Netherton syndrome previously misdiagnosed as hyper-IgE syndrome caused by a probable mutation in SPINK5

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Running short title: Netherton syndrome with unknown mutation in SPINK5

All authors declare their consent for publication of the manuscript. There is no conflict of interest between all authors. An informed consent was received from the parents of the patient to publish photographs and submitted with the manuscript.
Abstract

Netherton syndrome (MIM256500) is an autosomal recessive disorder that includes ichthyosis linearis circumflexa and a predisposition to allergies, asthma, and eczema, with hypereosinophilia, trichorrhexis invaginata, and elevated serum IgE levels. The genetic bases of Netherton syndrome are mutations in the gene SPINK5, and the lymphoepithelial Kazal type related inhibitor, which is a serine protease inhibitor, is encoded by SPINK5.

Here a case is presented which showed a probable splice site mutation in SPINK5, which was previously unknown in databases and the literature, to point out the misdiagnosis of hyper-IgE syndrome in the early presentation of the phenotype. This case highlights that a genetic test can be critical for identifying NS. The finding of underlying mutations contributes to the understanding of Netherton syndrome and is instrumental in indicating a specific therapy. Notably, treatment with acitretin has significantly improved both the ichthyosis linearis circumflexa and eczema in our patient.

Keywords: Netherton syndrome, Eczema, Hyper-IgE Syndrome, Serum IgE, Ichthyosis.
Introduction

Netherton syndrome (NS, MIM256500) is an autosomal recessive disorder that includes ichthyosis linearis circumflexa (ILC) and a predisposition to allergies, asthma, and eczema, with hypereosinophilia, trichorrhexis invaginata, and elevated serum IgE levels.\textsuperscript{1} Severe eczema and elevated serum IgE are common in various genodermatoses.\textsuperscript{2,3} In complicated cases, a genetic test can be critical for identifying NS. The genetic bases of NS are mutations in the gene \textit{SPINK5}, and the lymphoepithelial Kazal type related inhibitor, which is a serine protease inhibitor, is encoded by \textit{SPINK5}.\textsuperscript{1}

We think it is valuable to share this case, which showed a probable splice site mutation in \textit{SPINK5}, which was previously unknown in databases and the literature, to point out the misdiagnosis of hyper-IgE syndrome (HIS) in the early presentation of the phenotype.

Case Report

A four-year-old male presented to the dermatology clinic. He was the son of consanguineous parents (first cousins) who showed no signs of skin disease. His parents described the boy as having uneasiness, irritability, intensive scratching, and red scaly patches all over his body and scalp. He was given intravenous IgG therapy because of his diagnosis of HIES for one year, with no benefit seen.

Collodion membrane and congenital erythroderma were recorded in his medical files at birth (Figs. 1A and 1B). Numerous consultations and laboratory analyses from birth to the present are summarized in Table I. He experienced attacks of urticaria/angioedema and elevated serum IgE levels in his subsequent life. He had no other recurrent infections.

A red-purple patch was observed on the right half of his face, beginning from the right upper lip and extending to the upper part of the right cheek to the right temple. This was diagnosed as
capillary malformation. Erythematous and scaly patches were seen on the forehead, left arm, shoulder, back, trunk, upper chest, and thighs, respectively (Figs. 2A, 2B, and 3A). These lesions were diagnosed as ILC. Histopathological examination revealed psoriasiform dermatitis compatible with ILC. We did not observe any pathology on the patient’s hair.

Genetic analysis was performed on a DNA sample from the patient to evaluate possible mutations. Certainly, it is an important issue to evaluate the origin as it is de novo or parental. However, we were unable to make a family analysis because all family members refused genetic testing, and we did not obtain a skin sample to extract RNA. Sanger sequencing was applied to SPINK5 (ENST00000359874.7, NM_001127698.1), which revealed a homozygous mutation c.2112+2T>A in the splice region of intron 22. Following molecular confirmation of the diagnosis of NS, we administered acitretin 0.5 mg/kg/day and topical moisturizers. Figs. 2C, 2D, and 3B show the significant beneficial effect of acitretin after one year.

Discussion

The mutation (c.2112+2T>A) was not previously described and is neither included in the Netherton registry SPINK5 base nor in other data bases, including the 1000 Genomes Project, the Exome Aggregation Consortium, and the NHLBI Exome Sequencing Project. Because it affects the highly conserved second position of the splice donor site of intron 22, a deleterious effect can be expected. RNA samples from both the boy and his parents were unfortunately unavailable for further assessment of the pathologic mechanism. However, the MutationTaster algorithm predicted this mutation as “disease causing,” which suggests that it may represent a further, thus far unknown, mutation underlying NS as it is likely to disturb normal splicing. Moreover, two other mutations that affect the splice donor site of intron 22 were described previously in families from German/Irish and Argentinian descent, respectively: c.2108_2117del10 and c.2112+1G>A. In total, 84 different mutations of SPINK5 have been
registered in the Human Genome Mutation Database. Sarri et al.\textsuperscript{6} investigated 80 mutations that
were previously identified in 172 patients from 144 families and demonstrated a wide variety
of clinical phenotypes that are associated with these mutations.

