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An adolescent with marked hyperimmunoglobulinemia E showing minimal change nephrotic syndrome and a STAT3 gene mutation

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Key words

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Abstract. We encountered a patient with marked hyperimmunoglobulinemia E who had a mutation of the signal transducer and activator of transcription 3 gene (*STAT3*) and developed minimal change nephrotic syndrome (MCNS). From early infancy, the patient showed repeated episodes of refractory chronic eczema accompanied by impetigo vulgaris with cicatrization, as well as otitis media. Serum IgE was markedly increased (from 4,000 to 25,000 IU/ml). The nephrotic syndrome (NS) frequently relapsed, and was alternately responsive and resistant to corticosteroids. The *STAT3* mutation was heterozygous, located in exon 23 of the transactivation domain and causing A744V substitution. Presently treated with mycophenolate mofetil, the patient has less frequent MCNS recurrences. Increases in circulating Th2 cytokines and IgE combined with suppression of the Th1 cytokine interferon- γ caused by the *STAT3* abnormality, presumably caused MCNS by altering the Th1/Th2 balance among T-lymphocytes. To our knowledge, this is the first report of type I hyper-IgE syndrome (HIES) showing a *STAT3* gene mutation and MCNS.

Introduction

The cause of minimal change nephrotic syndrome (MCNS) has not been fully clarified. However, MCNS is considered to be related to abnormalities of cellular and humoral immunity, such as increases in T-helper 2 (Th2) cytokines caused by a Th2-dominant state among T lymphocytes and hypersensitivity of CD8⁺ cells upon exposure to antigenic stimuli [18]. In addition, allergic disorders such as atopic dermatitis and allergic rhinitis accompanied by an increase in serum IgE often are observed in patients with MCNS [16].

A clinical diagnosis of hyperimmunoglobulin (Ig) E syndrome (HIES) can be made based on three characteristics: marked increases in serum IgE (concentrations exceeding 2,000 IU/ml), chronic intractable eczema, and an immunocompromised state. As in MCNS, changes of Th1/Th2 balance arising from an interferon (IFN)- γ synthesis disorder coupled with increases in Th2 cytokines could underlie the disease [4]. Recently, abnormalities in the signal transducer and activator of transcription 3 (*STAT3*) and tyrosine kinase 2 (Tyk2) genes have been identified as causes of HIES. Type I HIES is caused by abnormality of *STAT3*. Patients with Type I HIES show autosomal dominant inheritance and usually exhibit structural abnormalities of bones, joints, and soft tissues [5, 9]. However, since type I HIES is caused by a monoallelic mutation of *STAT3*, occurrence is mostly sporadic [5].

The *STAT3* is a transcriptional factor for delivering cytokine or growth factor signals [14] to the nucleus. Particularly, *STAT3* is an essential factor for signal transmission involving interleukin (IL)-6 and IL-10, which are Th2 cytokines [7]. Additionally, a recent study by Li et al. [8] suggests that activation of JAK/STAT signaling is involved in the progression of glomerular diseases with proteinuric state and *STAT1* and *STAT3* was significantly inhibited by JAK2 inhibitor AG490, indicating the relationship between onset of nephrotic syndrome (NS) and *STAT3* gene.

Here we report a 27-year-old man who had type I HIES showing mutation of *STAT3*, subsequently developing MCNS.

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Figure 1. Findings in the patient's renal tissue and skin. Panel a: Glomerular alteration is minimal (PAS stain, $\times 100$). Panel b: Widely distributed severe eczema includes impetigo caused by *Staphylococcus aureus*.

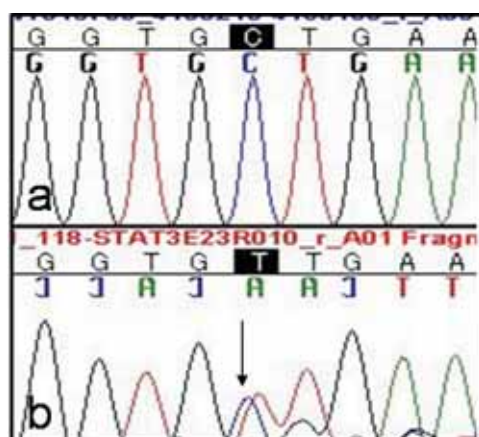


Figure 2. Analysis of the patient's STAT3 gene. Heterozygous mutation is observed in exon 23 of STAT3, A744V substitution in the transactivation domain (panel b: indicated by arrow). Panel a denotes a standard sequence of STAT3.

