

# HYPER IgE SYNDROME – WHERE ALLERGY AND IMMUNE DEFICIENCY MEET

Wim Wijnant, MD

Division of Paediatric Pulmonology, University of Pretoria, South Africa

## ABSTRACT

Hyper IgE syndrome is the rare combination of very high serum immunoglobulin E (IgE) levels with immune deficiency. The high concentration of IgE causes the atopic features, especially severe eczema. Mutations in the STAT3 gene are responsible for the deficient translation of the cytokine signals in effective immune responses. Patients are thus prone to severe destructive staphylococcal infections of skin and lungs, often with surprisingly few clinical symptoms. Other systemic consequences are characteristic facial features with retention of primary teeth, bone fractures from mild trauma, scoliosis and vascular aneurysms. Management includes control of the allergic features and early and aggressive treatment of infections.

## INTRODUCTION

Hyper IgE syndrome (HIES) is a condition that combines primary immune deficiency with features of severe allergy. It would probably be more correct to define it as a group of conditions because several subtypes have been discerned since the genetic background has been unravelled over the last two decades. The most common phenotype is the autosomal dominant (AD-HIES) form, related to STAT3 deficiency.<sup>1</sup> However, two distinct autosomal recessive forms (AR-HIES) have also been identified. A better understanding of the pathogenesis has enabled scientists to explain the broader systemic presentation. It was initially described as Job's syndrome<sup>2</sup> in 1966 with original triad of severe eczema, recurrent skin and lung infections and eosinophilia and later (in 1972) Buckley<sup>3</sup> added the striking high IgE level as a component of the condition. The clinical picture has now been extended to include skeletal and vascular problems as well as neurological and oncological manifestations.<sup>1</sup>

This article first presents a case to illustrate the condition and then touches briefly on the immunological background. However the focus is the clinical presentation and the diagnostic criteria of the problem. In conclusion the possible therapeutic approaches are discussed.

## CASE PRESENTATION

A 2-year-and-7-months-old boy was referred to the asthma and allergy clinic for severe atopic dermatitis and recurrent chest problems. A few weeks after birth he had developed an itchy and dry skin rash, extending over the whole body, which responded well to emollients and topical steroids. He had recurrent episodes of cough and respiratory distress. The cough was sometimes associated with wheeze, but there was no difference in occurrence of symptoms between night and day, or with rest and exercise. Some of these episodes were

treated with antibiotics after chest radiographs revealed non-persistent air bronchograms or patchy infiltrates in different lobes with each episode.

He was breastfed for 3 months, then changed to formula feeding, and solids were introduced at 6 months. He is now on a family diet, but refuses milk, fish and eggs. There is no family history of asthma or atopy. The mother has a double row of teeth.

Clinical examination revealed a thriving young boy with eczematous lesions on his face and arms, as well as the knees. The latter were complicated by crusty lesions. The chest was clear at presentation and no hyperinflation was noted. The nasal turbinates were swollen and inflamed. The palate was high and rough. There was no candidiasis and his teeth were well cared for.

Chest radiographs revealed some breakdown in the right upper lobe.

Because of the extensive skin lesions, skin-prick tests were deferred and ImmunoCAP RAST testing was conducted instead. The total IgE was more than 2 000 kU/l and significant high levels of specific IgE were noted to egg white, fish, peanuts and house-dust mite. There was also an eosinophilia of 823 cells/ $\mu$ l.

