Obstructive uropathy in STAT 3 hyper immunoglobulin E syndrome

A 5 year old Middle Eastern boy

Esraa M. Bukhari, *MD,* ***Ashwag A. Alsaidalani,*** *MD.*

ABSTRACT

تعد متلازمة الغلوبولين المناعي المفرط السائد (IgE) خطأ فطري نادر في المناعة يؤثر على واحد من كل مليون فرد تقريبًا في جميع أنحاء العالم. يظهر مع أعراض مختلفة بسبب ارتباط الأجهزة المتعددة (المناعية وغير المناعية). تعتبر الالتهابات المتكررة (بشكل رئيسي في الجلد والرئتين) من الأعراض الشائعة. ومع ذلك، لم يتم الإبلاغ سابقًا عن حالات العدوى العميقة الشديدة التي تسبب اعتلال المسالك البولية الانسدادي. نستعرض في هذا التقرير طفل يبلغ من العمر 5 سنوات يعاني من أعراض تشير إلى اعتلال المسالك البولية الانسدادي الناتج عن خراجات حوضية كبيرة متعددة وإصابة حادة في الكلى مع فرط بوتاسيوم الدم مما يستلزم الدخول في وحدة العناية المركزة. بعد مزيد من البحث، أظهر الاختبار الجيني للمريض (تسلسل الإكسوم الكامل) متغيرًا خاطئًا متغاير الزيجوت في جين STAT3. تعافى المريض تمامًا ولم يحتاج إلى التنويم بعد بدء العلاج بالمضادات الحيوية الوقائية. على الرغم من أن الالتهابات العميقة غير شائعة في متلازمة STAT3 فرط IgE، إلا أن التهابات الجلد والرئة هي الأكثر شيوعًا. يمكن أن تحدث مجموعات عميقة متعددة وتتطلب التدخل الفوري والعلاج العدواني.

Autosomal dominant hyper immunoglobulin E (IgE) syndrome is a rare inborn error of immunity that affects approximately one in a million individuals worldwide. It presents with various symptoms owing to multisystem involvement (immunological and non-immunological). Recurrent infections (mainly in the skin and lungs) are common presentations. A 5-year-old Middle Eastern boy presented with symptoms suggestive of obstructive uropathy secondary to multiple large pelviabdominal abscesses and acute kidney injury with hyperkalemia that necessitated admission to the intensive care unit. Upon further investigation, the patient's genetic test (whole exome sequencing) demonstrated a heterozygous missense variant in the STAT3 gene. The patient completely recovered and did not require further admission after initiating prophylactic antibiotics. Although deep-seated infections are uncommon in STAT3 hyper IgE syndrome, skin and lung infections are most commonly observed. Multiple deep collections can occur and require prompt intervention and aggressive treatment.

Keywords: STAT 3, HIES, AKI, pelvic abscess, eczema

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From the Department of Pediatrics, Faculty of Medicine, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia.

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Address correspondence and reprint request to: Dr. Esraa M. Bukhari, Department of Pediatrics, Faculty of Medicine, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia.
E-mail: Dr.e.bukhari@gmail.com
ORCID ID: https://orcid.org/0000-0001-6033-9661

STAT 3 hyper immunoglobulin E syndrome (STAT3-HIES) is a rare primary immune deficiency, accounting for approximately 1/1000000 patients worldwide.[1] It was first described as Job's syndrome in 1966, which later came to be known as STAT3-HIES, based on its characteristic clinical features and genetic mutations. The defect in STAT 3 is inherited as an autosomal dominant-negative mutation resulting from in-frame deletion or missense mutations. However, most cases have been identified as a de novo mutation.[2,3]

STAT 3 hyper immunoglobulin E (IgE) syndrome is a complex disease that affects the immune system, bone, connective tissue, and teeth. Patients present with various symptoms, including eczematous dermatitis, recurrent skin abscesses, pneumonia, bronchiectasis, pneumatocele, characteristic facial findings (broad nasal bridge, deep-set eyes, and prominent forehead), retained primary teeth, joint hyperextensibility, increased susceptibility to fracture, elevated serum IgE >2000 IU/ml, and an increased risk of aneurysm.[4,5]

The most common infections in these patients are those of skin (73%) and lung (90%).[5] Liver and other deep infections (pancreas, prostate, and breast) are rare but have been previously reported.[6] *Staphylococcus aureus* and *Candida* are the most common organisms that contribute to recurrent infections in patients with

STAT 3-HIES. Our patient presented with obstructive uropathy, acute kidney injury and hyperkalemia secondary to huge pelviabdominal collections.