Case presentation

The patient had no developmental abnormality evident in the perinatal period or early childhood. Chronic eczema accompanied by *Staphylococcus aureus* skin abscess, first noticed when the patient was 2 years old, gradually worsened thereafter. Other clinical history included frequent occurrences of otitis media since childhood.

He initially developed NS when he was 13 years old. Soon after admission to our clinic, renal biopsy was performed for definitive diagnosis. Among 18 glomeruli obtained, all showed minimal alteration (Figure 1a). No immunoglobulins or complement components were detected in the glomeruli and tubulointerstitium. Electron microscopic observation revealed diffuse podocyte foot-effacement. However, electron-dense materials

were not found in any parts of the kidney, leading to a diagnosis of minimal change NS. No hypocomplementemia, hypergammaglobulinemia, or circulating immune complexes were detected. He showed heavy proteinuria, but we did not observe hematuria accompanied by urinary cast. Since then, he has had more than 10 recurrences of NS, alternating between steroid-responsive and resistant episodes. Previous treatments included various immunosuppressants, including cyclosporine A (CyA) and mizoribine in addition to corticosteroids. Remission currently is maintained with mycophenolate mofetil (MMF).

Present physical findings reflect refractory chronic eczema accompanied by impetigo with cicatrization (Figure 1b). No skeletal or dental abnormality was present. The hair was relatively coarse and sparse. No cystic change was noted in the lungs. His parents were nonconsanguineous; while his family history included chronic glomerulonephritis affecting his father and paternal grandfather; details were unclear. No family members had clinical manifestations suggesting HIES or were suspected to be immunodeficient.

Hematologic examination showed an increased peripheral eosinophil count (661 – 1,440/ μ l) and marked increases in serum IgE (4,000 to 25,000 IU/ml). CAP-RAST was positive for IgE specific to *Staphylococcus aureus* enterotoxin and to fungi such as *Candida* and *Aspergillus*, which frequently infect HIES patients. Neutrophil phagocytic and bactericidal activities were 70% compared to those of healthy individuals. Serum IFN- γ , a Th1 cytokine that suppresses IgE production, was only 0.1 IU/ml or below. Since the patient was in remission with MMF

administration at the most recent clinical assessment, concentrations of the Th2 cytokines IL-4, -5, -6, -10, 13 and -21 reflected short-term effects of treatment. However, serum IL-4 (42.3 pg/ml), IL-5 (6.0 pg/ml), and IL-13 (52.4 pg/ml) were increased, while IL-6 (5.2 pg/ml), IL-21 (72.4 pg/ml), and IL-23 (< 156 pg/ml) concentrations were normal. Flow cytometry revealed that, in our patient, frequency of circulating Foxp3-positive cells in the CD4⁺ T-cell population was higher than that of a healthy individual (8.2% vs. 3.9%, respectively).

At the age of 26 years, the patient gave written consent for genetic testing. Analysis of STAT3 disclosed a heterozygous mutation in exon 23 of the transactivation domain causing A744V substitution (Figure 2), while no mutation of STAT3 was found in his parents, establishing a *de novo* mutation.

Discussion

Type I HIES has been reported to be complicated by various disorders such as systemic lupus erythematosus and membranoproliferative glomerulonephritis [12, 15]. A 10-year-old boy with HIES who developed MCNS was previously described by Bong et al. [2]; however, genetic abnormalities were not addressed. Thus, to our knowledge, this is the first report of type I HIES complicated with MCNS demonstrating a STAT3 gene abnormality.

MCNS sometimes accompanies allergic disorders showing increased serum IgE. This suggests a common etiologic mechanism shared by the two diseases. Our patient had been treated for refractory intractable eczema from early childhood and later developed MCNS. Much about the cause of MCNS has not been fully clarified. However, corticosteroids and immunosuppressants are effective for reduction of proteinuria, and allergic diseases such as bronchial asthma and atopic dermatitis may coexist. Some patients develop MCNS after vaccination or an insect bite [18]. All of this suggests an immunologic abnormality including hypersensitivity to antigenic stimulation. In an MCNS patient, the CD8⁺ T-cell antigen receptor structure exhibits a diversity not observed in healthy individuals; the receptor is reported to be sensitive to

multiple antigenic stimuli. Some reports also have indicated that binding of NF- κ B to intranuclear DNA in response to certain antigenic stimuli is enhanced at the onset or recurrence of MCNS [13]. In cultures of peripheral blood lymphocytes, T-helper lymphocyte activity tended to show a Th2-dominant state in MCNS patients, with consequent increases in serum cytokines such as IL-4, -5, -9, -10, and -13 [16]. The hypothesis that increases in these vascular permeability factors cause structural or functional impairment of the glomerular basement membrane, resulting in leakage evident as heavy proteinuria, is widely supported. However, serum concentrations of these cytokines vary considerably between patients, and MCNS cannot be induced by administration of these cytokines alone. Implicating a particular cytokine as the cause of MCNS is therefore difficult.

