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LETTER TO EDITOR

Autosomal Dominant Hyper-IgE Syndrome Without Significantly Elevated IgE

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Summary

Hyper-IgE syndrome (HIES) refers to a group of primary immunodeficiencies characterized by severe infections of the skin and lungs, particularly with *Staphylococcus aureus* and fungi, atopy, and significantly elevated serum IgE, together with various non-immunological manifestations. This condition may be caused by autosomal dominantly inherited mutations in *STAT3*, or by autosomal recessively inherited mutations in *DOCK8*, *PGM3*, *CARD11*, *IL6ST*, and *ZNF341*. Here, we describe three patients with a characteristic infectious history suggesting HIES but with only moderately elevated serum IgE levels. This led to delayed diagnosis of disease-causing *STAT3* mutations and autosomal dominant HIES well into adult age. We briefly review the clinical presentation, pathogenesis, diagnosis, and treatment of HIES with special emphasis on atypical presentations leading to delayed diagnosis.

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Background

Autosomal dominant hyper-IgE syndrome (AD HIES), originally termed "Job's syndrome," was described in 1966 with "cold" abscesses caused by *Staphylococcus aureus* as a prominent feature [1]. Other characteristics include atopy/eczematoid rashes presenting already during the neonatal period, recurrent sinopulmonary infections, skin abscesses, chronic mucocutaneous candidiasis (CMC), and eosinophilia, in combination with significantly elevated serum IgE > 2000 IU/mL, and frequently even higher. Infections with various fungal pathogens, including *Candida albicans*, *Pneumocystis jirovecii*, histoplasma, and aspergillus, have been evidenced [1–4]. Moreover, there is an extensive list of non-immunological manifestations reported to affect the joints, skeletal, dental, and vascular systems in AD HIES. Abnormal craniofacial features include characteristic facial appearance, craniosynostosis, high-arched palate, and retained childhood dentition. Within the musculoskeletal system hyperextensibility, scoliosis, osteoporosis, and minimal trauma fractures are observed. More recently, vascular abnormalities, particularly coronary artery aneurisms, were also attributed to AD HIES. Finally, AD HIES patients are at an increased risk of developing malignancies, particularly non-Hodgkin lymphoma [1–4].

STAT3 deficiency was identified as the genetic origin of HIES in 2007, providing improved insight into the pathogenesis underlying the infectious phenotype, immunological abnormalities, and somatic features of this condition. The immunological phenotype of HIES includes significantly elevated IgE levels, eosinophilia, low levels of Th17 cells, and memory B cell lymphopenia [1–4]. The basis of the complex immunodeficiency is a combined effect of impaired signaling downstream of important cytokines, such as interleukin (IL)-6, IL-21, IL-10, and TGFβ, and impaired Th17 T cell differentiation and Th17 responses, particularly affecting immune responses and neutrophil proliferation and chemotaxis to candida and staphylococci at

skin and mucous membranes. As to the origin of the highly elevated IgE levels characteristic HIES, this feature has been suggested to reflect a role for STAT3 downstream of IL-21 receptor signaling [1–4]. Beyond AD HIES caused by STAT3 mutations, HIES also exists in an autosomal recessive (AR) form that may be caused by defects in either dedicator of cytokinesis (*DOCK*)*8*, or phosphoglucomutase (*PGM*)*3*, although these present with a somewhat different phenotype, including a more pronounced tendency towards cutaneous viral infections and without the somatic phenotype characteristic of AD HIES. Along this line, heterozygous AD CARD11 deficiency has been identified as a cause of combined immunodeficiency with bacterial and viral infections, severe atopy, elevated IgE, and eosinophilia, with some resemblance to DOCK8 deficiency [5, 6]. In addition, biallelic mutations in *IL6ST* encoding the GP130 common receptor subunit downstream of IL-6, IL-11, IL-27, and oncostatin M have been described to lead to immunodeficiency with eczema, elevated IgE, defective B cell memory, impairment in T cell function, and craniosynostosis, and thus with significant similarities to AD STAT3 HIES [7, 8]. Most recently, deficiency of ZNF341, a transcription factor that binds to the promoter of *STAT3* in T cells and B cells causing lack of Th17 cells, excess of Th2 cells, and low memory B cells, has been identified as a novel genetic etiology of AR HIES [4, 9].

