

## Original Article

# Signal Transducer and Activator of Transcription 3 (STAT3) Gene Mutations in Two Patients with Hyperimmunoglobulin E Syndrome

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### Abstract

The autosomal dominant (AD) hyperimmunoglobulin E syndrome (HIES, Job syndrome) is a primary immunodeficiency with multiple systemic involvements. It is characterised by grossly raised serum immunoglobulin E (IgE) level with recurrent cutaneous and pulmonary infections, eczema, pneumatoceles, dental and musculoskeletal problems. The occurrence of the classic triads, namely recurrent cold abscesses, pneumatocele formation and raised serum immunoglobulin E should alert the clinicians on the diagnosis of HIES. Mutations in the signal transducer and activator of transcription 3 (STAT3) gene have been identified recently to be the cause of AD HIES. We report 3 patients with HIES, in whom 2 were found to have STAT3 gene mutations.

### Key words

Abscess; Hyperimmunoglobulin E syndrome; Job syndrome; Pneumatocoele; Signal transducer and activator of transcription 3

### Introduction

Hyperimmunoglobulin E syndrome (HIES) or Job syndrome was first described in 1966<sup>1</sup> and is

characterised by high serum immunoglobulin E (IgE) level, eczema and recurrent skin and lung infections. Some patients also have non-immune manifestations, including coarsening of skin, characteristic facies, dental and skeletal abnormalities. There is substantial variation in the constellation of symptoms and signs. Grimbacher et al reported that the classic triad of abscesses, pneumonia, and an elevated IgE level was present in 77% of all patients and in 85% of those older than 8 years old in a series of 30 patients of HIES and their relatives.<sup>2</sup> However, among the infants and young children, eczematoid eruptions may be the only manifestation. To differentiate the skin lesions of HIES from atopic dermatitis is challenging even for experienced dermatologists or paediatricians.

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The Department of Paediatrics and Adolescent Medicine of Queen Mary Hospital is a tertiary centre receiving referrals for children with immunological problems, we report here 3 consecutive cases of HIES. The last patient (Patient C) who was reported by Kwok et al in 2006<sup>3</sup> will also be briefly discussed in our series as his STAT3 gene mutation was elucidated after the publication of the original report.

## Case Reports

### Patient A

She is a 3 years old Chinese girl, who presented in the first month of life with vesiculopustular eruptions and crusting over scalp and face. The skin lesions subsequently spread to trunk, limbs and perineum. Viral culture for *Herpes simplex virus* was negative. Impetigo was diagnosed clinically and she was treated with intravenous cloxacillin. She then developed a 2 x 2 cm cold abscess over both sides of scalp and multiple pustules over scalp and neck at 2 months of age. Five ml of pus was drained and subsequently grew methicillin sensitive *Staphylococcus aureus* (MSSA). She was successfully treated with intravenous ampicillin and cloxacillin. The peripheral eosinophil counts were raised with a peak count of  $6.94 \times 10^9/L$  at 2 months old. Her serum IgE level was mildly elevated at 54 IU/ml, and IgG, A and M levels were normal. Nitroblue tetrazolium test (NBT) and lymphocyte subpopulation profile were also normal. She suffered from stomatogingivitis and pneumonia at 8 and 9 months of age respectively. She developed a 3 x 4 cm left shoulder swelling, proximal to the *bacilli Calmette Guerin* (BCG) inoculation site, when she was 10 months old. Incision and drainage grew BCG. There was no systemic or pulmonary involvement. Her serum IgE level increased to 441 IU/ml. Before she was 1 year old, she suffered from otitis externa with otorrhoea. She defaulted follow-ups subsequently as she was taken care of in China.

She was admitted again at 3 years old for febrile convulsion and upper respiratory tract infection. Moderately severe eczema-like rashes were noted over her face. A pneumatocele without fluid level was noted from her chest X-ray (CXR) (Figure 1a). She developed right upper and middle lobe pneumonia subsequently. Computer tomography of thorax (CT thorax) confirmed 2 pneumatoceles [one thin-walled, air-filled cyst (57.4 mm) in right lower lobe and the other smaller cystic lesion (6.8 mm) with moderately thickened wall in the posterior segment of right upper lobe] over her right lung (Figure 1b). That episode of pneumonia and her skin condition were successfully treated with intravenous ceftriaxone. At that time, her serum IgE level had raised to >5000 IU/ml. Repeated neutrophil function test, including chemotactic function, was normal. In retrospect, she reported recurrent skin rashes and otitis media/ externa with otorrhoea while she was staying in China. History of pneumonia was denied.