STAT3, a cytoplasmic protein that responds to extracellular signals such as cytokines, growth factors, and hormones, is phosphorylated by tyrosine kinase [14]. STAT3 does not directly influence signal transmission involving IL-4, which affects the production of serum IgE. However, STAT3 is involved in Th2 cytokine signaling by IL-6 and IL-10 [7]. The homodimer of wild-type STAT3 shows DNA-binding activity; this activity is highly suppressed in heterodimers composed of wild-type STAT3 and mutant STAT3 or homodimers of mutant STAT3 [10]. Since STAT3 also activates the suppressor of cytokine signaling gene 3 (SOCS3), a negative-feedback regulator of the IL-6 signal, *STAT3* abnormality disturbs the signal interplay [6]. Therefore, *STAT3* abnormality affects synthesis of cytokines belonging to the IL-6 family, resulting in a Th2-dominant state. Additionally, *STAT3* influences synthesis of TNF-family and IL-2-family cytokines, affecting Th17 cell differentiation [1]. Since recent reports characterized Th17 cells as crucial in regulating the production of IgE [17], abnormalities in these cells presumably may induce hyperimmunoglobulinemia E in type I HIES patients.

Nevertheless, our patient remained in remission with MMF therapy, despite the fact that some of the circulating Th2 cytokines increased. While serum Th2 cytokines have not been evaluated in the absence of treatment, abnormality of *STAT3* may have induced a

Th2-dominant state accompanied by hyperimmunoglobulinemia E which, together with suppression of the Th1 cytokine IFN- γ , caused a Th1/Th2 imbalance that facilitated development of MCNS in our patient.

In this report, we have described a patient with MCNS who has an abnormality of *STAT3*. We noted a novel heterozygous mutation in exon 23 of *STAT3* (A744V) in the transactivation domain in this patient. The frequency of base change at the contiguous position 4193129 of *STAT3* is extremely low, suggesting that this mutation was involved in the onset of HIES in our patient. Sites of *STAT3* mutation previously reported in Type I HIES have involved predominantly the DNA binding and SH2 domains; abnormalities of bone and soft tissues were noted in some patients [5]. Heterodimers composed of wild-type and mutant *STAT3* have been shown to have impaired binding activity for the target genes [6, 11], presumably affecting development of bone, soft tissues, and teeth. Such abnormalities were not observed in our patient. Possible reasons include the likely de novo nature of his mutation, since abnormal development is seen mainly in cases with autosomal dominant inheritance. In addition, his *STAT3* mutation was located in the transactivation domain rather than in the DNA binding domain, which has a direct effect on signal transmission. However, since the phosphorylation site of STAT is conserved in the transactivation domain, mutation of this domain like ours may cause insufficient tyrosine kinase-dependent phosphorylation, resulting in disturbance of the transcriptional function of *STAT3* for target genes.

Regarding the therapeutic intervention for hyper-IgE syndrome, CyA may be effective for ameliorating a series of symptoms as well as hyperimmunoglobulinemia E [3]. Additionally, Bong et al. reported that CyA therapy for a patient with HIES accompanying MCNS improves hyperimmunoglobulinemia E and prevents recurrence of NS [2]. In our patient, CyA improved, not only hyperimmunoglobulinemia E, but also the recurrence rate of NS for a few years. However, these conditions concomitantly flared up again despite an appropriate blood concentration of CyA being maintained. Presently, the patient's eczema and MCNS are well controlled by administration of MMF. Since this agent

affects activated T and B lymphocytes by specifically inhibiting inosine monophosphatase, this drug may be effective for treatment of both HIES and MCNS, especially considering these diseases share some underlying immunologic abnormalities. To our knowledge, this is the first report of type I HIES with a *STAT3* mutation to be complicated by MCNS. *STAT3* may be related to onset of MCNS with marked hyperimmunoglobulinemia E.

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