Might there be a link between high expression of interleukine 10 and Netherton Syndrome?

IL-10’un yüksek ekspresyonu ve Netherton Sendromu arasında bir ilişki olabilir mi?

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Özet

Netherton Sendromu (NETH) nadir görülen otozomal reesif bir hastalıktır olup, konjenital iktiyozis, yaygın eritroderni, bambu saç ve şişletli atopi bulguları ile karakterizedir. Çalışmanın amacı; sitokin gen polimorfizmirleri (ekspresyonlar) ile NETH arasında bir ilişki nin olup olmadığını NETH tanısı alan çocukta sahip bir aileden anal iz etmektedir. NETH tanısı alınmış 18 aylık kız hasta ile sağlıklı olan iki erkek kardeşi ve ebeveynlerin periferal kanından izole edilen DNA örnekleri kullanıldı. Beş farklı sitokin geninde bulunan 8 polimorfizm PCR-SSP yöntemi ile analiz edildi [IL-6 (-174), IL-10 (-1082; -819; -592), IFN-γ (+874), TGF-β1 (+10; -25), TNF-α (-308)]. Elde edilen sonuçlar değerlendirildiğinde; NETH hastasının diğer aile bireylerinden farklı olarak, IL-10 geninde GCC GCC haplotipi taşıdığı ve yüksek ekspresyonun olduğu bulunludur. Bu çalışmada; immünoregulasyon ve inflamasyonda pleiotropik etkisi bulunan IL-10 geni ait yüksek ekspresyon NETH’undaki literatürde ilk kez gösterilmiştir.

Anahtar kelimeler: Netherton Sendromu, Sitokinler, Polimorfizm/Ekspresyon, PCR-SSP

INTRODUCTION

Netherton Syndrome (NS; OMIM 256500) is a rare, autosomal recessive multisystemic disorder (1). Its incidence is estimated to be 1/200,000 (2). The disease is characterized by congenital ichthyosiform erythroderma, hair shaft abnormalities, and atopic manifestations (1). Netherton syndrome can be caused by mutations in the SPINK5 gene (serine protease inhibitor Kazal-type 5) locus on chromosome 5q32 encoding the serine protease inhibitor LEKTI (lympho-epithelial Kazal type related inhibitor). The inhibitor may play a role in skin and hair morphogenesis and anti-inflammatory and/or antimicrobial protection of mucous epithelia (2-5). However, no clear correlation between disease and phenotype was seen, suggesting that the degree of severity may be influenced by other factors. Therefore, considering the recognized influence of cytokines in NS development, the aim of this study was to investigate whether this disease may be associated with polymorphisms of IL-6, IL-10, IFN-γ, TGF-β1 and TNF-α genes.

CASE REPORT

An eighteen-month-old girl applied to the Dermatology Clinic with complaints of postnatally emerging wounds on the face and no growth of hair. The patient in family history: First degree cousin marriage. In the physical examination of the patient, it was observed that clarity in hair follicles on the skin and keratinous plugs were present and that the hair was sparse and in vellus hair form (Figure 1 A and B). Erythema and desquamations as well as papules and pustulae were detected on the face, legs and arms while desquamation was detected on the palm and sole. No oral infections could be detected in intraoral examination and it was decided to keep the patient under follow-up together with the Section of Child Allergy. In the examination on hair shafts of the patient, the appearance of trichorrhexis invaginata (bamboo hair) was detected (Figure 2). Moisturizers, topical steroid and oral treatment with Clemastin and Cetirizine were applied to the patient under observation; however, the patient did not respond to the treatment.

Laboratory Findings: Eosinophil and IgE in the blood were found to have increased in peripheral smear [Eosinophil count: 780/µL (normal: 0-700), IgE: 200 IU/ml, (normal: 0-100)]. When “skin prick” test was applied to the patient with cow’s milk, egg white, egg yolk, grass pollens, house dust mites and alternaria, it was found to be negative. Specific IgE was examined with "Food

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Abstract

Netherton Syndrome (NS) is a rare autosomal recessive disorder, characterized by congenital ichthyosiform erythroderma, trichorrhexis invaginata and severe atopic diathesis. Considering that cytokines are involved in NS pathogenesis and that cytokine gene polymorphism may affect cytokine production, our purpose was to investigate the association between NS and IL-6, IL-10, IFN-γ, TGF-β1 and TNF-α polymorphisms. Cytokine genotyping and haplotyping were performed in a family with NS by PCR-SSP method. We observed GCC GCC haplotype of IL-10 gene in proband with NS and no association with all other polymorphisms. We conclude that GCC GCC haplotypes of IL-10 gene polymorphisms (−1082 A/G, −819 T/C, −592 C/A) have been associated with NS. In this study, pleiotropic effects in immunoregulation and inflammation with high expression of IL-10 gene in the nether shown for the first time in the literature.

