A Novel *STAT3* Mutation in a Patient with Hyper-Immunoglobulin E Syndrome

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The hyper-immunoglobulin E syndrome (HIES) was first described in 1966 as a clinical triad of eczematoid dermatitis, recurrent sinopulmonary and staphylococcal skin infections. Soon after, it was realized that these patients have elevated levels of IgE [1]. Over the next decades, the multisystem characteristic of this syndrome unfolded.

The immunological and infectious manifestation of HIES consists of a rash that usually appears early in life with pustular or eczematoid eruption on the scalp and face, which is eosinophilic on histology. The rash may progress to eczematoid dermatitis and is invariably colonized by *Staphylococcus aureus* [2]. Boils and furuncles are the cause of the skin infection and abscesses [1].

Recurrent sinopulmonary infections are a major cause of morbidity and mortality among HIES patients [1,2]. The main pathogens responsible for the infections are *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Haemophilus influenzae* [1]. HIES patients also suffer from fungal infections, with up to 80% of patients affected by chronic mucocutaneous candidiasis [3]. In addition, HIES patients are at higher risk of malignancy [1], and disseminated infections with Histoplasmosis and Cryptococcus have been described involving the gastrointestinal tract [2].

The non-immunological features of HIES include coarse facial features, facial asymmetry and hemi-hypertrophy, prominent forehead and chin, deep-set eyes, increased inter-alar width, and high arched palate [1,2]. Musculoskeletal abnormalities include hyperextensibility, scoliosis, minor trauma fractures and osteopenia [1]. Approximately 70% of all patients demonstrate a delay and even failure in exfoliating the primary teeth, which sometimes requires surgical intervention [1,2]. Other oral cavity abnormalities in HIES include midline ridges and fissures of the palate, and deep grooves on the tongue and buccal mucosa with multiple mucosal fissures [2]. Vascular abnormalities are a newly recognized feature of HIES. Coronary tortuosity, dilation and aneurysms were reported, as was hypertension [1].

The inheritance of HIES is either autosomal-dominant (AD) or recessive (AR). The majority of cases identified are AD-HIES and exhibit the typical manifestation of HIES as described above [2]. The clinical manifestations of AR-HIES comprise not only the classical triad of HIES, but also increased susceptibility to intractable viral infections, severe allergies, vasculitis of the central nervous system, and frequent autoimmune complications. These patients will not have the typical skeletal and dental abnormalities [4].

In 2007 dominant negative mutations in the signal transducer and activator of transcription 3 (*STAT3*) gene were identified as the cause of AD-HIES [1,5]. Disease-causing mutations in *STAT3* are mainly missense or in-frame deletions located primarily in the SH2 and DNA binding domains [1,5]. This report describes a patient demonstrating the multisystem characteristics of AD-HIES with a novel mutation in *STAT3*.

PATIENT DESCRIPTION

A 16 year old male previously diagnosed with HIES presented to the emergency room with complaints of pain in the posterior thigh, fever, and lack of response to treatment with cephalexin. The patient was born in Ukraine where he was diagnosed with HIES at the age of 7 based on clinical features including recurrent skin infection and abscesses, recurrent bacteremia, recurrent pneumonia, and delayed shedding of the primary teeth. No recurrent mucocutaneous candidiasis was reported. At age 9 he was treated with cyclosporin due to recurrent infections and severe eczematous rash, resulting in a significant decrease in the occurrence of the skin infections. At presentation to our hospital, he was treated solely with topical treatment for his skin infection (pimecrolimus, gentamycin, prednisolone).

The patient's family history revealed healthy parents and sister; however, four of his grandfather's sisters (on his mother side) died at a young age due to severe infections including skin infections.

A physical examination revealed normal facial features, tenderness over the posterior thigh with no erythema and no sign of abscess. In addition, he had multiple old scars from previous abscesses and walked with a limp. His blood work revealed elevated C-reactive protein, and he was admitted for intravenous treat-

ment with antibiotics due to fever and elevated inflammatory markers. A tissue ultrasound did not reveal an abscess in the thigh and a blood culture was positive for methicillin-sensitive *Staphylococcus aureus*. The patient's IgE level was 9070 U/ml and his blood count demonstrated eosinophilia of 6988 x 10^3/mm^3. Genetic analysis that included sequencing of all *STAT3* gene exons demonstrated a V713M mutation.