Presently, management of STAT3-HIES primarily involves intensive care for dermatitis, prompt administration of broad-spectrum antibiotics or antifungal medications to treat infections, surgical drainage of abscesses, prevention of infection by antibiotic prophylaxis +/- antifungal prophylaxis, immunoglobulin replacement, and long-term follow-up. Recent data on hematopoietic stem cell transplantation (HSCT) have shown promising outcomes compared with previous studies.[7-9] However, the effects of HSCT on non-immunological aspects of the disease remain uncertain.[10]

Case Report. A 5-year-old Middle Eastern boy from non-consanguineous parents presented to the emergency room (ER) with 2 months of progressive abdominal distention, abdominal pain, decreased appetite, scrotal swelling with urinary frequency, and enuresis. Two months before the current admission to our hospital, the patient was admitted to another hospital with progressive abdominal distention for one month. Abdomen computed tomography (CT) revealed multiple large intraabdominal abscesses. The patient was discharged against medical advice (due to financial reasons) after receiving ceftriaxone, clindamycin, and ciprofloxacin. Due to limited access to the healthcare system, the patient stayed at home from discharge with progressive abdominal distention until presentation to the ER, when he developed more severe symptoms that necessitated ER visits.

The patient was born at full term and his mother had an uncomplicated pregnancy. Since infancy, the patient experienced severe uncontrolled eczema with recurrent otitis media.

At the age of 1.5 years, the patient was admitted to the pediatric intensive care unit (PICU) in another hospital for 40 days with complicated pneumonia and left-sided empyema with febrile seizures. The patient received mechanical ventilation and required high-frequency ventilation and chest tube insertion. The pleural fluid was positive for *Staphylococcus aureus* and *Streptococcus pneumoniae*. A few months later, the patient developed an inguinal abscess that required aggressive debridement at a polyclinic site. At the age of 2 years and 3 months the patient developed another complicated pneumonia that required admission for a month with chest tube insertion and no intubation. Between the age of 2.5 years to date the patient has had >10 incisions and drainages (I&D) for recurrent skin abscesses, and the last 2 were in the axilla region.

The patient exhibited no previous mucocutaneous infection, viral skin infection, or fracture and his weight was appropriate for age. The patient was vaccinated until 2 years of age, without any complications. The patient had 2 younger healthy siblings (aged 1 and 2 years). No family history of atopy, autoimmune disease, or recurrent infections was noted.

Clinical findings. Upon examination, the patient was febrile at 39°C and tachycardic at 135 bpm. The patient exhibited coarse facial features, a prominent forehead, a broad nasal bridge, and multiple dental caries with retained primary teeth. The abdomen was largely distended with an everted umbilicus, visible abdominal veins, and 2 visible non-pulsating abdominal masses with scrotal swelling and lower limb edema. Furthermore, the skin exhibited moderate-to-severe eczema on the lower limbs and around the mouth, with multiple scars from previous I&D for abscesses.

Diagnostic assessment. Chest and abdominal CT revealed multiple thick-walled collections compressing the ureters, nondisplaced rib fractures, and pneumatoceles (**Figures 1&2**).

The patient was required to be admitted to PICU due to hyperkalemia (potassium of 6.4 mmol/L) that was found on initial labs. The patient was referred to the immunology department to investigate the possibility of an underlying inborn error of immunity based on the significant past medical history. Laboratory results are presented in **Table 1**.

