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Hyperimmunoglobulin-E Syndrome (HIES) in a Nigerian child: case report and review of literature

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Abstract

Introduction: Hyperimmunoglobulin-E syndrome (HIES), also called Job's syndrome, has an autosomal dominant (AD-HIES) form caused by mutations in the STAT3 gene and autosomal recessive (AR-HIES) forms caused by mutations in the dedicator of cytokinesis 8 (DOCK8) tyrosine kinase 2 (TYK2) mutations or phosphoglucomutase 3 (PGM3) genes.
Case: A 7 year old boy presented with the classical triad of staphylococcal skin infections, recurrent sinopulmonary infections, and elevated IgE levels. He had characteristic facial and dental features, and a high National Institutes of Health HIES (NIH HIES) score suggestive of AD-HIES. His chest CT showed multiple abscess cavities in the lungs, and infection with *Acinetobacter baumannii*. Genetic testing was not available, and therefore not done to confirm diagnosis of HIES. He is presently on bacterial and fungal prophylaxis and chest physiotherapy.
Discussion: AD-HIES is a rare primary immune deficiency condition that presents with a plethora of dental, musculoskeletal and immunological features. Genetic testing aids in the diagnosis, but this is often not available in resource limited settings. The NIH HIES scoring system retains clinical utility and is very useful in resource poor settings to facilitate early diagnosis and prevention of pulmonary complications which are associated with poor outcomes.

Keywords: *Hyperimmunoglobulin-E, Job's syndrome, Nigerian, Child*

Résumé

Introduction : Le syndrome d'hyper-immunoglobuline E (SHIE), aussi appelé syndrome de Job, présente une forme autosomique dominante (AD-SHIE) causée par des mutations du gène STAT3 et des formes autosomiques récessives (AR-SHIE) causées par des mutations dans le dédicateur de la cytokinèse 8 (DOCK8) mutations de la tyrosine kinase 2 (TYK2) ou gènes de la phosphoglucomutase 3 (PGM3).
Cas: Un garçon de 7 ans s'est présenté avec la triade classique d'infections cutanées à staphylocoques, d'infections sino-pulmonaires récurrentes et de taux élevés d'IgE. Il présentait des caractéristiques faciales et dentaires et un score élevé de l'Institut National de Santé INS (INS SHIE) suggérant AD-SHIE. Le scanner thoracique présentait de multiples cavités d'abcès dans les poumons et une infection à *Acinetobacter baumannii* .Les tests génétiques n'étaient pas disponibles et n'ont donc pas été effectués pour confirmer le diagnostic du SHIE. Il suit actuellement une prophylaxie bactérienne et fongique et une physiothérapie pulmonaire.
Discussion: AD-SHIE est une rare condition de déficit immunitaire primaire qui présente une pléthore de caractéristiques dentaires, musculo-squelettiques et immunologiques. Le test génétique facilite le diagnostic, mais ceci n'est souvent pas disponible dans les contextes où les ressources sont limitées. Le système de notation INS SHIE conserve son utilité clinique et est très utile dans les environnements à ressources limitées pour faciliter le diagnostic précoce et la prévention des complications pulmonaires qui sont associées à des résultats médiocres.

Mots - clés : *Hyper-immunoglobuline E, Syndrome de Job, Nigérian, Enfant*

Introduction

Hyperimmunoglobulin-E syndrome is a rare Primari Immune Deficiency PID characterized by a triad of markedly elevated IgE level, recurrent staphylococcal skin abscesses and pneumonia. In the initial report by Davis *et al* in 1966 [1], its characteristic multiple recurrent cold abscesses, often staphylococcal, akin to that seen in the biblical Job earned it the name Job's syndrome. This report in two red haired girls detailed the typical features of severe dermatitis, recurrent cold staphylococcal skin abscesses and sinopulmonary infections. In 1972, Buckley *et al* [2] reported similar features with dermatitis, characteristic coarse facies and markedly elevated IgE levels. This was thought