Key words: Netherton Syndrome, Cytokines, Polymorphism/Expression, PCR-SSP

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7 panel (egg white, cow’s milk, wheat, rice, peanut, soy bean)” and it was detected to be negative (below 0.10 kU/L).

Genotyping; DNA was extracted from whole peripheral blood by salting out procedure (6). Cytokine genotyping was performed by the polymerase chain reaction sequence-specific primer method, using the ‘Cytokine Genotyping Tray’ (One lambda Inc, USA) according to manufacturer instructions. The polymorphisms analyzed in the present study were IL-6 (-174 G/C), IL-10 (-1082 A/G,-819 T/C, -592 G/A), IFN-γ (+874 A/T), TGF-β1 (+10 T/C; +25 C/G) and TNF-α (-308 G/A) (7). Data were analyzed by the chi-square test with the level of significance set at P<0.05.

Figure 2. Light microscopy of representative hair defect of trichorrhexis invaginata

DISCUSSION

Although, as far as we know (Pubmed November, 2014), there are around 218 published studies in the literature on NS, there is no research on cytokine gene polymorphisms. The studies on NS in literature contain the mutations in LEKTI gene (3, 4, 8). In addition, there is also one study that puts forward the association of IL-10 genetic variation with atopic reactivity in asthma and/or atopy (9). Our patient has the highest IgE levels among NS cases previously published (5, 7).

IL-10, the protein encoded by this gene, is a cytokine produced primarily by monocytes and, to a lesser extent, by lymphocytes. This cytokine has pleiotropic effects on immunoregulation and inflammation. It down-regulates the expression of Th1 cytokines, MHC class II Ags, and costimulatory molecules on macrophages. It also enhances B cell survival, proliferation, and antibody production. This cytokine can block NF-kappa B activity, and is involved in the regulation of the JAK-STAT signaling pathway (10). In our study, it was determined that the child with Netherton syndrome, unlike the other family members, carried GCC GCC haplotype in IL-10 gene and that she had high expression. The increased serum IgE level in NS patients was also found to be high in our patient in agreement with the literature and provoked to think that it might be associated with the high expression of IL-10.

In conclusion, the high expression of IL-10 gene, with a pleiotropic effect on immunoregulation and inflammation, was first associated with the Netherton syndrome, thereby making a contribution to the literature. However, further studies with larger samples are needed to address the exact role of IL-10 in NS ethiopathogenesis.

RESULTS

The Cytokine genotyping and haplotyping were evaluated in a family with NS by using PCR-SSP method. Cytokine haplotypes of the family members were shown in Table 1. The proband was determined to be different (GCC/GCC- high expression) from those of other family members in terms of IL-10 haplotype.
Table 1. Cytokine genotypes/haplotypes in the family members (Asterisks were indicated different haplotype).

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<thead>
<tr>
<th>Polymorphisms</th>
<th>Haplotypes</th>
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<tr>
<td></td>
<td>Father</td>
</tr>
<tr>
<td>TNF-alpha</td>
<td>low</td>
</tr>
<tr>
<td>-308 G/A</td>
<td>G/G</td>
</tr>
<tr>
<td>TGF-beta</td>
<td>high</td>
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<tr>
<td>+10 T/C</td>
<td>T/T G/G</td>
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<tr>
<td>25 C/G</td>
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<tr>
<td>IL-10</td>
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</tr>
<tr>
<td>-1082 G/A</td>
<td>GCC/ACC</td>
</tr>
<tr>
<td>-819 T/C</td>
<td></td>
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<tr>
<td>-592 C/A</td>
<td></td>
</tr>
<tr>
<td>Haplotype (1082 + 819 + 592)</td>
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</tr>
<tr>
<td>IL-6</td>
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<tr>
<td>-174 G/C</td>
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REFERENCES