After discharge, she suffered from recurrent folliculitis mainly affecting her face and forehead (Figure 1c). Prophylactic flucloxacillin was commenced. Despite that,

she suffered from another episode of pneumonia, which was complicated by lung abscess (Figure 1d). She was again treated with intravenous ceftriaxone. Follow-up CT thorax showed resolution of the lung abscess. A new pneumatocele was noted over her right lung on subsequent CXR (Figure 1e). Her teeth were mal-aligned (Figure 1f), and no skeletal problem was identified. Her growth was normal.

She is the second child of non-consanguineous couples. Both parents enjoy good health with no atopic disease. Her elder sister and younger brother are healthy. There is no family history of immunodeficiency or early infant death.

Her clinical diagnosis of HIES was confirmed by detecting a mutation of the STAT3 gene. PCR-direct sequencing of the whole blood genomic DNA was performed. Novel heterozygous missense mutation c.2134T>C, with predicted amino acid substitution p.712C>R in exon 22, was identified in the transactivation domain (Figure 2). Both parents do not have this STAT3 gene mutation.

### Patient B

She is a 7 years old Chinese girl, who presented with right periorbital abscess at 1 year old. Magnetic resonance imaging (MRI) of the orbit showed abscess collection with no osseous involvement. She was treated with surgical drainage and intravenous cloxacillin and cefotaxime. The pus grew scanty MSSA subsequently. Seven months later, she was admitted for left axillary lymphadenitis presented with a swollen, firm, mobile axillary mass. Excisional biopsy showed features consistent with dermatopathic lymphadenopathy and the tissue culture grew MSSA. She was treated with intravenous ampicillin and cloxacillin. Peripheral eosinophil count was raised to a peak at  $1.68 \times 10^9/L$ . Her serum IgE level was elevated at 2687 IU/ml, with normal IgG, A and M. Lymphocyte subpopulation profile was normal. Neutrophil function test including chemotaxis test was normal. She was diagnosed clinically to have HIES, and put on rotation antibiotic prophylaxis with flucloxacillin and co-trimoxazole.

She had another episode of periorbital cellulitis when she was 35 months old. She was successfully treated with intravenous and topical antibiotics. A right thigh subcutaneous abscess with right groin lymphadenopathy developed when she was 5 years old. Ultrasonography of thigh confirmed fluid collection with no muscular involvement. Needle aspiration yielded 2.5 ml of pus which grew heavy MSSA. She was treated with intravenous cloxacillin. Eighteen months later, she had left leg cellulitis