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to be a different syndrome from Job's syndrome and termed Buckley's syndrome. The initial two cases by Davis *et al* were later found to have elevated IgE levels as well and the name Hyperimmunoglobulin-E syndrome (HIES) was adopted. While most cases of HIES are sporadic, there appears to be two distinct phenotypes, an autosomal dominant HIES (AD-HIES) [3] and an autosomal recessive HIES (AR-HIES) [4]. The exact aetiology remained unknown for a long time until 2007 when mutations in signal transducer and activator of transcription 3 (STAT3) gene was found to be the cause of AD-HIES [5, 6]. Subsequent studies found AR-HIES was due to dedicator of cytokinesis 8 (DOCK8) [7-9] and tyrosine kinase 2 (TYK2) mutations [10]. Recent reports suggest phosphoglucomutase 3 (PGM3) mutations are also associated with AR-HIES [11-13]. The phenotypic presentation of AD-HIES and the various forms of AR-HIES appears to be quite distinct [4]. In general, while all have the typical triad of markedly elevated IgE level, recurrent staphylococcal skin abscesses and pneumonia, patients with AD-HIES in addition have cyst forming sinopulmonary infections, characteristic facies with protruding forehead and broad base of the nose, oral, dental, skeletal and connective tissue anomalies [3]. Most infections are initially due to common respiratory pathogens like *Staphylococcus aureus*, *Streptococcus pneumoniae* or *Haemophilus influenzae* but later colonization by *Pseudomonas aeruginosa*, fungi like *Pneumocystis jiroveci*, *Aspergillus fumigatus*, *Cryptococcus* and disseminated histoplasmosis occurs. Other gram negative bacilli, usually *Pseudomonas*, are not uncommon. The pulmonary infections in them tend to be cavitary. These patients typically live into adulthood. In contrast, most AR-HIES tends to have marked allergic manifestations, including asthma, viral infections, CNS malformations and mortality in childhood is common. Infections in AR-HIES are often due to viruses like herpes simplex virus (HSV), herpes zoster virus (HZV), Epstein barr virus (EBV), human papillomavirus (HPV) and molluscum contagiosum virus (MCV). The pulmonary infections in them are usually not cavitary. Due to the variability in phenotypic expression of AD-HIES, a scoring system was developed in 1999 by Grimbacher *et al* and other researchers at the National Institute of Health to determine those likely to have the AD-HIES genotype [14]. This has been validated in a cohort of 78 patients with suspected HIES and retains clinical utility needed to facilitate initiation of appropriate therapy [15]. This is especially important in settings where genetic testing is not available.

A little over 500 cases have been reported in published English literature, very few in Africa and none identified from Nigeria [16]. We here report a case from Nigeria and review the current literature on HIES with a discussion in the context of a resource limited setting.

Case

In May 2015, a 7-year old boy presented with fever and haemoptysis. He had been admitted four times since age 5years for pneumonia and multiple cold suppurative skin infections, mostly due to *Staphylococcus aureus*. He recently completed a 6months course of anti-tuberculosis medications (he had four drugs for 2 months then 2 drugs for four months) 3 months before presentation. He was delivered at term; normal sized, birth weight unknown and had completed the Nigerian primary immunization schedule. His parents and younger sister were well with no history of similar features and no history of consanguinity in the family.

