Title: STAT3-deficient hyperimmunoglobulin E syndrome: Report of a case with orofacial granulomatosis-like disease.

Running title: STAT3-deficient HIES with OFG

Authors: Barbara Carey[a], Valeria Mercadante[a,b], Stefano Fedele[a,b], Mary Glover[c], Catherine Cale[d], Stephen Porter[a]

Affiliations:

[a]Oral Medicine, UCL Eastman Dental Institute and UCLH Eastman Dental Hospital, 256 Gray's Inn Road, London WC1X 8LD, UK

[b]NIHR Biomedical Research Centre, University College London Hospital NHS Foundation Trust, University College London, 149 Tottenham Court Road, London W1T 7DN, United Kingdom

[c]Department of Paediatric Dermatology, Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond Street, London WC1N 3JH

[d]Department of Immunology, Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond Street, London WC1N 3JH

Corresponding author:

Dr Barbara Carey,

Oral Medicine

UCL Eastman Dental Institute and UCLH Eastman Dental Hospital

256 Gray's Inn Road,

London, WC1X 8LD.

Telephone: +44 2034561175.

Fax: +44 2034561105

Email: barbara.carey@nhs.net

Keywords: STAT3 Transcription Factor; hyperimmunoglobulin E syndrome; Interleukin-17; Immunologic Deficiency Syndromes.

Conflict of interest: None to declare

Funding statement: The authors received no specific funding for this work

Word count: xxx

Number of figures: 3

Number of tables: 1

Number of references: 39

Statement of Clinical relevance: This paper highlights the common clinical features of hyper IgE syndrome, the genetic mutations responsible, disease pathogenesis, as well as current treatment strategies.

Abstract

Hyperimmunoglobulin E syndrome (HIES) is a rare heterogenous primary immunodeficiency disorder characterised by infections of the lung and skin, elevated serum IgE, and involvement of the soft and bony tissues. Autosomal dominant HIES (AD-HIES) and related disorders are due to defects in the Janus activated kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway leading to reduced numbers of Th17 cells and impaired production of IL-17A, IL-17F, and IL-22. In addition, neutrophils have chemotactic defects resulting in impaired responses at skin and lung sites. We report a case of orofacial granulomatosis-like disease in a

teenage boy ultimately found to have autosomal dominant HIES due to a heterozygous mutation in the STAT3 gene.

Introduction

Hyper-IgE syndrome (HIES) is a heterogenous group of primary immunodeficiency diseases characterised by recurrent staphylococcal abscesses, sinopulmonary infections, severe eczema, candidosis and elevated serum levels of immunoglobulin E (IgE)[1]. The exact prevalence is unknown, although, there are approximately 200 cases reported worldwide[2]. Autosomal recessive (AR) and autosomal dominant (AD) (Job's syndrome) types exist.

Most patients with autosomal dominant HIES (AD-HIES) have a mutation in signal transducer and activator of transcription 3 (*STAT3*), which is encoded on chromosome 17q21[3,4,5]. STAT3 plays a key role in the signal transduction induced by a broad range of cytokines, hormones and growth factors, which is consistent with the multi-system manifestations of the disorder. STAT3 is crucial for the IL-6 and IL-23–mediated regulation of T helper cell type 17 (Th17) differentiation and function. Defective Th17 function results in decreased neutrophil proliferation and chemotaxis, decreased inflammation, and increased susceptibility to *Candida* and bacterial infections[5,6,7].

There are seven publications on STAT3 mutations reporting on 155 patients with HIES[6]. The majority of reports have focused on the molecular and cellular defects, providing little clinical information. The full extent and variation of the phenotype, including nature and severity of the infectious events, the impact of prophylaxis, age at diagnosis, and clinical outcome are incompletely documented and described. Here we describe the clinical features of a patient with orofacial granulomatosis (OFG)-like disease, dermatitis and atopy, but without significant other clinical features of HIES who was found to have STAT3-deficient HIES, with an emphasis upon its oral implications.