## IMMUNOLOGY

High IgE levels have for many years been the main feature for diagnosis of HIES, easy to test and central to some of the clinical manifestations. Since the pathogenesis has been traced further upstream to mutations in the STAT3 gene, this 'signal transducer and activator of transcription' has become the focus of the pathogenesis of AD-HIES.<sup>1</sup> STAT3 indeed activates the transcription of a whole range of genes important in immune response and modulation in response to multiple cytokines. These cytokines need to bind to their specific receptor and this process is mediated by Jak1, Tyk2 and probably DOCK8 phosphorylate STAT3.<sup>4</sup>

In normal individuals pathogens entering a host are detected by either the innate or adaptive immunity system. Both responses may produce extensive cytokine production tailored to the specific antigen in question and this would guide and augment or diminish the appropriate immune response. STAT3 plays a key role in the translation of the cytokine signal into the specific action from the immune system. Figure 1 illustrates how STAT3, after activation by cytokines, migrates to the nucleus, binds to DNA and results in expression of specific effector genes. Owing to mutation in the STAT3 gene (located on chromosome 17) in AD-HIES, the structure of the process is altered and binding to the DNA is deficient. Activation of STAT3 is less effective rather than completely inactive, as the latter process would be incompatible with life.<sup>4</sup>

In the nucleus, STAT3 would initiate the transcription of genes important to neutrophil trafficking and signalling pathways and reactive oxygen species generation. Both are important in bacterial infection, especially those caused by staphylococcal species. The expression of interleukin (IL)-17 and further activation of T-helper (Th) 17 cells is also affected, explaining the susceptibility