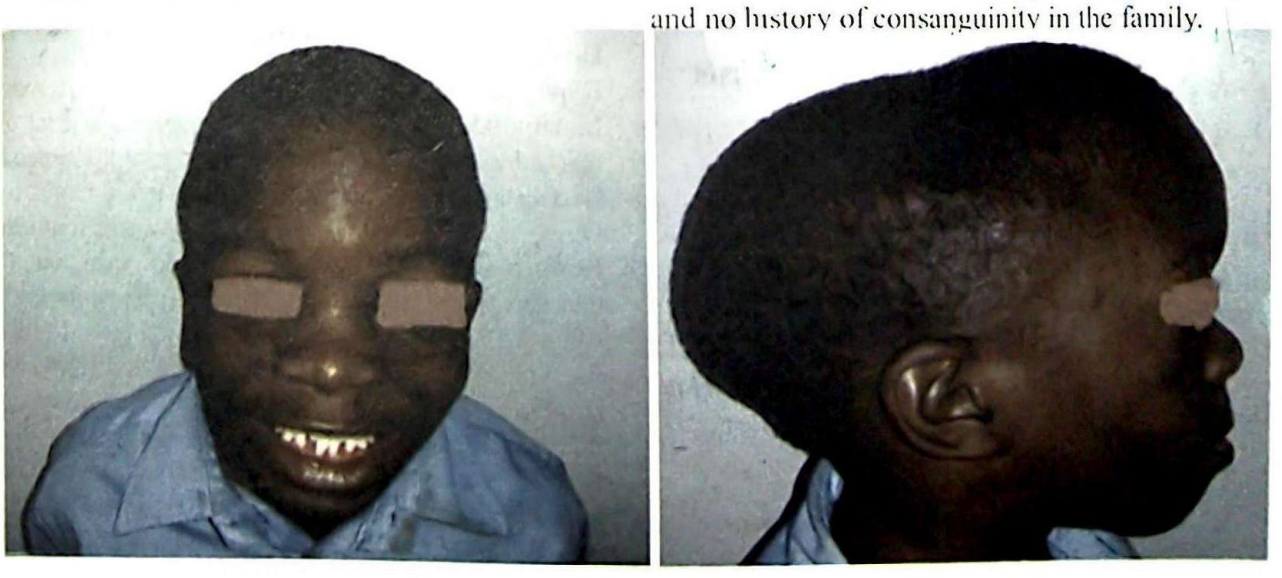

Fig.1: Scaphocephaly with marked frontal and occipital bossing, wide base of the nose and mandibular hyperdontia.

Table 1: National Institutes of Health HIES (NIH HIES) score of the patient

Clinical feature	Findings in patient	Score
Highest Serum IgE level	>3000KU/L	10
Skin abscesses	1-2	2
Pneumonia episodes	>3	8
Parenchymal lung anomalies	Pneumatocoeles	8
Retained primary teeth	>3	8
Scoliosis, maximum curvature	None	0
Fractures with minor trauma	None	0
Highest eosinophil count	<700	0
Characteristic face	Present	5
Midline abnormality	None	0
Newborn rash	None	0
Eczema (worst stage)	Moderate	2
Upper respiratory infections per year	3 per year	3
Candidiasis	Oral	1
Other serious infections	Severe	4
Fatal Infections	Present	4
Increased nasal width	<1SD	0
High palate	None	0
Hyperextensibility	None	0
Lymphoma	None	0
Young age correction	>5 years	0
Total		55

On examination he had coarse facial features, scaphocephaly with marked frontal and occipital bossing and wide base of the nose (Figure 1). He had oral thrush, mandibular hyperdontia, multiple cold abscesses on the scalp and axillae with a healed incisional scar in the left axilla. In addition, he had generalized lymphadenopathy, grade 4 digital clubbing with eczematous lesions on the forearms and trunk. His weight was 18kg and height, 105cm with Z-scores of weight-for-age of +1.0, height-for-age of +1.0 and weight-for-height of +0.77. The percussion notes were dull over the left hemithorax with reduced air entry and crepitations. He also had genu varum deformity of both lower limbs. The NIH score for HIES was 55, highly suggestive of AD-HIES (table 1).

The full blood count revealed mild anaemia, normal white cell count, no eosinophilia and normal