Case

A 12-year-old male presented to the Oral Medicine Department, Eastman Dental Hospital, with a worsening 4-year history of persistent upper and lower lip swelling. At the time of presentation, the lip deformity was impacting on psychological well-being and the patient was concerned regarding facial aesthetics but reported minimal discomfort. Additionally, he reported occasional gingival bleeding and oral dryness secondary to a mouth-breathing habit.

The medical history was significant for atopy including well-controlled asthma and allergic rhinitis. Spontaneous perinatal pneumothorax was reported, for which no definite cause was identified. There was a history of a widespread erythematous cutaneous eruption at four weeks of age which led to a diagnosis of eczema. At 13 years of age, whilst under our care, the patient developed an extensive acneiform rash and folliculitis on the chest, back and buttocks and pronounced erosions and exudation on the scalp. The cause of this rash had not formally been investigated. There was a history of recurrent ear infections, requiring grommet insertion, and recurrent upper respiratory tract infections, none of which required hospital admission or antibiotic therapy. He was fully immunized without complications, except for measles, mumps and rubella. There was a history of probable urticarial reaction to fish. The history was negative for gastrointestinal disease, invasive or fungal infections. The dental history was negative for delayed tooth eruption and no fractures were described. There was a strong family history of atopy with maternal asthma and allergic rhinitis and eczema in a male sibling. The patient's score on the NIH scoring system[1] was in the indeterminate range for AD-HIES[8].

On systemic examination, excoriated lesions on the scalp, an acneiform rash on the torso and mid-facial dermatitis were noted. Extra-orally, there was evidence of submental lymphadenopathy and lip incompetence. The lip was firm to palpation with evidence of crusting at the vermilion border (Fig. 1). The facial nerve was intact. Intraorally, there was evidence of cobblestoning of the lower labial mucosa and mild fissuring of the tongue. Erythematous and hyperplastic gingivae

were noted on the labial aspects of the upper right first premolar extending to the upper left first premolar (Fig. 2). The oral cavity appeared well lubricated with clear saliva expressed from the major duct openings. There was no adenotonsillar hypertrophy. The clinical features of the lips and oral cavity accorded with those expected of orofacial granulomatosis (OFG) or another granulomatous process, hence appropriate confirmatory investigations were undertaken (Table 1).

Complete blood count revealed eosinophilia 2.45 x 10^9 (reference range 0.0-0.4). In light of the history of atopy, immunoglobulin E (IgE) serology was undertaken to exclude allergic angioedema. IgE levels were notably elevated at 16151kIU/L (reference range 0-200). Histopathological examination of the affected upper gingiva demonstrated acute on chronic inflammation but no granulomas and necrosis. The gingiva was the preferred site for biopsy to avoid the potential morbidity associated with a lip biopsy. Ultrasound guided core biopsy of the enlarged submental nodes for the presence of granulomatous disease was undertaken and showed histopathological features in keeping with a reactive lymphadenopathy. Skin prick testing was positive to wheat along with other foodstuffs.

Following referral to immunology, the patient had very low class switched memory B cells (1.0%, reference range 6.5-29.1) and non-switched memory B cells (1.0%, reference range 7.4-32.5) with increased transitional B cell (9.0%, reference range 0.6-3.4). The patient received the pneumococcal vaccine (Pneumovax) to assess antibody response to polysaccarchide antigens. He generated specific antibody responses to 5 of the 13 pneumococcal serotypes in Pneumovax. Genetic testing revealed a STAT3 heterozygous mutation c.2102-2A>G. This substitutes an invariant base at the splice acceptor site and is therefore considered to be pathogenic and consistent with a diagnosis of STAT3-deficient HIES.

The diagnosis was in keeping with plaque-related gingivitis with OFG-like disease secondary to a heterozygous mutation in the STAT3 gene.