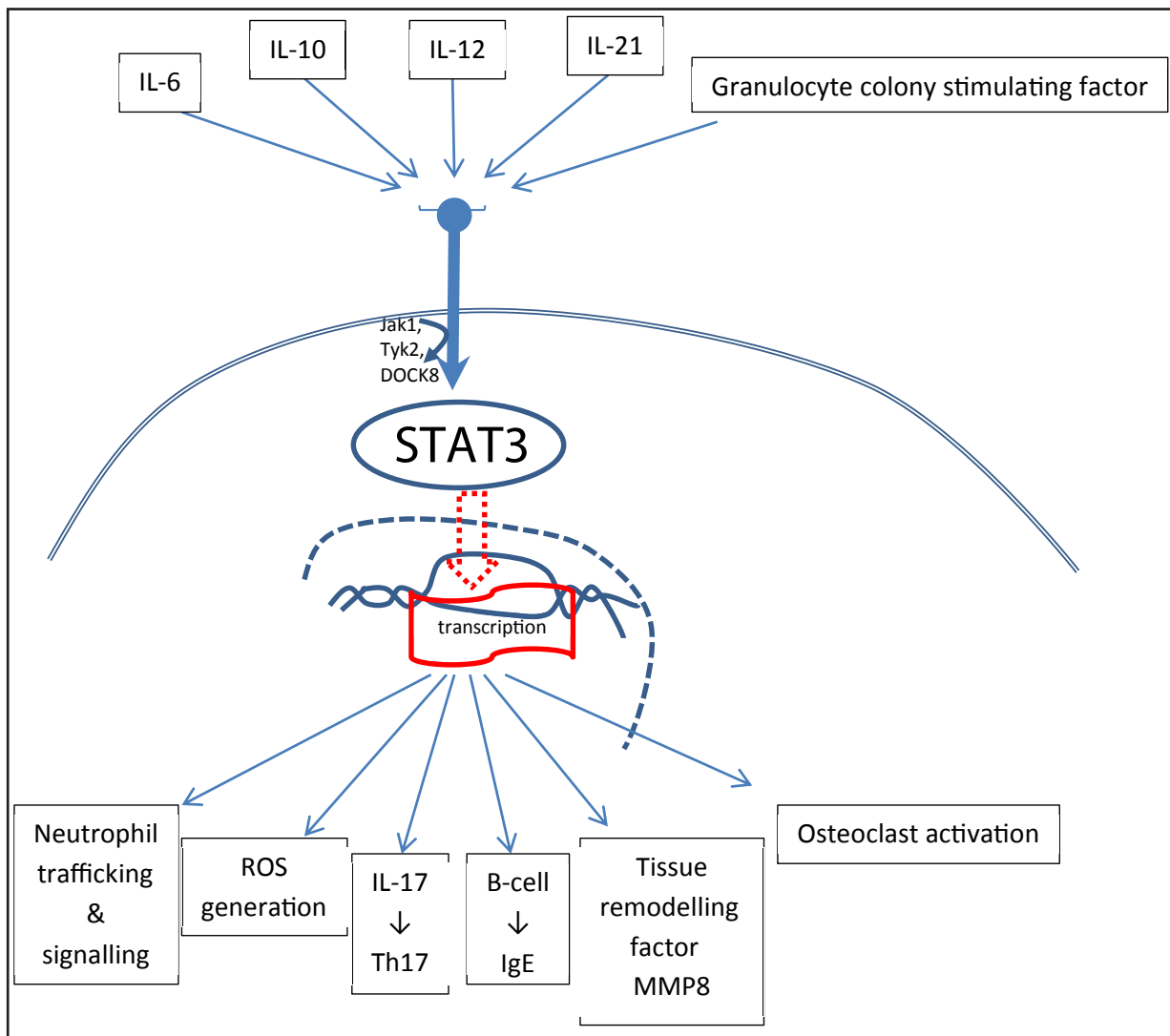


Fig. 1. STAT3 triggered by cytokines migrates to the nucleus to activate the transcription of genes (based on Rael et al.<sup>1</sup>). IL-interleukin; ROS – reactive oxygen species; Th – T helper; MMP – matrix metalloproteinase

to fungal infections. IL-17 deficiency also seems to be important in causing eosinophilia and raised IgE levels. However, deficiency in STAT3 can also directly affect the link between IL-21 and B-cell differentiation and subsequent IgE production. The tissue remodelling factor, matrix metalloproteinase (MMP)-8 is also influenced by STAT3 activity, explaining the problems in lung repair as well as osteoclast proliferation and activity.

The AR-HIES can be attributed to other mutations causing defects in DOCK8 and Tyk2. They present with slightly different clinical conditions to individuals with classic AD-HIES.

## CLINICAL PRESENTATION

HIES is a systemic disease, as it affects the function of the immune system, integument, respiratory and cardiovascular system, skeleton and central nervous systems. AD-HIES and AR-HIES manifest slightly differently, but skin and lungs are always involved.

### Severe eczema

A pustular or papular rash, from the neonatal period, is commonly the first manifestation of hyper IgE syndrome. It can mimic neonatal acne, but it is typically an extensive and severe eczema, extending from the face and scalp downwards to involve the whole body. Staphylococcal infection of the skin lesions is common

rendering the eczema more difficult to treat. Deep infections can cause abscesses that typically lack the expected inflammatory reaction of dolor, rubor and calor, hence the term 'cold abscesses'.<sup>2</sup> Drainage of the pus might be necessary and antimicrobial treatment and antiseptic prophylaxis helps to control the eczema.

### Recurrent pneumonia and pneumatocele formation

From early in life, recurrent lung infections are another important feature of the syndrome. They are typically caused by *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Haemophilus influenzae*. Inflammation is typically milder with lack of fever and an impaired cough reflex. Therefore clinical symptoms are milder and more insidious than usual and the diagnosis is often missed or delayed. Damage is consequently more extensive and severe. Lung tissue repair is impaired, necessitating delay in pneumonia healing and early bronchiectatic scarring or pneumatocele formation (Fig. 2). As in other forms of chronic suppurative lung disease, these dilated airpockets are deficient in clearing and become prone to chronic colonisation and infection by Gram-negative bacteria or fungi (typically *Pseudomonas aeruginosa* and *Aspergillus fumigatus*). Therefore, a high index of suspicion for lower respiratory tract infections, aggressive antibiotic therapy and support in airway clearance are important to avoiding persistence of this vicious cycle of inflammation and infection.