Case Presentation and Investigations

Patient (P)1 is a 57-year-old female of Caucasian (Danish) origin, who suffered from recurrent otitis media and cutaneous abscesses since childhood, but no eczema and no failure to shed primary teeth. At age 22, she had a nasal skin graft due to sequelae after abscesses. At age 31, she was referred to the Department of Infectious Diseases on suspicion of primary immunodeficiency (PID) due to oral candidiasis, recurrent pneumonias, and cutaneous abscesses. Serum IgE was 156–194 IU/mL (< 150 IU/mL). Serum immunoglobulin levels and hematological parameters, including eosinophil count, were normal. In addition, lymphocyte subpopulation and stimulation tests, granulocyte function tests (superoxide production, chemotaxis, intracellular killing, and CD11/18 expression), and complement activation, were all within normal ranges. Chest X-ray showed bronchiectasis, but bronchoscopy was normal. At that time, HIES was excluded because of the low serum IgE, and she was misdiagnosed as having isolated furunculosis and bronchiectasis. At age 56, she was referred for reevaluation on suspicion of PID. Except from elevated IgA = 9.71 g/L (0.8–4.9 g/L) and IgE of 332 IU/mL (< 115 IU/mL), other immunological parameters were normal. The patient was noted to display characteristic coarse facial features (Fig. 1a). Although the National Institutes of Health (NIH)-HIES score was only 27.5, AD HIES was suspected. Whole exome sequencing (WES) was performed and revealed a c.1406G>A (p.Q469R) mutation in *STAT3* within the DNA binding domain. The variant is not reported in gnomAD; it has a combined annotation dependent depletion (CADD) score of 27 and was previously shown to be associated with AD HIES [10–13], thus confirming the diagnosis. Additional rare variants identified in P1 and predicted to be potentially disease-causing are listed Supplementary Table 1.

P2 is a 27-year-old male and the son of P1. As a child, he had recurrent otitis media, but no eczema. Following varicella at age four, he was suffering from recurrent facial erysipelas and was later admitted to hospital with a 5 × 5-cm submandibular abscess with positive cultures for both *S. aureus* and hemolytic streptococci group A. At age six, he was admitted to the pediatric ward with pneumonia and was screened for PID. The CD4 T cell count was low (141–517 cells per μL), but he was HIV1/2 and HTLV I/II negative. Serum IgE was in the range of 224–332 IU/mL (<115 IU/mL). Other hematological parameters, including eosinophil count, serum immunoglobulin level, granulocyte function tests, and complement activation, were all normal. Due to recurrent infections, prophylactic antibiotic (co-trimoxazole) was prescribed. Retention of primary teeth was noted at age seven. Twenty years later, when his mother, P1, was diagnosed with AD HIES, he was subsequently called in for genetic testing. He also had characteristic coarse facial features (Fig. 1b). Except from low CD4 T cell count of 161 cells per μL, slightly elevated serum IgE of 160 IU/mL (<115 IU/mL), and serum IgA of 6.22 g/L (0.8-4.9 g/L), other immunological parameters were all normal. As expected, Sanger sequencing identified the same *STAT3* mutation (c.1406G>A, p.Q469R) found in his mother. Chest X-ray (Fig. 1c), HRCT (Fig. 1d, e), and PET-CT (Fig. 1f) of lungs were suggestive of aspergilloma in the right lung, and he was treated with itraconazole. Notably, the NIH-HIES score at diagnosis was only 21.

P3 is 26-year-old Caucasian male born in Croatia with no known PID in the family and without eczema or retention of primary teeth. He had a history of a subdural abscess at the age of two years and a boil in the groin at age fourteen. In his early 20s, he had several admissions to hospital with aortic endocarditis and liver abscesses caused by *Streptococcus intermedius*, and later sepsis and liver abscesses caused by *Streptococcus anginosus*, and finally a perianal abscess. Screening for PID showed slightly elevated serum IgE of 639–1.082 IU/mL, but normal hematological parameters, serum immunoglobulins, CD4 T cell count, and superoxide production. The fraction of isotype switched memory B cells was slightly reduced. The NIH-HIES score was only 14 and HIES was therefore initially deemed unlikely. However, WES was performed and demonstrated a c.1780G>A (p.E594K) mutation in *STAT3* with a CADD score of 29.3; this variant is also not present in gnomAD and since none of the parents harbored this variant, it was concluded to be *de novo* in the patient. The *STAT3* E594K variant has not been previously published, but is referenced in ClinVar (variation ID 36789). One additional