HIES includes other autoimmune disorders and musculoskeletal system anomalies that have
not been described in NS. Perivascular dermatitis in HIES is different from psoriasisform
dermatitis in NS. Omenn Syndrome exhibits the absence of B cells and anomalous T cell clones,
which are not present in NS.\textsuperscript{2,3} PSDB shows similar features to NS; however, the clinical
outcome is less severe, and the dermatopathology reveals perivascular dermatitis and
subcorneal acantholysis.\textsuperscript{2,5} SAM syndrome consists of metabolic wasting, gastroesophageal
reflux, and minor cardiac defects, which are not compatible with NS.\textsuperscript{7} Enteropathy,
hypoalbuminemia, and urinary extraction of glycine, histidine, and serine may be seen in NS.\textsuperscript{2,3}
Metabolic tests, including blood levels of biotinidase enzyme, were conducted on our patient,
and the results were normal (Table I). Wiskott-Aldrich syndrome includes thrombocytopenia
and normal/low B and T cell levels.\textsuperscript{7}

ILC is described as erythematous patches with two distinct features: it represents typically
double-edged scales at the periphery of the lesions and it is migratory. ILC is rarely an isolated
clinical manifestation; it is mostly included in NS with congenital ichthyosiform erythroderma,
trichorrhexis invaginata (TI), and atopic manifestations.\textsuperscript{8,9} We examined ILC in our patient
(Figs. 3A, 3B, and 4A), and his parents described a migratory appearance of the lesions. Guerra
et al.\textsuperscript{10} described two cases of ILC without congenital erythroderma, trichorrhexis invaginata,
and symptoms of atopy and claimed ILC may be an isolated sign of NS. Hair anomalies, such
as shorth and brittle hair and trichorrhexis invaginata, were absent in our patient, which
highlighted the clinical heterogeneity of NS.
NS can represent urticaria/angioedema.\(^1\) Attacks of urticaria/angioedema were reported in the medical files of our patient. Hazelnut and egg white allergies were defined via laboratory methods, which are summarized in Table I. In addition, we examined eczema in our patient during follow-up visits. Flare-ups of eczema and the need to use topical corticosteroids decreased after acitretin therapy. We found that both ILC and flare-ups of eczema improved during acitretin therapy; however, attacks of urticaria/angioedema did not. We did further consultations with the Department of Pediatric Nutrition and Metabolism, in which a low percentile of both height and weight were found. Whole blood counts, including liver enzymes and blood lipid analyses, were assessed every three months, and no negative effect of acitretin was found.

Our case highlights that a genetic test can be critical for identifying NS. We cannot conclude that this is the definite disease-causing variant. Further investigations like the family genetic testings, and RNA testing are necessary to determine the variant as a mutation. The finding of underlying mutations contributes to the understanding of NS and is instrumental in indicating a specific therapy. Notably, treatment with acitretin has significantly improved both the ILC and eczema in our patient.

References


Figure Legends:

Figure 1A, B: Diffuse erythematous and scaly patches on the body and scalp, in the neonatal period of the patient.

Figure 2A: Red-purple patch on the right half of the face (capillary malformation), beginning from the right upper lip and extending to the upper part of the right cheek to the right temple, in the neonatal period of the patient.

Figure 2B: Capillary malformation in the 4th year of life and erythematous and scaly patches on forehead and scalp, before the treatment with acitretin.

Figure 2C: The same regions as in Figure 2B, after the treatment with acitretin.

Figure 3A: Diffuse erythematous and scaly patches (ichthyosis linearis circumflexa) on trunk and arms before acitretin treatment.

Figure 3B: Diffuse erythematous and scaly patches on the left shoulder and arm before acitretin treatment.

Figure 3C: The same regions as in Figure 3A, after acitretin treatment.

Figure 3D: The same regions as in Figure 3B, after acitretin treatment.

Figure 4A: Diffuse erythematous and scaly patches on the thighs before acitretin treatment.

Figure 4B: The same regions as in Figure 4A, after acitretin treatment.
### Table 1: Clinical and laboratory summary of patient from birth.

<table>
<thead>
<tr>
<th>Age</th>
<th>E %</th>
<th>IgE (IU/ml)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 years old:</td>
<td>8.1</td>
<td>1780</td>
<td>FIPILI/ PDGFRA Mutation: Negative Skin Prick Test: Positive reaction for Hazelnut and Egg white DC: Atopic dermatitis, PIC: HIES? OS?</td>
</tr>
<tr>
<td>2-4 years old:</td>
<td>15</td>
<td>2750</td>
<td>Phadiatop Test: Elevated Serum Specific IgE for Hazelnut and Egg white Anti-gliadin IgA: Negative, Anti-endomysial IgA: Negative DC: Atopic dermatitis, PIC: HIES? OS?</td>
</tr>
<tr>
<td>4 years old until now:</td>
<td>10.9</td>
<td>3420, 7.1</td>
<td>SPINK5 mutation: Positive. DC: NS, PIC: NS.</td>
</tr>
</tbody>
</table>

Abbreviations: Eosinophil: E, Dermatological consultation: DC, Pediatric Immunology consultation: PIC, Hyper IgE syndrome: HIES, Ommen syndrome: OS, Netherton syndrome: NS.