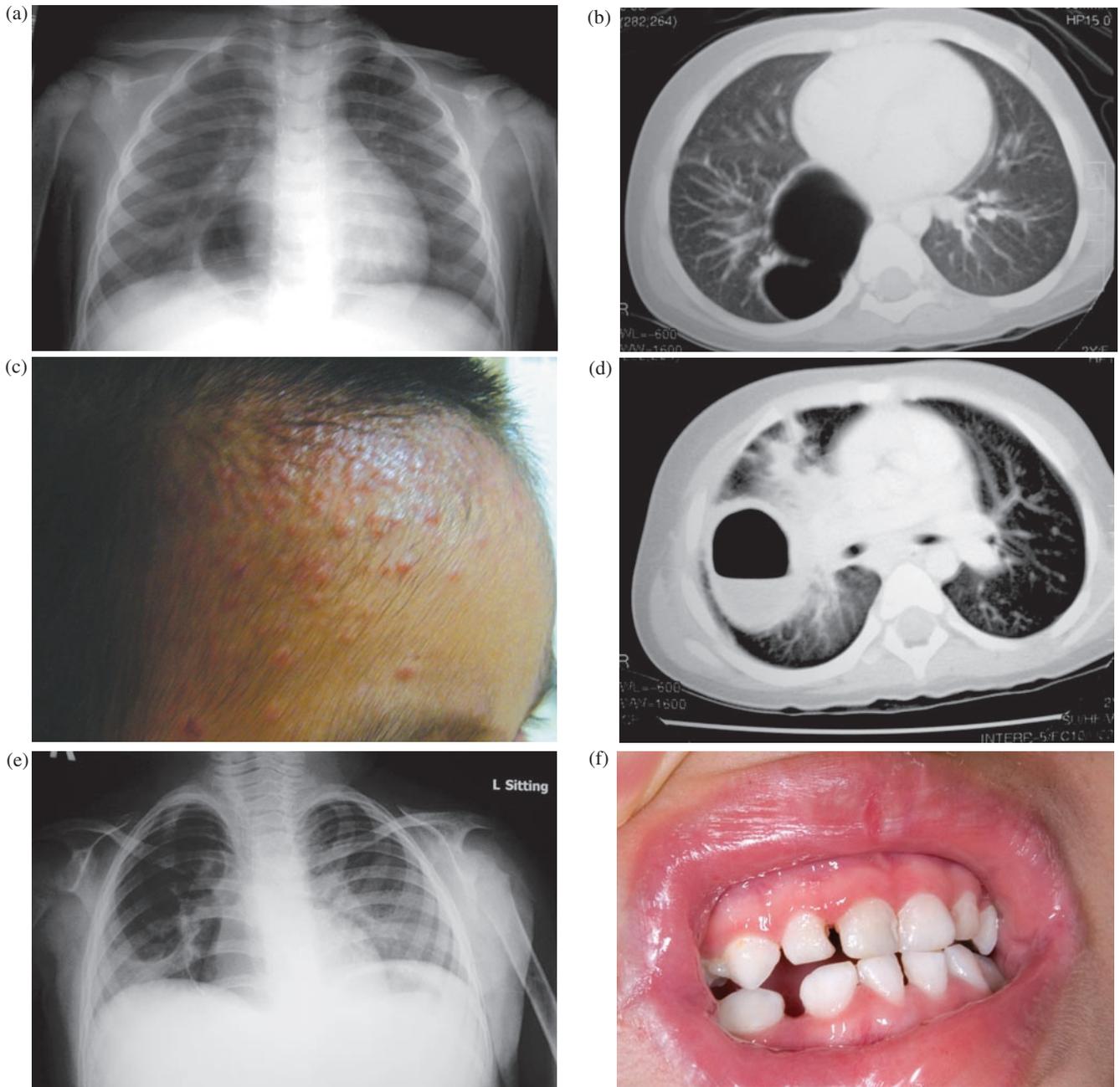


Figure 1 Clinical features of Patient A.

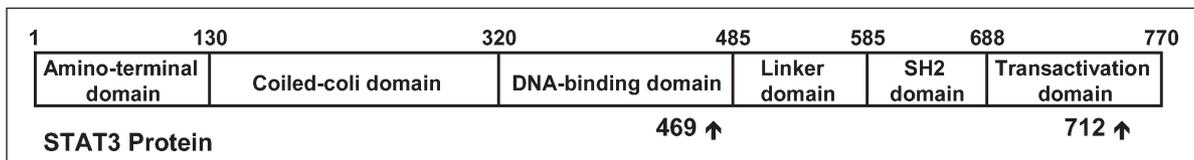


Figure 2 Schematic diagram of STAT3 protein structure according to Minegishi, et al. 2007. The amino acid positions of the mutations are indicated. p.469Q>P and p.712C>R are located at the DNA binding domain and transactivation domain respectively. The mutations were confirmed by sense and antisense PCR-direct sequencing of 2 independent PCR products. 110 normal alleles sequencing have been performed in order to exclude the possibility of being polymorphism.

after a mosquito bite. The cellulitis was extensive with a 10 x 14 cm erythema. She was treated again with intravenous cloxacillin. She had normal primary teeth shedding and no skeletal problem. Her growth was normal. She has no atopic manifestations throughout. No mutation was found in her STAT3 gene locus.