The lip swelling was treated with intralesional injections of triamcinolone acetonide (40mg/ml) to the upper and lower lips. A total of 96mg (2.4ml) was administered over three weeks, with injections spaced one week apart. At each visit, 0.4ml was administered to each lip, totaling 32mg (0.8ml) per visit. Eight weeks post therapy, there was complete resolution of the swelling with the lips returning to normal size, shape and consistency (Fig. 3). The patient underwent an intensive course of hygiene therapy which led to an improvement in gingival swelling. Fixed orthodontic appliances were placed in the upper and lower arches. Following orthodontic therapy, the gingival enlargement persisted on the upper anterior labial and palatal gingiva and the patient was referred for gingivectomy. The lips have remained stable at 30-month follow-up. The eczematous eruption and the scalp lesions remain partially controlled with regular topical corticosteroid application. The skin remains partially controlled with topical corticosteroid cream three times weekly to affected skin areas and corticosteroid scalp application. At the present time, treatment remains empirical in terms of preventing infections (azithromycin 500mg three times weekly), managing infections and other complications relevant to STAT3 deficiency.

Discussion

Autosomal dominant hyper IgE syndrome (Job's syndrome) was first described in 1996 by Davis et al[9] in two sisters with eczema, cold boils, and pneumonias. Since then, HIES has been increasingly recognised as a multisystem immunodeficiency disorder characterised by the triad of high serum IgE levels, eczema and cutaneous and sinopulmonary infections.

The autosomal dominant form of HIES reflects missense or in-frame deletions resulting in one amino acid change or loss in STAT3. In contrast, the autosomal recessive form is due to Dedicator

of Cytokinesis 8 (DOCK 8) mutation[10]. The STAT3 protein has a central role in cell development and inflammation control. It is crucial for the IL-6 and IL-23–mediated regulation of T helper cell type 17 (Th17) differentiation and function which appears to be critical in control of extracellular microbes. Heterozygous loss of-function mutations in STAT3 cause a dominant negative effect on STAT3 function resulting in defects in signal transduction for IL-6 and IL-23, leading to low levels of Th17 cells but not Th1 cells[11,12]. Defective Th17 function results in decreased neutrophil proliferation and chemotaxis[13], impaired interferon (IFN)-gamma production[14,15], decreased inflammation, and increased susceptibility to *Candida* and bacterial infections[5,6,7,16].

Affected patients usually have characteristic facial features including increased alar width, broad nasal bridge, frontal bossing, wide outer canthal distances, 'coarse facies' and deep-set eyes[17]. These features tend to become more accentuated with age. Intra-oral features include prominent arched palate, recurrent oral candidiasis, delayed healing, failure of exfoliation of primary teeth and periodontitis[18]. Oral lesions involving the hard palate, dorsal tongue, buccal mucosa, and lip mucosa, have been identified in over 75% of patients[19,20]. Mucosal lesions can consist of surface fissures and keratotic striations, patches, or plaques. Palatal lesions have been documented in the majority, manifesting as a midline fibrotic bridge, occasionally surrounded by grooves or clefts. A deep midline cleft anterior to the circumvallate papillae on the dorsum tongue has been observed in some patients. The patient in this case lacked any of these oral features, which made the diagnosis more challenging.

A spectrum of other features can arise including dermatitis, recurrent infections (principally bacterial sinopulmonary and skin infections mainly caused by *Staphylococcus aureus* and *Candida sp*), skeletal abnormalities (scoliosis, osteoporosis, bone fractures), central nervous system abnormalities (e.g. focal hyperintensities on MRI, Chiari type 1 malformations), and arterial aneurysms[1,21]. As with many other immunodeficiency syndromes, there is an increased risk of

malignancy in HIES particularly for haematological solid and non-solid tumours, vulval, hepatic and lung cancers[22,23]. AD-HIES STAT3 deficient patients have an increased level of IgE but paradoxically appear to be relatively protected from atopic disease[24,25]. Patients with AR-HIES types do not have the skeletal and connective tissue abnormalities seen with AD-HIES, nor do they appear to have the same oral manifestations observed in AD-HIES. They may be more susceptible to severe fungal and viral infections, as well as asthma, food allergies, and malignancies[21,26,27].