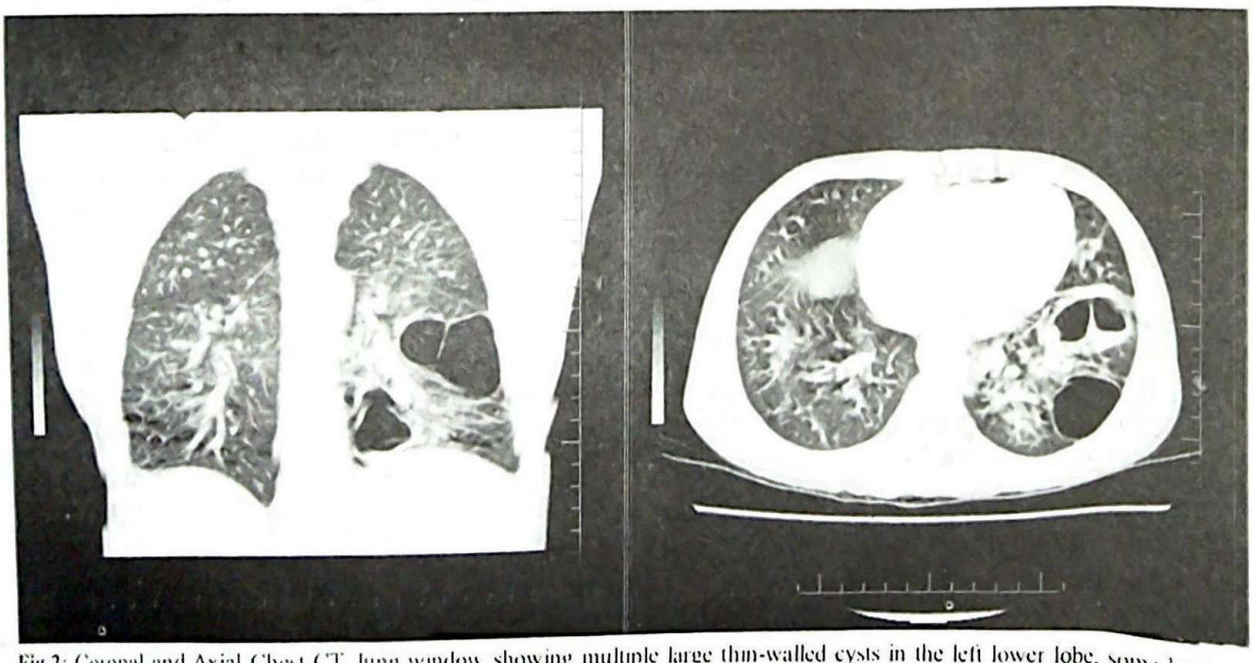

Fig.2: Coronal and Axial Chest CT, lung window showing multiple large thin-walled cysts in the left lower lobe, some having air-fluid levels consistent with an abscess cavity other having septations.

platelets. His haemoglobin genotype was Hb-AA, rapid HIV screen was negative. The serum IgE was >3,000KU/L (Range 1.0-5.6). Sputum was negative for acid-fast bacilli and GeneXpert MTB/RIF did not detect mycobacterium tuberculosis complex. Sputum microscopy and culture yielded *Acinetobacter baumannii* sensitive to gentamycin, cefuroxime, ceftriaxone and ceftazidime but resistant to meropenem, augmentin and amikacin. Chest CT revealed multiple cystic lesions in the left lung, some with abscesses and some huge pneumatoceles, with background consolidative changes. Multiple focal consolidations were also noted in the right lung (figure 2). Genetic testing for STAT3 gene mutation to confirm HIES and other immunological assessments were not done as these are not available in our setting. He completed a 2-week course of cefuroxime with significant improvement. A decision was made to defer surgery at this point as he remained stable following medical management and in view of the high risk associated with surgery and anaesthesia. He remains on follow up on prophylaxis with cotrimoxazole, itraconazole and chest physiotherapy.

Discussion

HIES is a relatively rare PID with a prevalence of about 1 in 1,000,000, with just about 500 cases reported in literature [17]. This patient presented with the classic triad of recurrent cold skin abscesses, cavity forming pneumonia and elevated IgE level. His symptoms date back to infancy with repeated episodes of pneumonia and the chest CT showed multiple cavities with pneumatoceles and abscesses. The initial isolates were *Staphylococcus aureus*, and later a carbapenem-resistant *Acinetobacter baumannii* was isolated, most likely a colonizer. This organism is a common pathogen in our ICU, though he has never been admitted to the ICU, previous admissions to this hospital might have exposed him to this organism. Sinopulmonary infections are one of the hallmarks of HIES and include recurrent pneumonia, sinusitis, otitis media, otitis externa and mastoiditis.