She is the third child of non-consanguineous couples. Her father had history of recurrent skin abscesses before 7 years of age. The serum IgE level of her father was 293 IU/ml. Her father do not have dental or skeletal problem. Her mother and her 2 elder siblings are healthy. Family history is otherwise unremarkable.

### Patient C<sup>3</sup>

He is a 26 years old Chinese and was referred to Queen Mary Hospital at 16 years of age with the diagnosis of HIES. He initially presented with oral ulcerations, eczema and pustular abscesses on his face in the first few weeks of life. He had extensive recurrent skin or even intramuscular abscesses (Figure 3) requiring multiple surgical drainages, which grew *Staphylococcus* mostly. His skin was affected by severe eczema and folliculitis extensively. He had history of primary teeth retention requiring dental extractions. He had progressive coarsening of skin and characteristic facial features, namely broad nasal bridge and wide nasal tip. No skeletal problem was identified. His peak serum IgE level was >10000 IU/ml and his peak eosinophil count was  $2.6 \times 10^9/L$ . Neutrophil function test showed mild defect in candida killing whilst NBT and neutrophil chemotaxis were normal. Lymphocyte subpopulation profile and



**Figure 3** CT thigh of Patient C.

immunoglobulin pattern were normal. He was started with oral co-trimoxazole, clindamycin and flucoxacillin rotation as antibiotic prophylaxis, and a course of gamma-interferon had been used, but with no response.

He was detected to have a mutation of the STAT3 gene. PCR-direct sequencing of the whole blood genomic DNA was performed. Novel heterozygous missense mutation c.1406-1407AG>CC, with predicted amino acid substitution p.469Q>P in exon 16, was identified in the DNA binding domain (Figure 2).

## Discussion

### Genetics

HIES is a rare disorder with estimated incidence of  $<10^{-6}$ .<sup>4</sup> HIES occurs in patients of diverse ethnic backgrounds and does not seem to be more common in any specific population.<sup>2</sup> Most cases of HIES are sporadic. In 1999, Grimbacher et al elucidated that HIES is inherited as autosomal dominant trait with variable expressivity based on a study of 30 patients and their relatives. Younger generation apparently has a more severe phenotype, which may suggest genetic anticipation.<sup>2</sup> Subsequently, they demonstrated a linkage to a region on chromosome 4q in several affected families.<sup>5</sup> However, in 2004, Renner et al reported 13 patients with classical immunological findings of HIES, who have the inheritance pattern most consistent with an autosomal recessive mode. This autosomal recessive form of HIES (AR-HIES) is considered as a distinct entity to the autosomal dominant form of HIES (AD-HIES). The AR-HIES is also characterised by elevated IgE, hypereosinophilia, respiratory tract infections and dermatitis with recurrent staphylococcal infections, but is distinguished from the AD-HIES by increased susceptibility to viral and fungal infections, absence of non-immune manifestations (facial features, dental and skeletal abnormalities), lack of pneumatocoles formation, higher prevalence of neurological manifestations and association with autoimmune diseases.<sup>6</sup>

The genetic defects of HIES were identified recently. In 2006, Minegishi et al revealed a homozygous mutation in tyrosine kinase 2 (Tyk2) gene in a patient with AR-HIES and susceptibility to intracellular bacterial infections.<sup>7</sup> They also demonstrated the restoration of defective cytokine signaling in the patient's T-cell by transducing the intact Tyk2 gene. This breakthrough finding has directed the identification of the defective gene of AD-HIES, signal

transducer and activator of transcription 3 (STAT3) gene, by tracing along the signal cascade of tyrosine kinase 2.<sup>8-10</sup> STAT3 gene is located on human chromosome 17q21, but not 4q.<sup>8</sup> Most of the mutations including hot spots are identified in the SH2 and DNA-binding domains of STAT3.<sup>10</sup> It was identified as the predominant underlying genetic defect in sporadic and dominant AD-HIES, although other genomic loci may also be involved.<sup>8,9</sup>

In our cases, the 2 mutations identified are novel mutation. For p.712C>R identified in transactivation domain, the cysteine residue may play an important role in protein structure but the effect of substitution on protein function still needs to be elucidated. For p.469Q>P identified in DNA binding domain, different amino acid substitution mutation (p.469Q>H) had been identified in the same position.<sup>10</sup> The result implies the importance of the residue in protein function. According to the previous findings, it is likely that STAT3 mutations are dominant negative *de novo* mutation.<sup>8</sup> For patient B without STAT3 mutation identified, genetic analysis of the AR-HIES causative gene (TYK2) had been performed but no mutation was found.