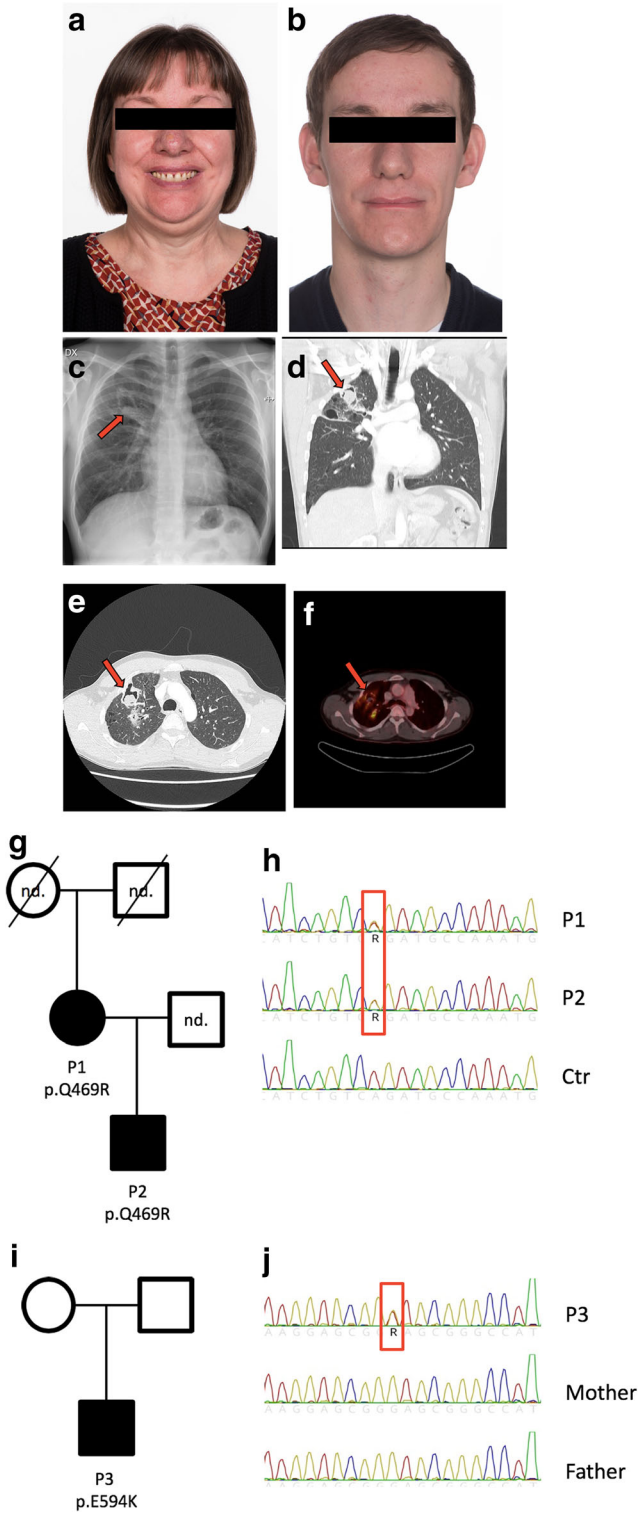

Fig. 1 Patients with Hyper-IgE syndrome without significantly elevated IgE. **a** P1 and **b** P2 showing characteristic coarse facial features. **c** Chest X-ray, **d**, **e** High resolution CT (HRCT), and **f** PET-CT of the lungs of P2 suggestive of aspergilloma (arrows) in the right lung. **g**, **i** Pedigrees of P1–P3. Black squares represent affected male subjects, white squares represent unaffected male subjects. Black circles represent affected female subjects. White open circles represent unaffected female subjects. **h**, **j** Sanger sequencing of the two *STAT* mutations identified. Red boxes indicate nucleotide change. Predictive effects of *STAT3* variants Q469R (CADD score of 27.5) and E594K (CADD score of 29.3) were determined by using PolyPhen-2, SIFT, MutationTaster, and CADD software.

rare variant in *TYK2* identified in P3, inherited from the healthy mother and predicted to be potentially disease-causing, is listed Supplementary Table 1.