A clinical scoring system was introduced in 1999 by the US National Institutes of Health (NIH) based on 19 clinical and laboratory findings[8]. A score of 30 has a specificity of 80.6 percent and sensitivity of 87.5 percent for the diagnosis of HIES. Oral findings in the scoring system include retained primary teeth, candidosis, high palate and characteristic facial features. The patient scored below this (22). A score of 20-40 is considered indeterminate. This patient therefore falls into the small percentage of patients with genetically defined HIES for which the scoring system does not provide a definitive diagnosis. When interpreting a clinical score, it is important to be aware of its limitations. As genetic testing has developed in recent years, we are identifying more patients with an incomplete phenotype. Historical scoring systems may under-diagnose these patients.

The management of patients with HIES can be challenging with therapy focused on improving skin care, preventing infection, aggressively managing infections and controlling pulmonary complications. Maintaining skin hydration and controlling the associated pruritus requires the use of topical agents for treatment of eczema and antiseptic washes to decrease *S. aureus* colonisation. Prophylactic antimicrobials are given to prevent pneumonia and skin infections. Maintenance antifungals are used in individuals with recurrent mucocutaneous candidiasis. Immunomodulatory agents have been used with varying success. Recombinant

human interferon (IFN)-gamma can slightly lower immunoglobulin E (IgE) levels and decrease respiratory secretions[28]. There is anecdotal evidence that high-dose intravenous immunoglobulin (IVIG) may cause improvement in some individuals[29]. Results from bone marrow transplantation (BMT) have been mixed and it has not been pursued as a treatment option in this cohort[30,31], though two patients with HIES showed sustained benefit over 10 and 14 years of follow-up[32]. Omalizumab, a monoclonal antibody that blocks IgE-mediated histamine release from mast cells, was used successfully in one case[33].

A number of immunodeficiency disorders, hereditary and acquired (e.g. ataxia telangiectasia, CVID, chronic granulomatous disease), present with non-infectious granulomatous inflammation at a variety of body sites[34,35,36]. Understanding the genetic overlap between HIES and granulomatous conditions is key to elucidating common pathways. As mentioned previously, heterozygous loss of-function mutations in STAT3 cause defects in signal transduction for IL-6 and IL-23. Several primary immunodeficiencies characterised by mutations in IL-23 pathway present with granulomatous inflammation[36]. Granulomatous inflammation and ulceration involving the buccal mucosa was reported in one child with DOCK8 deficiency[37]. Interestingly, ustekinumab, which targets the p40 unit of both IL-12 and IL-23, has been shown to reduce disease burden of Crohn's disease[38]. The diagnosis of OFG requires a) the presence of typical orofacial clinical features, and b) the exclusion of systemic disorders that may mimic the condition by taking a thorough medical history with appropriate serologic, radiological, or endoscopic investigations where clinically justified. Histopathological confirmation of non-caseating granulomas is not an essential criterion, though may prove useful in excluding other causes of granulomatous inflammation. The clinical features of the lips and oral cavity in this case were consistent with an OFG-like condition and lip biopsy was not indicated for confirmation of the diagnosis. Intralesional corticosteroids have been successfully used to manage lip swelling in patients with OFG, with remission of lip swelling for up to 10–12 months[39].

Conclusion

STAT3 deficiency is a rare disorder that can be challenging to diagnose. Identifying specific genetic defects not only confirms the diagnosis and facilitates genetic counselling but allows for improved risk stratification. Importantly, the identification of genetic defects also allows for the use of specific but rare therapeutic management strategies. A strong collaborative approach by various specialists is essential for the diagnosis and management of patients with such disease. This patient illustrates that broad genetic testing strategies are identifying patients with an extended phenotype of immunodeficiencies and other conditions.

Figure Legends

Figure 1: Upper and lower lip swelling with lip incompetence. The lip was firm and there was evidence of crusting at the vermilion border.

Figure 2: Erythematous and hyperplastic gingivae were noted on the labial aspects of UR4 extending to UL4.

Figure 3: Resolution of lip swelling following Intralesional triamcinolone to upper and lower lips. There is evidence of drying of the superior inner labial lip mucosa.

295 **References**

[1] Grimbacher B, Holland SM, Gallin JI, Greenberg F, Hill SC et al. Hyper-IgE syndrome with recurrent infections - An autosomal dominant multisystem disorder. N Engl J Med 1999; 340:692-702.