### Laboratory Findings

Grossly elevated serum IgE level is one of the important characteristics, but is not the underlying immunological defect leading to recurrent infections. Dreskin et al demonstrated that the incidence of infection at mucosal surfaces and adjacent lymph nodes is lower with increasing levels of serum anti-*S. aureus* IgA, serum anti-*S. aureus* IgE, serum IgE, and total serum IgD.<sup>11</sup> Therefore, it suggests that elevated IgE level may be protective against *Staphylococcus aureus* infection.<sup>12</sup> Donabedian et al proposed a lower limit of 2000 IU/ml, as an arbitrary cut-off for diagnosis of HIES.<sup>13</sup> A very low to non-detectable IgE levels are normal for infants younger than 6 months of age. As a result, infants with HIES may not reach the characteristic serum IgE level. Once elevated, serum IgE levels are usually stable. However, a gradually declining level has been reported.<sup>2</sup>

Peripheral eosinophilia is another common laboratory finding in HIES patients. Grimbacher et al reported that eosinophil counts are at least 2 standard deviations (SD) above normal values in 93% of the patients. There is no correlation between the count of eosinophils and serum IgE level.<sup>2</sup>

Originally, neutrophil functional abnormalities were the proposed mechanisms of immunodeficiency in HIES.

Abnormal neutrophil chemotaxis was firstly described by Hill et al.<sup>14</sup> However, subsequent observations revealed that chemotactic defect of neutrophils is not a constant feature and may vary over time in the same patient.<sup>13</sup> Other neutrophil function, including oxidative burst assay by NBT is normal in HIES.<sup>15</sup>

### Cutaneous Manifestations

Skin manifestation is the first presentation of HIES among all symptoms. "Eczema-like" eruptions from early childhood with subsequent development of skin abscesses is the classical description. However, Chamlin et al reported that papulopustular, folliculocentric eruptions over face and scalp is the characteristic skin involvement at initial presentation.<sup>16</sup> Crusting of papules and pustules are prominent features. Majority of them presented within the first month of life.

Despite the skin eruptions of HIES share pruritus and some extent of lichenification of atopic dermatitis, they are distinguished by atypical distribution (including neck, axillae and diaper area), lack of scales, resistance to conventional therapy, chronicity of the dermatitis, and absence of personal or family history of atopy.<sup>16,17</sup>

Patients with atopic dermatitis are susceptible to *S. aureus* cutaneous infection and a high percentage of these patients are colonised with *S. aureus* without overt infection.<sup>18</sup> However, deep-seated *S. aureus* infections occur rarely in atopic dermatitis and should raise the suspicion of HIES.<sup>19</sup> Cold abscess, described as peculiarly large abscess which lacks local inflammation, is characteristic of HIES. The infectious agent is always *S. aureus*. Cold abscesses can present in any parts of the body, usually as fluctuant masses which may be mistaken for cysts or benign tumors.<sup>13</sup> It is neither hot, erythematous, tender and is not associated with fever.

Candidiasis affecting the mucocutaneous tissue is common in HIES. Dystrophic nails are often chronically infected by *Candida albicans*.

### Immunodeficiency and Recurrent Infections

Sinopulmonary infection is the commonest infection other than recurrent staphylococcal cold abscesses. Pneumonia is recurrent and severe. *Staphylococcus aureus* and *Haemophilus influenzae* are the most common infecting organisms. Pneumatocoeles and pulmonary abscesses have long been known to accompany HIES. Superinfection of pneumatocoeles is associated with *Pseudomonas aeruginosa* and *Aspergillus fumigatus*. Surgical

intervention, thoracotomy or drainage, may be required in half of these complicated patients.<sup>13</sup>

Otitis externa and chronic otitis media are also common. The otitis has a wide variety of causative agents with *S. aureus*, *H. influenzae*, *Proteus mirabilis*, group D *Streptococcus* and *Pseudomonas* prominent among bacteria isolated from the external canal.<sup>13</sup> Sinusitis is less common than otitis.