COMMENT

Our patient presents a novel dominant mutation in *STAT3* with the typical features of AD-HIES: recurrent skin infection and "cold" abscesses, recurrent pneumonia, staphylococcal bacteremia, and elevated serum level of IgE. However, recurrent mucocutaneous candidiasis was not observed. The clinical presentation was accompanied by a significant family history of early death due to severe infections.

In 2007, *STAT3* mutations were shown to be the cause of AD-HIES [1,5]. In 2009 *DOCK8* mutations were identified as the cause of AR-HIES and added to a previously reported mutation in Tyk2 [1,2]. *STAT3* plays a key role in the signal transduction of a broad range of cytokines [5] and its activation involves a series of processes that end in cytokine binding and Janus kinase (JAK) activation. Subsequently STAT3 is phosphorylated, dimerized and translocates to the nucleus, where it controls transcription of the target genes [5]. *STAT3* regulates multiple cytokine signaling pathways involved in the innate and adaptive immune response, including interleukin (IL)-6, IL-21, IL-23, IL-27 and IL-10, as well as granulocyte-stimulating factor and leptin [4]. Many of these cytokines are critical for the differentiation of Th17 CD4+ cells [5]. Differentiated Th17 cells secrete IL-17A, IL-17F, IL-21, IL-22 and IL-26 cytokines, which promote cutaneous anti-fungal immunity and play a critical role in the inflammatory response to bacterial and fungal pathogens and to the mucosal immunity [3,4]. Thus, STAT3 mutations negatively affect the Th17 CD4+ cell differentiation. It was recently reported that Th17 was also involved in the anti-fungal activity of saliva. Levels of β-defensin 2 and histatins (anti-fungal proteins) were markedly decreased in the saliva of AD-HIES patients, and IL-17 significantly enhanced the expression of histatins. These findings can explain the common observation of recurrent mucocutaneous candidiasis in approximately 80% of AD-HIES patients [3].

A few studies from recent years have tried to link the genotype and phenotype of AD-HIES patients but found no correlation in most features of the syndrome; however, there may be some evidence of a modest correlation between *SH2* mutations and the non-immune features of HIES, such as high palate, increased interalar distance and scoliosis [1].

About 70 mutations have been identified to date, most of which are either missense or in-frame deletions that cluster in the DNA and Src homology 2 (SH2) binding domains [1,4]. In contrast, our novel missense mutation is located in the trans-activation domain, resulting in amino acid substitution from valine to methionine (V713M). The mutation is located between the two phosphorylation sites (Y705, S727) near the carboxylic end of the STAT3 protein and is highly conserved among various species. This area connects the critical phosphotyrosine residue (Y705) to the SH2 domain. Models based on the crystal structure of *STAT3* reveal a flexible loop that positions the Y705 residue adjacent to the opposite SH2 domain and is critical for normal function of the STAT3 protein. Mutations affecting this loop were demonstrated to compromise the *STAT3* dimerization and activation [4].

Our analysis of the possible impact of amino acid substitution on the structure and function of the protein was conducted using several prediction programs such as Polyphen, SNP3D and Mutation Taster. All these programs indicated a high probability of protein damage. A literature review of *STAT3* mutations reveals only seven reported mutations in the trans-activation domain and only one at the same codon (2137 G>C) causing an amino acid substitution from Valine to Leucine (V713L) [4,5]. Renner's group demonstrated low Th17 cell numbers and decreased *STAT3* phosphorylation resulting from this mutation [4]. These changes can explain our patient's clinical presentation.

In summary, we describe a patient with typical AD-HIES immunological and clinical features and a novel missense mutation in *STAT3* (V713M), which is located in the trans-activation domain of *STAT3* and not in the SH2 or DNA binding domains as in most reported *STAT3* mutations. This mutation is located in a loop containing two phosphorylation sites (Y705, S727) which are crucial for normal dimerization and activity of *STAT3*.

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"The love of one's country is a splendid thing. But why should love stop at the border"

Pablo Casals (1876-1973), Spanish Catalan cellist and conductor. He is generally regarded as the pre-eminent cellist of the first half of the 20th century, and one of the greatest cellists of all time