[2] Yong PF, Freeman AF, Engelhardt KR, Holland S, Puck JM, Grimbacher B. An update on the hyper-IgE syndromes. Arthritis Res Ther 2012;14:228

[3] Minegishi Y, Saito M, Morio T, Watanabe K, Agematsu K, et al. Human Tyrosine Kinase 2 Deficiency Reveals Its Requisite Roles in Multiple Cytokine Signals Involved in Innate and Acquired Immunity. Immun 2006; 25:745-755.

[4] Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G et al. STAT3 mutations in the hyper-IgE syndrome. N engl J Med. 2007; 357(16):1608-1619.

[5] Mogensen TH. STAT3 and the Hyper-IgE syndrome: Clinical presentation, genetic origin, pathogenesis, novel findings and remaining uncertainties. JAKSTAT 2013; 2:e23435

[6] Woellner C, Gertz EM, Schäffer AA, Lagos M, Perro M, et al. Mutations in STAT3 and diagnostic guidelines for hyper-IgE syndrome. J Allerg Clin Immunol 2010; 125:424-432.

[7] Ochs HD, Oukka M, Torgerson TR. TH17 cells and regulatory T cells in primary immunodeficiency diseases. J Allergy Clin Immunol 2009;123:977-83.

[8] Grimbacher B, Schäffer AA, Holland SM, Davis J, Gallin JI et al. Genetic linkage of hyper-IgE syndrome to chromosome 4. Amer J Human Gen 1999; 65:735-744.

[9] Davis SD, Schaller J, Wedgwood RJ. Job's Syndrome. Recurrent, "cold", staphylococcal abscesses. Lancet 1996;1:1013-1015.

[10] Freeman AF, Holland SM. The hyper IgE syndrome. Immunol Allergy Clin North Am 2008; 28:277-91.

[11] Ma CS, Chew GY, Simpson N, et al. Deficiency of Th17 cells in hyper IgE syndrome due to mutations in STAT3. J Exp Med 2008; 205:1551–1557.

[12] Milner JD, Brenchley JM, Laurence A, Freeman AF et al. Impaired TH17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. Nature 2008; 452:773-776.

[13] Hill HR, Ochs HD, Quie PG, et al. Defect in neutrophil granulocyte chemotaxis in Job's syndrome of recurrent "cold" staphylococcal abscesses. Lancet 1974;2:617-619

[14] Del Prete G, Tiri A, Maggi E, et al. Defective in vitro production of gamma-interferon and tumor necrosis factor-alpha by circulating T cells from patients with the hyper-immunoglobulin E syndrome. J Clin Invest 1989; 84:1830-1835.

[15] Ives ML, Ma CS, Palendira U, et al. Signal transducer and activator of transcription 3 (STAT3) mutations underlying autosomal dominant hyper-IgE syndrome impair human CD8(+) T-cell memory formation and function. J Allergy Clin Immunol 2013; 132:400-411.

[16] Antachopoulos, C. Invasive fungal infections in congenital immunodeficiencies. Clin Microbiol Inf 2010;16:1335-1342.

[17] Borges WG, Hensley T, Carey JC, et al. The face of Job. J Pediatr 1998;133:303-5.

[18] Peacock, M.E., Arce, R.M. & Cutler, C.W. Periodontal and other oral manifestations of immunodeficiency diseases. Oral Dis 2017; 23:866-888

[19] Freeman, A.F., Domingo, D.L. & Holland, S.M.Hyper IgE (Job's) syndrome: A primary immune deficiency with oral manifestations. Oral Dis 2009; 15:2-7.

[20] Domingo DL, Freeman AF, Davis J, Puck JM, Tianxia W, Holland SM, et al. Novel intraoral phenotypes in hyerimmunoglobulin E syndrome. Oral Dis 2008;14:73-81.

[21] Freeman AF, Collura-Burke CJ, Patronas NJ, Ilcus LS et al. 2007. Brain abnormalities in patients with hyperimmunoglobulin E syndrome. Pediatr 2007; 119:e1121-e1125.