If not diagnosed early and treated, with prophylaxis commenced, patients with AD-HIES and TYS2 AR-HIES may develop complications such as bronchiectasis, bronchopleural fistulae and cavitary lung lesion, with lung abscesses or pneumatoceles from the recurrent pulmonary infections. In earlier reports, these pulmonary infections are usually due to *Staphylococcus aureus*, *Streptococcus pneumoniae* or *Haemophilus influenzae* and later colonization with *Pseudomonas aeruginosa*, other gram negatives or fungi such as *Aspegillus fumigatus*. These can get disseminated and are often responsible for morbidity and mortality in them. Opportunistic infections with *Pneumocystis jiroveci [18]*, disseminated Histoplasmosis and disseminated infection following *Bacillus Calmette Guerin* (BCG) immunization are also seen in them [17, 19].

This patient also had other features of AD-HIES. The characteristic facies, prominent fore head and broad base of the nose were all manifestations of the initial and subsequent reports of AD-HIES. Other facial features seen in AD-HIES include deep set eyes, increased inter-alar distance, full lower lip and thickening of the nose and ears [3]. This characteristic facie has been correlated with oral findings in an attempt to define oral phenotypes of HIES [20]. In the report, mid-line intraoral lesions were found in 76.7% of patients and included various forms of palatal defects, fissures and grooves on the tongue, keratosis and fissures on the oral mucosa and lips. Eczematous dermatitis often without associated elevated eosinophils is common in children with AD-HIES, unlike patients with AR-HIES where eczematous dermatitis is often associated with eosinophilia and other allergic manifestations like asthma. These eczematous skin lesions are often difficult to manage and in patients treated with hematopoietic stem cell transplant (HSCT), most symptoms resolved except the eczema. Other skin lesions, often seen in AR-HIES, are of viral origin and include infection with herpes simplex, molluscum contagiosum and varicella zoster viruses. This is likely responsible for the higher proportion of squamous epithelial cancers observed in these individuals.

Dental and skeletal anomalies as well as malignancies, usually lymphomas, are also common features of AD-HIES, often not seen in AR-HIES [3, 4]. In this patient he had hyperdontia and genu varum deformity. In a series by Grambacher *et al,* 72% of patients studied had at least one form of dental anomaly [3]. Reported dental anomalies include retained primary dentition, double row of teeth with delayed eruption of permanent teeth and supernumerary teeth [3, 20]. Skeletal anomalies seen in AD-HIES include fractures following unrecognized or minimal trauma, scoliosis, craniocynostosis and reduced bone density. The scoliosis tends to present with advancing age and was seen in 76% of those aged 16years or above [3]. This patient did not have clinical or radiologic evidence of scoliosis. The phenotypic features of HIES has varying penetrance and some, especially the skeletal and connective tissue features, are age dependent, becoming apparent with time. Connective

tissue abnormalities manifest in the form of hyperextensible joints, arterial tortuosity and dilatations, and aneurysms, with reports of strokes resulting from these.

Markedly elevated IgE as observed in this patient, is a common feature of HIES. In a study of 30 patients with HIES and 70 relatives by Grimbacher *et al*, 97% of patients with AD-HIES had IgE level of >2000IU/L [3]. In neonates and infants who usually do not have such high IgE levels, a ten-fold increase in IgE levels is considered significant. Though eosinophilia was not observed in our patient, this is not uncommon in AD-HIES. It is often seen in AR-HIES where allergic features are common, often without evidence of parasitic infestations [4].

The exact immunologic deficiency in HIES remains unclear. A variety of immunologic impairments in neutrophil, lymphocyte and NK function with low CD4+ and CD8+ and reverse CD4+/CD8+ ratio have been reported. Most of these findings are consistent but their import in the diagnosis and management is still unclear. However, reduced IL-17 appears to be responsible for the infections seen in HIES [21, 22]. This is needed for bacterial and fungal killing [23] and defects in IL-17 receptors with increased susceptibility to *Staph. aureus* and candida infections has been reported [24]. In the absence of STAT3 signalling, there is impaired Th17 differentiation leading to reduced IL-17 production [21, 25]. Impaired neutrophil killing due to impaired INF-γ production has also been demonstrated [26].