Therapeutic intervention. The patient was admitted to the PICU and underwent pigtail I&D of approximately 500 cc of pus from the abdominal abscess that was sent for culture but did not grow any organism. He was administered intravenous antibiotics (meropenem and linezolid).

He stayed in the PICU for 3 days and was subsequently discharged to general pediatric ward. The patient was admitted for a total of 29 days during which he was on meropenem and linezolid then switched to oral clindamycin for another 2 weeks.

Follow-up and outcomes. As the patient exhibited a high HIES score (score of ≥60) based on the scoring system (**Appendix 1**), whole exome sequencing (WES) was directly carried out, which identified a heterozygous missense pathogenic variant of the STAT3 gene. STAT3 (NM_139276.3): c.1145G>A (p. Arg382Gln), Chr17(GRCh37): g.40481660C>T. This mutation was

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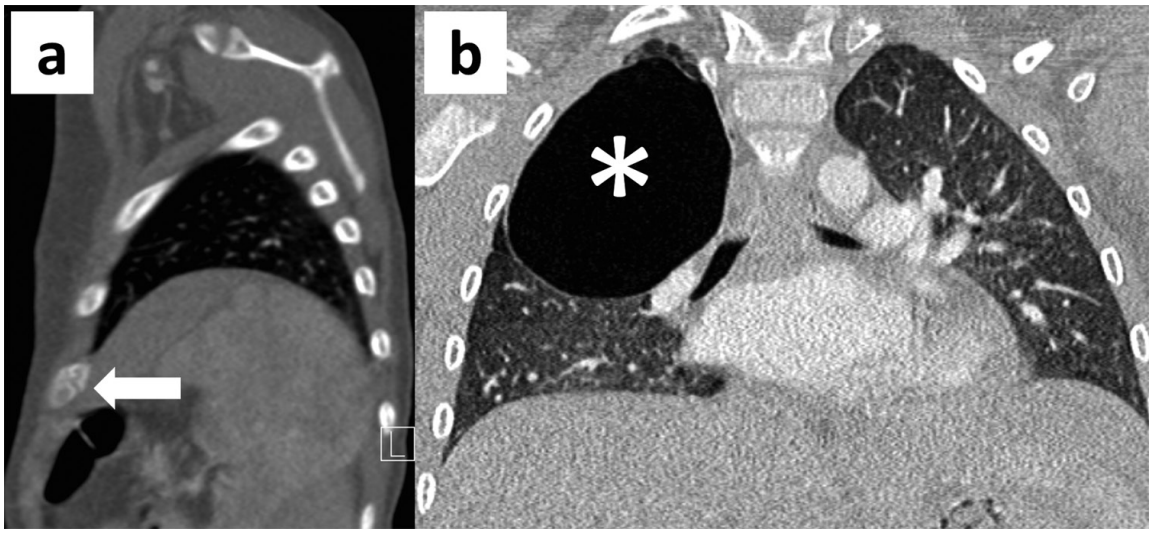

Figure 1 - Enhanced CT of the chest. **a)** Sagittal reformats in bone window showing a rib fracture (**arrow**). **b)** Coronal reformats showing right upper lobe pneumatocele (**asterisk**).