[22] Gorin LJ, Jeha SC, Sullivan MP, Rosenblatt HM, Shearer WT. Burkitt's lymphoma developing in a 7-year-old boy with hyper-IgE syndrome. J Allerg Clin Immunol 1989; 83:5-10.

[23] Oztop I, Demirkan B, Tarhan O, Kayahan H, Yilmaz U, Kargi A, Alakavuklar M. The development of pulmonary adenocarcinoma in a patient with Job's syndrome, a rare immunodeficiency condition. Tumori 2004;90:132-135.

[24] Siegel AM, Stone KD, Cruse G, Lawrence MG, Olivera A, Jung MY, et al. Diminished allergic disease in patients with STAT3 mutations reveals a role for STAT3 signaling in mast cell degranulation. J Allerg Clin Immunol 2013;132:1388–96.

[25] Boos AC, Hagl B, Schlesinger A, Halm BE, Ballenberger N, Pinarci M, et al. Atopic dermatitis, STAT3- and DOCK8-hyper-IgE syndromes differ in IgE-based sensitization pattern. Allergy 2014; 69:943–53.

[26] Hagl B, Heinz V, Schlesinger A, Spielberger BD, et al. Key findings to expedite the diagnosis of hyper-IgE syndromes in infants and young children. Pediatr Allergy Immunol 2016;27:177-84

[27] Keles S, Jabara HH, Reisli I, et al. Plasmacytoid dendritic cell depletion in DOCK8 deficiency: rescue of severe herpetic infections with IFN-alpha 2b therapy. J Allergy Clin Immunol 2014;133: 1753–5 e3.

[28] Petrak BA, Augustine NH, Hill HR. Recombinant human interferon gamma treatment of patients with Job's syndrome of hyperimmunoglobulin E and recurrent infections. Clin Res 1994;42:1A.

[29] Kimata H. High-dose intravenous gamma-globulin treatment for hyperimmunoglobulinemia E syndrome. J Allergy Clin Immunol 1995;95:771-4.

[30] Gennery AR, Flood TJ, Abinun M, Cant AJ. Bone marrow transplantation does not correct the hyper IgE syndrome. Bone Marrow Transplant 2000;25:1303–5.

[31] Patel NC, Gallagher JL, Torgerson TR, Gilman AL. Successful Haploidentical Donor Hematopoietic Stem Cell Transplant and Restoration of STAT3 Function in an Adolescent with Autosomal Dominant Hyper-IgE Syndrome. J Clin Immunol 2015;35:479–85

[32] Goussetis E, Peristeri I, Kitra V, et al. Successful long-term immunologic reconstitution by allogeneic hematopoietic stem cell transplantation cures patients with autosomal dominant hyper-IgE syndrome. J Allergy Clin Immunol 2010;126:392-4.

[33] Chularojanamontri L, Wimoolchart S, Tuchinda P, et al. Role of omalizumab in a patient with hyper-IgE syndrome and review dermatologic manifestations. Asian Pac J Allergy Immunol 2009;27:233-6.

[34] van den Berg JM, van Koppen E, Åhlin A, et al. Chronic granulomatous disease: the European experience. PLoS One 2009;4:e5234.

[35] Chiam LYT, Verhagen MMM, Haraldsson M, et al. Cutaneous granulomas in ataxia telangiectasia and other primary immunodeficiencies: reflection of inappropriate immune regulation? Dermatol 2011;223:13–19.

[36] Petersen H, Smith A. The role of the innate immune system in granulomatous disorders. Front Immunol 2013;24:120.

[37] Sanal O, Jing H, Ozgur T, Ayvaz D et al. Additional diverse findings expand the clinical presentation of DOCK8 deficiency. J Clin Immunol 2012;32:698-708.

[38] Sandborn WJ, et al. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. N Engl J Med 2012;367:1519–1528.

[39] Fedele S, Fung PPL, Bamashmous N, Petrie A, Porter S. Long-term effectiveness of intralesional triamcinolone acetonide therapy in orofacial granulomatosis: An observational cohort study. Br J of Dermatol 2014;170:794-801.