Discussion

Prior to the identification of the genetic etiology of HIES and the demonstration of the association of AD HIES with *STAT3* mutations, the diagnosis was based on clinical and laboratory findings. The NIH-HIES score has been developed and used to identify patients with HIES [14]. Patients with a score > 40 have a high probability for AD HIES and a score < 20 is considered to make the diagnosis unlikely. In addition, IgE > 1000 IU/mL and a weighted score > 30 of five cardinal clinical features have been used to identify patients. However, as illustrated by the present cases, this score is not very reliable in excluding HIES. No consistent immunological defects, except from a reduced number of Th17 cells, have been demonstrated, but highly increased serum IgE (> 1.000 IU/mL), eczema, and eosinophilia is seen in most patients with AD HIES [1, 2]. However, previous publications on HIES have reported the existence of a minority of adult STAT3 HIES patients with normal or only slightly elevated IgE [15, 16]. Moderately elevated serum IgE is common in the general population, and a long list of differential diagnoses for elevated IgE exists. These include among others atopy/asthma, parasitic infections, malignant hematological conditions, and rare PIDs [1, 2]. Moreover, several reports have described that IgE levels in STAT3 HIES tend to diminish with age, which may further complicate the diagnosis, if it is delayed into adulthood [1, 3, 4]. None of our patients had highly elevated serum IgE, eczema, nor eosinophilia, and all had an NIH-HIES score < 40, with P3 having a score < 20. This clearly demonstrates that serum IgE and lack of eczema cannot be used to exclude AD HIES. The cases described here, together with previous reports in the literature, therefore illustrate that *STAT3* mutations may cause AD HIES with only slightly elevated IgE, leaving an important place for genetic testing in the diagnosis of HIES.

Of note, the elevated IgA levels found in P1 and P2 and the CD4 T cell lymphopenia in P2 are not typical of STAT3 HIES. The *STAT3* Q469R variant has been previously published by several independent groups. One of these described a 4-year-old patient diagnosed at 46 months of age with peak serum

IgE > 2000 IU/mL, eosinophilia, boils, CMC, skin abscesses, pneumonia, characteristic facies, retained primary teeth, and an NIH score of 46, thus more classically suggestive of STAT3 HIES [10, 11]. Another publication reported the Q469R variant in a patient with a HIES NIH score > 40, although the specific IgE levels are not available [12]. Importantly, the *STAT3* Q469R variant was investigated by computer modeling and predicted to be of structural and functional importance with a predicted destabilizing effect on the STAT3 molecule (deceased $T_{1/2}$ and decreased phosphor-Tyr-STAT3), although with no specific evidence for a dominant negative effect [17]. The *STAT3* E594K variant has not been previously published and to our knowledge not functionally tested, and thus, no evidence on the disease-causing potential of this variant exists. In cases of novel genetic variants identified in patients with a HIES-like phenotype, it is preferable to include functional testing of loss-of-function of the variant and evaluate the impact on cytokine production and Th17 responses.

Overall, clinicians should be aware that HIES may exist in patients even with near-normal serum IgE levels. We suggest that genetic testing for mutations in *STAT3* should be performed in patients with recurrent infection, particularly staphylococcal abscesses in the skin and staphylococcal and aspergillus infections in the lungs, suggestive of AD HIES. With the increased availability of WES, it may be an effective and rational strategy to perform WES instead of single gene sequencing, in order to not miss other genetic etiologies with a possibly less marked or slightly different presentation, including HIES caused by mutations in *DOCK8*, *PGM3*, *CARD11*, *IL6ST* or *ZNF341* [1–4]. The heterogeneous infectious, immunological, and somatic phenotype, the pleiotropic nature of STAT3, and the different genetic etiologies affecting different cellular pathways and cell types have led to the suggestion that the term HIES should be restricted to refer exclusively to AD HIES due to *STAT3 deficiency* plus AR ZNF341 deficiency, indirectly affecting STAT3 biology [4]. The continuous reports and descriptions of atypical presentation of these PIDs serve to broaden our knowledge and understanding of these intriguing and complex inborn errors of immunity. Optimally, novel potentially disease-causing *STAT3* variants should be subjected to functional testing. In summary, it should be remembered that elevated IgE together with a relevant clinical presentation should alert clinicians and prompt investigation for HIES or other causes of elevated IgE, keeping in mind that HIES may exist even in the absence of significantly elevated IgE, since high IgE levels may, paradoxically, not always be present in HIES.

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Compliance with Ethical Standards

All patients provided consent to participate in the study.