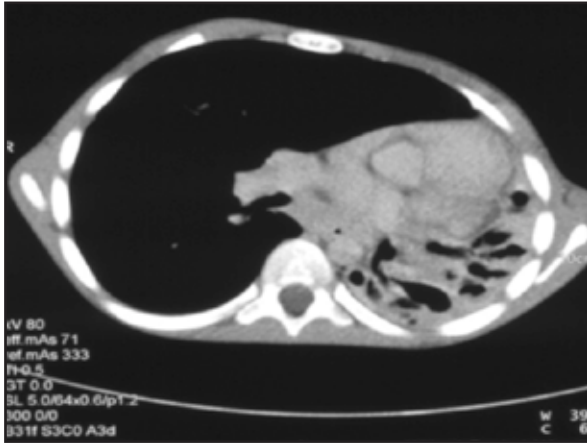


Fig. 2. CT scan of bronchiectatic airways.

### **Coarse facial features and retention of primary teeth**

Failure to exfoliate primary teeth can cause delayed eruption of secondary teeth; however, more commonly it will lead to the typical feature of a double row of teeth (Fig. 3).



Fig. 3. Typical feature of double row of teeth due to failure of exfoliation of primary teeth.

Individuals also often have a high-arched palate with fibrotic bridges parallel to the molar row, mirrored by prominent fissures on the tongue and this may or may not be accompanied by oral thrush. There is commonly a prominent forehead, large and wide nose, deep eyes and rough facial lines.

There is a higher incidence of craniosynostosis and Chiari 1 malformations in AD-HIES, rarely, however, requiring surgical intervention.

### **Skeleton and joints**

Because of abnormal osteoclast and osteoblast activity patients with AD-HIES often present with osteopenia and osteoporosis. This causes long bone fractures from surprisingly minimal impact.

Both small and large joints suffer degenerative disease, initially only manifesting as hyperextensibility, but from adolescence this can cause extensive arthritis. Scoliosis is a common feature, requiring early intervention as it may aggravate pulmonary function.

### **Miscellaneous**

Vascular abnormalities such as aneurysms of the aorta, coronary and cerebral arteries are common. The coronary arteries are particularly vulnerable and are typical tortuous, resulting in an increased size of infarction. There is a higher risk of lymphoma development.

## **FEATURES IN AR-HIES**

The AR-HIES variants manifest slightly differently, often with less destructive lung features despite recurrent respiratory tract infections. The coarse facial features, retention of teeth and other skeletal abnormalities are also absent. These individuals, however, have more severe allergies, both to foods and inhalants. The immune deficiency also appears to be more severe and extends to increased viral infections. There is a higher mortality in this condition.

## **DIAGNOSIS**

The diagnosis is usually made on clinical suspicion together with eosinophilia and very high serum IgE titres, often exceeding 2 000 kU/l. IgE can normalise though into adulthood.

Several clinical guidelines have been proposed to help with bedside differential diagnosis and classification (Tables I and II). Most recently a taskforce proposed specific diagnostic criteria for the STAT3-deficient HIES,<sup>5</sup> simplifying previous scoring systems. The guideline grades the diagnosis of STAT3 deficiency from possible to definite according to the extent of immunological and genetic investigations available. A clinical scoring system (Table I) is used in assessing the severity of the five most typical features: number of radiologically proven pneumonias, neonatal skin rash, pathological bone fractures, characteristic facial features and a 'cathedral palate'. These features are then weighted differently. The diagnosis of STAT3-deficient AD-HIES is possible if a patient with total IgE levels of more than 1 000 kU/l has a weighted score of at least 30 points. The diagnosis is considered probable when this is combined with low IL-17 levels or when a family member has a definite diagnosis of HIES. The definite diagnosis is made only on genetic testing of the common mutations but this is not offered in South Africa.

These scoring systems might be more problematic in children since counting of pneumonic events and pathological fractures will be affected by the age of the child. Retention of teeth is also only possible after the normal age for exfoliating has been reached. The scoring system still has the advantage that it provides the clinician with evidence-based guidance in bedside diagnosis, without the need for expensive (or unavailable) immunological testing. The simplification from the original 21 criteria<sup>6</sup> seems convenient, but might disadvantage the younger patient.

Applying both systems on our patient reveals their shortcomings. It seems that the extensive scoring system favours the diagnosis of HIES, while the most recent one would not.