Deep-seated infections other than pneumonia are unusual in HIES patients. Osteomyelitis occurs, but usually in spatial and temporal relation to an infected focus such as a paronychia.<sup>13</sup>

### **Musculoskeletal Manifestations**

Musculoskeletal abnormalities are part of the key clinical features of AD-HIES, but not AR-HIES. Characteristic facial features, delayed shedding of primary teeth and skeletal abnormalities are frequently identified over years of clinical observations. Distinctive facial features are universal by the age of 16 years in an observational study.<sup>2</sup> Facial asymmetry, prominent forehead, deep-set eyes, broad nasal bridge, mild prognathism, wide and fleshy nasal tip are the facial characteristics.<sup>2</sup> Increased width of the nose, full lower lip, thickening of the nose and ears are added by Borges et al.<sup>20</sup> The mean alar width and outer canthal distance are significantly increased compared to normal population. Midline facial developmental anomalies, including high-arched palate, cleft lip and palate, are also observed in some of the patients.

Grimbacher et al also reported that 72% of the HIES patients have retained primary teeth, non-eruption of permanent teeth, or double rows of the teeth. Most patients require extraction of more than 8 retained primary teeth.<sup>2</sup> This is simply a problem with teeth shedding as anomalous tooth formation is not observed. None of the patients experience problems with eruption of primary teeth, and eruption of first and second permanent molars also occur on time.

Bone fractures due to unrecognised or minor trauma occur frequently in HIES, although the exact incidence remains unknown. The frequently involved bones are long bones, ribs and pelvis. Misinterpretation of recurrent fractures in a HIES patient as a victim of non-accidental injury has been reported.<sup>21</sup> Osteopaenia has been demonstrated in HIES patients.<sup>22</sup> However, decreased bone mineral density does not predict fractures. Scoliosis, hyperextensible joints and genu valgum are other associated skeletal abnormalities in HIES.<sup>2</sup>

### **The Role of Scoring System for HIES**

Before the genetic defects are identified, diagnosing HIES is based on constellation of symptoms and signs which can be variable and diverse. No verified clinical tool is available for diagnosis till now. Formulated by Grimbacher et al, a scoring system was created to assess the involvement of family members of HIES patients for inheritance studies. It was used by Holland et al to calculate the risk of carrying the HIES trait in their study.<sup>9</sup> This scoring system provides insight and convenience for practitioners to weight the significance of signs and symptoms in diagnosing HIES. However, its accuracy remains undetermined and unverified. Together with the lack of exclusion criteria, it should be used with cautions. In addition, patients with HIES accumulate clinical features and complications over years. Therefore, this scoring system is unlikely to indicate the diagnosis if the patients present at infancy or early childhood. High index of suspicion is the key to successfully diagnose HIES.

### **Treatment**

No treatment is more effective than antibiotics, skin care and surgical incision and drainage. Prompt intravenous antibiotics with effectiveness against *Staphylococcus* and/or *Hemophilus* species should be initiated during infections. The threshold for surgical intervention in draining abscesses should be lower compared with individuals without HIES. The value of prophylactic use of antibiotics is uncertain. Multi-drug resistant bacteria is a growing problem in HIES patients using prophylactic antibiotics. They should also receive full evaluations for fractures after even minor trauma, be monitored and treated for scoliosis, and have retained primary teeth removed. Reports on using cyclosporine A,<sup>23</sup> intravenous immunoglobulins<sup>24,25</sup> and interferon gamma<sup>26,27</sup> do not have conclusive outcomes. The single report of bone marrow transplantation for HIES is ineffective.<sup>28</sup> Recent report of impaired T-helper 17 cells differentiation as a mechanism underlying the susceptibility to recurrent infections in patients with AD HIES has suggested a way to possibly using interleukin 17 as treatment option.<sup>29</sup>

### **Conclusion**

HIES is a primary immunodeficiency with multiple systemic involvement. Early diagnosis before full clinical manifestations is now feasible with genetic diagnosis and

can lead to early aggressive treatment of infections, thereby improving prognosis for these patients.

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