented a significant worsening of the clinical condition, with dysphagia associated with dyspnea, nasal congestion, headache, and asthenia. He developed peripheral saturation drop (87%), requiring oxygen therapy at 1L/min. He had significant drooling and difficulty swallowing or speaking normally. Physical examination revealed diffuse bilateral wheezing on pulmonary auscultation and tenderness to digital pressure in the sinuses, with a preference in the maxillary region.

Laboratory tests showed elevated levels of platelets and leukocytes, as well as a decrease in potassium. Due to the severity of the clinical condition, it was not possible to perform magnetic resonance imaging of the skull and orbit. The patient had been hospitalized for 6 days when he developed a severe anaphylaxis episode, followed by orotracheal intubation and transfer to the intensive care unit (ICU).

During the hospitalization period, the patient underwent several attempts at extubation, without success. He developed severe bronchospasm and respiratory failure, followed by a cutaneous rash. After a prolonged period of intubation, a tracheostomy was performed.



A computed tomography (CT) scan showed consolidation with atelectatic component in the left lower lobe and inflammatory bronchopathy. In addition, other complications were observed, such as discrete pericardial effusion and moderate bleeding via tracheostomy.

The suspicion of hyper IgE syndrome was raised due to the highly nonspecific and infection-filled clinical picture, in addition to laboratory tests showing elevated IgE

(1304 IU/L), rheumatologic tests were requested, and new tests and treatment with Xolair were initiated. Medical opinions were requested from teams in allergology and immunology, neurology, rheumatology, pulmonology, and thoracic surgery. After analysis, the allergology team suggested continuing corticosteroids and antihistamines, avoiding dipyrone and ceftriaxone for now, and sending a report with medications used during hospitalization to them.

With the introduction of immunoglobulin, the patient showed significant improvement in his condition, progressing to tracheostomy removal. After 34 days of hospitalization, the patient was discharged from intensive care. The medical team continues to monitor the patient's progress and remains available for additional interventions as necessary.

Conclusion:

HIES is a rare and complex disease, still not fully understood, but over the years, various discoveries have been made about the condition. This syndrome presents a significant challenge for both diagnosis and therapy due to the enormous variability of symptoms. Management requires careful patient care, necessitating a multidisciplinary approach

Exam	Results	Reference value
Rubella - IgG antibodies	18.4 UI/mL	Reagent: ≥ 10.0 UI/mL
Measles - IgM Antibodies	0.1	Negative: < 0.90
Immunoglobulin M - IgM	114 mg/dL,	Over 12 years old: 50 to 300 mg/dL
Immunoglobulin A - IgA	94 mg/dL	11 to 60 years old: 103 to 591 mg/dL
Total Proteins and Fractions - Blood		
Total Proteins:	6.5 g/dL	6.0 to 8.0 g/dL
Albumin:	3.9 g/dL	3.2 to 4.5 g/dL
Globulinas:	2.6 g/dL	2.2 to 4.32 g/dL
Lymphocyte Subpopulation CD3-CD4-CD8		
Total leukocytes	8,797 cells/uL	3,800 to 1,1000 cells/µL
Total lymphocytes	398 cells/uL	1,000 to 4,000 cells/µL
%CD3	66.00%	53.5 to 75.3%
%CD4 (CD3+CD4+/CD3+)	32.40%	30.7 to 46.0%
CD8 (CD3+CD8+/CD3+)	28.60%	16.2 to 28.7%
CD3 T lymphocytes	263 cells/uL	1,088 to 2,087 cells/µL
CD4 T Lymphocytes (CD3+CD4+)	129 cells/uL	639 to 1,278 cells/µL
CD8 T lymphocytes (CD3+CD8+)	114	211 to 724 cells/µL
CD4/CD8 interface	1.13	0.98 a 3,24
Immunoglobulin E - IgE	1304 UI/mL	2 to 629 UI/mL
Hepatitis B - Total Anti-HBc	Non-reactive	Non-reactive
T Lymphocytes helper CD4+		
Total leukocytes	8,256 cells/uL	3,800 to 11,000 cells/µL
Total Lymphocytes	485 cells/uL	1,000 to 4,000 cells/µL
% CD4 (CD3+CD4+/CD3+)	27,80%	30.7 a 46.0%
CD4 T Lymphocytes (CD3+CD4+)	135 cells/uL	639 to 1,278 cells/µL
Anti-pneumococcal IgG antibodies	24,9 mg/L	Pre-vaccines: < 38,2 mg/LPos-vaccines: Variable

to treat recurrent infections and dermatological manifestations, as well as to prevent possible complications. The case presented illustrates a patient with suspected syndrome and emphasizes the difficulties that the medical team encountered in their treatment and therapeutic approach. Continuous research and the development of new therapies are crucial to offering a better prognosis to individuals affected by this syndrome.

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