## **TREATMENT**

Because no definite treatment is available, the main role of management is supportive and symptomatic.<sup>7</sup> Severe eczema is aggressively treated with emollients and topical steroids, while staphylococcal infections are treated, and prevented, with bleach baths.

Destructive lung disease is prevented by treating pneumonias with appropriate antibiotics. A high index of suspicion is important because of the paucity of symptoms. Trimethoprim-sulphamethoxazole prophylaxis can be useful as well as chest physiotherapy to help clearance of secretions since the cough reflex is often inadequate. Anticoagulation to prevent vascular accidents is controversial and may increase the risk for pulmonary haemorrhage into pneumatoceles.

Bone marrow transplant is an experimental modality in this condition.

**Table I. Clinical scoring table\***

Clinical features	Points						Attributed points	Correction factor	Total
	0	2	4	5	6	8			
1. X-ray confirmed pneumonias: number in lifetime	None	1	2	–	3	>3		x2.5	
2. Newborn rash	Absent	–	Present	–	–	–		x2.08	
3. Pathological bone fractures	None	–	1–2	–	–	>2		x3.33	
4. Characteristic facial features	Absent	Mild	–	–	–	–		x3.33	
5. Cathedral palate	Absent	Present	–	–	–	–		x2.5	

\* Scores of >30 in patients with total IgE >1 000 kU/l indicate possible STAT3-deficient hyper IgE syndrome. A scoring of <10 excludes it. Adapted from Woellner *et al.*<sup>5</sup>

**Table II. Original clinical scoring table for hyper IgE syndrome (1999) (from Grimbacher *et al.*<sup>6</sup>)\***

Clinical and biochemistry findings	Points									
	0	1	2	3	4	5	6	7	8	10
1. Highest serum IgE	<200	200–500			500–1000				1000–2000	>2000
2. Skin abscesses	None		1–2		3–4				>4	
3. Pneumonia (episodes over lifetime)	None		1		2		3		>3	
4. Parenchymal lung anomalies	Absent						Brochiectasis		Pneumatocele	
5. Retained primary teeth	None	1	2		3				>3	
6. Scoliosis (maximum curvature)	<10°		10–14°		15–20				>20	
7. Fractures with minor trauma					1–2				>2	
8. Highest blood eosinophil count	<700			700–800			>800			
9. Characteristic face	Absent		Mild			Present				
10. Midline anomaly	Absent					Present				
11. Newborn rash	Absent				Present					
12. Eczema (worst stage)	Absent	Mild	Moderate		Severe					
13. Upper respiratory infections per year	1–2	3	4–6		>6					
14. Candidiasis	None	Oral	Fingernails		Systemic					
15. Other serious infections	None				Severe					
16. Fatal infection	Absent				Present					
17. Hyperextensibility	Absent				Present					
18. Lymphoma	Absent				Present					
19. Increased nasal width	<1 SD	1–2 SD		>2 SD						
20. High palate	Absent		Present							
21. Young age correction	>5y			2–5 y		1–2 y		≤1 y		

\* An individual with a scoring of ≥15 is likely to be diagnosed with HIES, while the diagnosis is unlikely with a scoring of <10. The presence of HIES genotype is indeterminate for in between scores.

**CONCLUSION**

HIES is the association of very high IgE levels with typical atopic clinical features such as severe eczema from the neonatal period. Immune deficiency results in recurrent suppurative lung infections and destruction of lung parenchyma. Patients usually have typical facial features and retention of primary teeth. This triad was described in the 1960s and 1970s, but since then genetic and immunological progress has helped to unravel the pathogenesis and clarify different phenotypes. The

most common type, AD-HIES, is related to STAT3 deficiency and is often associated with skeletal and vascular abnormalities. The diagnosis remains clinical, although more advanced immunological (Th 17) and genetic (variety of mutations) testing can be helpful in prognosis. The treatment remains supportive with prevention of recurrent infections.

**Declaration of conflict of interest**

The author declares no conflict of interest.

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