The first report of genetic mutations in HIES was in 2006 by Minegishi *et al*, who identified TYK2 mutation in a patient who had been clinically diagnosed with HIES [10]. In 2007, STAT3 mutation were shown to be the cause of AD-HIES, the same mutation was later found in the original patient described with Job's syndrome [5, 27]. AR-HIES has predominantly immunologic features and appears to be caused by a variety of genetic mutations, DOCK8, TYK2 and PMG, albeit with distinct phenotype variations [28]. Following the identification of mutations associated with HIES, genetic testing has significantly improved the certainty with which HIES is diagnosed.

Unfortunately, access to this and immunologic evaluations like immunoglobulin levels or lymphocyte subsets are not available in resource constrained settings like ours. This is a major challenge in the evaluation of children with PID and has been highlighted by similar reports from Africa [16]. Therefore detailed immunologic evaluation and genetic testing to confirm STAT3 mutation were not carried in this patient. But, the limited evaluation, characteristics of AD-HIEs and high NIH HIES score, strongly supports a diagnosis of AD-HIES. The NIH HIES scoring guide therefore remains a very important tool for diagnosis of HIES. This is particularly important in resource limited settings to facilitate early institution of prophylactic therapy which has been found to improve quality of life and outcomes in HIES [29].

The management of HIES remains a challenge and optimal therapy remains unclear. Antimicrobial prophylaxis is an important management focus, mainly cotrimoxazole for anti-staphylococcal prophylaxis and itraconazole for fungal prophylaxis. Prophylaxis with cloxacillin having good outcomes has been reported, but development of resistance with repeated exposure and increasing prevalence of methicillin resistant *staphylococcus aureus* (MRSA) are issues of concern. In this regard, cotrimoxazole appears to be a good option, as it also provides additional prophylaxis against Pneumocystis pneumonia. Itraconazole appears to be the ideal choice for fungal prophylaxis as it is effective against most fungi; including *Aspergillus* spp.

Various modalities have been employed with variable success rates [19]. There have been reports of successes with IVIG and IFN-gamma therapy [30]. Some other studies have reported favourable outcomes following HSCT) with some patient being cured of the immunologic and haematologic dysfunctions [31-36]. There appears to be better response in AR-HIES, and in some it has been curative [36, 37]. However, in some AD-HIES, HSCT was curative while in others the eczematous and pulmonary complications did not resolve after HSCT [32, 38-40]. In another report, the features of HIES resolved in the patient, but he later died from a complication of HSCT [41].

Pulmonary complications with cavity formation and severe haemoptysis are a major cause of morbidity and mortality in patients with HIES. Once the pulmonary complications develop, the management becomes very challenging and optimal surgical management remains unclear. Surgical management is often associated with perioperative complications, with bronchopulmonary fistulae being the commonest post-op complication [42]. Wound healing and tissue remodelling is impaired probably as a result of the underlying defect from STAT3 mutation. The other parts of lungs often do not compensate enough after surgery and anaesthesia remains a major risk in them [43]. Therefore, surgery is generally not advised, except in cases of recurrent

severe haemoptysis and failed medical therapy [42]. It is therefore imperative that the diagnosis of HIES be made early and infections adequately treated, with early institution of antibacterial and antifungal prophylaxis.

In general, the outcome of HIES is poorer in patients with AR-HIE and in patients with sinopulmonary complications or malignancies. In resource limited settings, advanced therapeutic options for evaluation and diagnosis are generally unavailable, or extremely expensive. Early identification and characterization, using the NIH HIES scoring system, *Staphylococcus aureus* decolonization therapy, and antimicrobial prophylaxis along with patient education will continue to form the main stay of management.

Ethics

The manuscript was prepared in full compliance with the principles of the revised Helsinki declaration and written consent was obtained from the parent of the patient for use of the clinical details and pictures for publication.

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