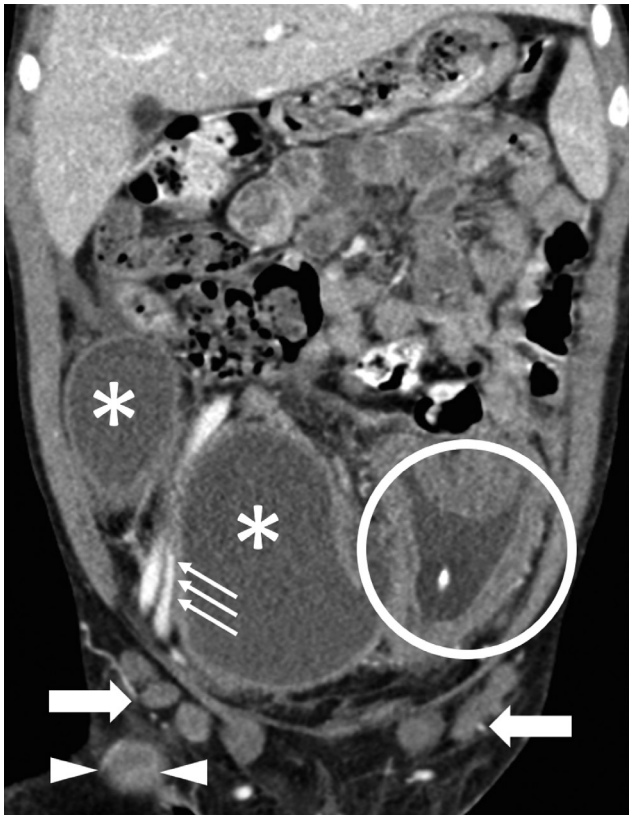

Figure 2 - Coronal enhanced CT abdomen and pelvis showing multiple walled-off collections (**asterisks**) displacing the thickened urinary bladder (**circle**) and compressing the right iliac vein (**small arrows**). Multiple bilateral inguinal enlarged lymph nodes (**bold arrows**), one showing central necrosis (**arrowheads**). These collections were compressing the ureters causing bilateral upstream pelvicalyceal dilatation (not shown).

previously reported in several reports. Th17 response and STAT3 phosphorylation were not measured in this patient due to the unavailability of the tests in our institute.

Once the patient improved with no more fever, abdominal pain, and repeated abdominal ultrasound showed decreasing abscess size. After completing the antibiotics course, the patient was provided prophylactic trimethoprim (TMP)-sulfamethoxazole (2.5 mg/kg of TMP component twice daily). Since discharge with prophylactic antibiotics, the patient did not require another admission for the last 2 years with regular phone follow-up.

The timeline from the initial patient presentation until the discharge is summarized in **Figure 3**.

Discussion. Hyper IgE syndrome results from different mutations, among which autosomal dominant STAT3-HIES and autosomal recessive DOCK8 mutations are the most common. Our patient exhibited a high HIES score (score of 60) based on the scoring system; therefore, we directly carried out WES, confirming the diagnosis.[3]

Given the disease's rarity and the general pediatricians and family physicians' unfamiliarity with the characteristic clinical features, a considerable delay is usually observed in the diagnosis from the onset of the symptoms with a mean delay of 13.7 years.[6] Our patient was diagnosed 4 years after the initial presentation as he had a significant past infectious history that required PICU admission and clinical characteristic features of HIES.

Table 1 - Laboratory results.

Variables	Complete blood count	Reference range
WBC	15.12 k/uL	4-11 k/uL
neutrophils	8.27 k/uL	1-8.5 k/uL
lymphocytes	4.83 k/uL	2-8 k/uL
eosinophils	1.29 k/uL	0.2-0.8 k/uL
Hemoglobin	8.5 k/uL	10.2-15.2 k/uL
Hematocrit	29.1 k/uL	34-48 k/uL
Platelet	272 k/uL	150-450 k/uL
CRP	22.7 mg/L	0-3 mg/L
Urea and electrolytes		
Urea	19.6 mmol/L	3.2-8.2 mmol/L
creatinine	309 µmol/L	
potassium	6.4 mmol/L	3.5-5.1 mmol/L
sodium	134 mmol/L	136-145 mmol/L
Albumin	42 g/L	40.2-47.6 g/L
Serology		
HIV	Negative	
Immunoglobulins		
IgA	1.01 g/L	0.4-2 g/L
IgG	11.9 g/L	4.9-16.1 g/L
IgM	1.27 g/L	0.5-2 g/L
IgE	14100 IU/ml	150-1000 IU/ml

Methicillin-resistant *Staphylococcus aureus* nasal swab, positive; tuberculosis quantiferone, negative.
WBC: white blood cells, CRP: C-reactive protein, HIV: human immunodeficiency virus, IgA: immunoglobulin A, IgG: immunoglobulin G, IgM: immunoglobulin M, IgE: immunoglobulin E