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Sowerwine KJ, Holland SM, Freeman AF. Hyper-IgE syndrome update. Ann N Y Acad Sci. 2012;1250:25–32. https://doi.org/10.1111/j.1749-6632.2011.06387.x.
2. Mogensen TH. Primary immunodeficiencies with elevated IgE. Int Rev Immunol. 2016;35(1):39–56. https://doi.org/10.3109/08830185.2015.1027820.
3. Yong PF, Freeman AF, Engelhardt KR, Holland S, Puck JM, Grimbacher B. An update on the hyper-IgE syndromes. Arthritis Res Ther. 2012;14(6):228. https://doi.org/10.1186/ar4069.
4. Zhang Q, Boisson B, Beziat V, Puel A, Casanova JL. Human hyper-IgE syndrome: singular or plural? Mamm Genome. 2018;29(7–8):603–17. https://doi.org/10.1007/s00335-018-9767-2.
5. Ma CA, Stinson JR, Zhang Y, Abbott JK, Weinreich MA, Hauk PJ, et al. Germline hypomorphic CARD11 mutations in severe atopic disease. Nat Genet. 2017;49(8):1192–201. https://doi.org/10.1038/ng.3898.
6. Dadi H, Jones TA, Merico D, Sharfe N, Ovadia A, Schejter Y, et al. Combined immunodeficiency and atopy caused by a dominant negative mutation in caspase activation and recruitment domain family member 11 (CARD11). J Allergy Clin Immunol. 2018;141(5):1818–30 e2.
7. Schwerd T, Twigg SRF, Aschenbrenner D, Manrique S, Miller KA, Taylor IB, et al. A biallelic mutation in IL6ST encoding the GP130 co-receptor causes immunodeficiency and craniosynostosis. J Exp Med. 2017;214(9):2547–62. https://doi.org/10.1084/jem.20161810.
8. Shahin T, Aschenbrenner D, Cagdas D, Bal SK, Conde CD, Garncarz W, et al. Selective loss of function variants in IL6ST cause hyper-IgE syndrome with distinct impairments of T-cell phenotype and function. Haematologica. 2019;104(3):609–21. https://doi.org/10.3324/haematol.2018.194233.
9. Frey-Jakobs S, Hartberger JM, Fliegauf M, Bossen C, Wehmeyer ML, Neubauer JC, et al. ZNF341 controls STAT3 expression and thereby immunocompetence. Sci Immunol. 2018;3:24. https://doi.org/10.1126/sciimmunol.aat4941.
10. Lee WI, Huang JL, Lin SJ, Yeh KW, Chen LC, Hsieh MY, et al. Clinical aspects and genetic analysis of Taiwanese patients with the phenotype of hyper-immunoglobulin E recurrent infection syndromes (HIES). J Clin Immunol. 2011;31(2):272–80. https://doi.org/10.1007/s10875-010-9479-1.
11. Lee WI, Huang JL, Lin SJ, Yeh KW, Chen LC, Ou LS, et al. Clinical, immunological and genetic features in Taiwanese patients with the phenotype of hyper-immunoglobulin E recurrent infection syndromes (HIES). Immunobiology. 2011;216(8):909–17. https://doi.org/10.1016/j.imbio.2011.01.008.
12. Schimke LF, Sawalle-Belohradsky J, Roesler J, Wollenberg A, Rack A, Borte M, et al. Diagnostic approach to the hyper-IgE syndromes: immunologic and clinical key findings to differentiate hyper-IgE syndromes from atopic dermatitis. J Allergy Clin Immunol. 2010;126(3):611–7 e1. https://doi.org/10.1016/j.jaci.2010.06.029.
13. Wu J, Chen J, Tian ZQ, Zhang H, Gong RL, Chen TX, et al. Clinical manifestations and genetic analysis of 17 patients with autosomal dominant hyper-IgE syndrome in mainland China: new reports and a literature review. J Clin Immunol. 2017;37(2):166–79. https://doi.org/10.1007/s10875-017-0369-7.
14. Woellner C, Gertz EM, Schaffer AA, Lagos M, Perro M, Glocker EO, et al. Mutations in STAT3 and diagnostic guidelines for hyper-

IgE syndrome. J Allergy Clin Immunol. 2010;125(2):424–32 e8. https://doi.org/10.1016/j.jaci.2009.10.059.

15. Grimbacher B, Holland SM, Gallin JI, Greenberg F, Hill SC, Malech HL, et al. Hyper-IgE syndrome with recurrent infections–an autosomal dominant multisystem disorder. N Engl J Med. 1999;340(9):692–702. https://doi.org/10.1056/NEJM199903043400904.
16. Donabedian H, Gallin JI. The hyperimmunoglobulin E recurrent-infection (Job's) syndrome. A review of the NIH experience and the literature. Medicine (Baltimore). 1983;62(4):195–208. https://doi.org/10.1097/00005792-198307000-00001.
17. Bocchini CE, Nahmod K, Katsonis P, Kim S, Kasembeli MM, Freeman A, et al. Protein stabilization improves STAT3 function in autosomal dominant hyper-IgE syndrome. Blood. 2016;128(26):3061–72. https://doi.org/10.1182/blood-2016-02-702373.