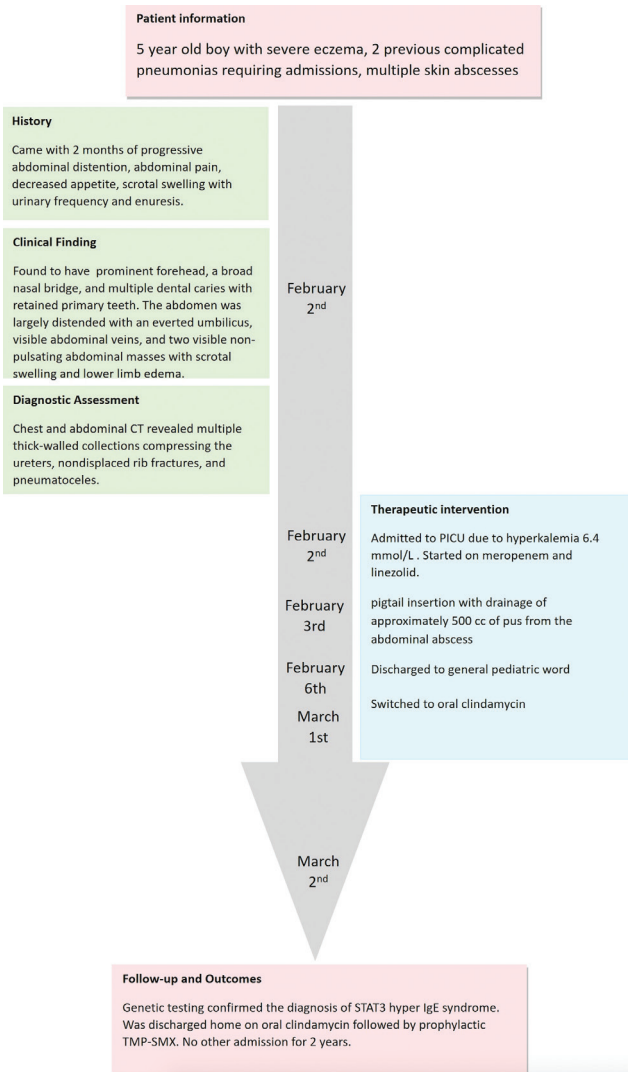

Figure 3 - The timeline from the initial patient presentation until the discharge.

Hyper IgE syndrome affects the immune system as well as other systems and connective tissues. This disorder is known to cause staphylococcal skin and lung infections but rarely affects deep organs such as the liver and kidney.[7] However, our patient presented with huge thick-walled abscesses and low inflammatory markers (highest C-reactive protein was 22.7) with secondary uropathy. This substantial infection could be attributed to a delay in presentation to the healthcare system. Although the patient exhibited signs and symptoms suggestive of STAT3-HIES, such as uncontrolled eczema, 2 previous severe complicated pneumonia, recurrent skin abscesses, and facial features, the patient was not diagnosed earlier because they were seeking medical care at different centers without proper follow-up. Once the patient was diagnosed and treated with trimethoprim/sulfamethoxazole prophylaxis, the patient experienced less frequent and less severe infections, with no admissions in the last 2 years.

Managing HIES continues to present challenges owing to the aforementioned rarity of HIES. Complications in HIES are not limited to infections and can be life threatening. In our patient, hyperkalemia developed secondary to obstructive uropathy which could lead to cardiac arrythmias if left untreated. Fortunately, our patient completely recovered with normalization of renal function once the obstructive abscesses were drained.

In conclusion, trainees and physicians are encouraged to take a detailed past medical history, especially in children with a significant past infectious history that includes unusual pathogens or required PICU admissions. Furthermore, we recommend an early referral to a clinical immunologist, especially with inborn errors of immunity are suspected, this leads to the early diagnosis of this syndrome, and early intervention like starting prophylactic antibiotics in our patient was life-changing with no recurrence of the symptoms.

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Appendix 1 - Hyper immunoglobulin E syndrome scoring system/Grimbacher scale.

	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).