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Netherton syndrome: report of identical twins presenting with severe atopic dermatitis

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Abstract We report the cases of 4-year-old identical twin sisters who presented with severe atopic dermatitis with intractable skin manifestations and multiple food allergies. Netherton syndrome (NS) (OMIM 256500) was suspected due to very high serum IgE levels, growth retardation, severe food allergies and typical hair finding (trichorrhexis invaginata). A definite diagnosis was made by genetic analysis. Our cases are unique in being the first identical twins with NS diagnosed by a novel mutation in the *SPINK5* gene. NS should be considered in differential diagnosis in children who have generalized erythema with intractable eczematous lesions and elevated levels of IgE.

Keywords Atopic dermatitis · Children · Netherton syndrome · Trichorrhexis invaginata

Abbreviations CIE: Congenital ichthyosiform erythroderma · ILC: Ichthyosis linearis circumflexa · LEKTI: Lymphoepithelial Kazal-type related inhibitor · NS: Netherton syndrome · TI: Trichorrhexis invaginata

Introduction

Comel-Netherton syndrome is a rare autosomal recessive disorder that was first described by Comel in 1949 [6] and

later by Netherton in 1958 [17]. Netherton syndrome (NS) (OMIM 256500) is characterized by congenital ichthyosiform erythroderma (CIE) or ichthyosis linearis circumflexa (ILC), hair shaft abnormalities and atopic diathesis (elevated serum IgE and allergy). Other features include failure to thrive, enteropathy, hypoalbuminemia, amino aciduria, mental retardation, hypernatraemic dehydration and recurrent infections.

Netherton syndrome can be incorrectly diagnosed as atopic dermatitis due to the presence of eczematous skin lesions and allergic problems; serum IgE levels in NS patients are not very high early on. In this report we present two identical twin sisters with NS who had been treated for an extended period of time for atopic dermatitis with intractable skin manifestations and multiple food allergies. These two cases are unique in being the first identical twins with NS diagnosed by a novel mutation in the *SPINK5* gene.

Case report

Four-year-old twin sisters were referred to our clinic with intractable pruritus, scaling dry skin and generalized eczematous lesions resistant to atopic dermatitis therapy. They were born by caesarean section at the 36th week of gestation after an uneventful pregnancy to healthy unrelated parents. Their history revealed that shortly after birth they were treated for desquamative skin disease. During the following 9 months the desquamation resolved, but they subsequently developed generalized, pruritic, erythematous lesions. They were treated with emollients, topical steroids and tacrolimus creams for severe atopic dermatitis during the next 3 years. At 1 year of age, serum IgE levels were 624 IU/ml and 514 IU/ml, respectively. Hen's egg and cow's milk allergies were diagnosed by high serum specific IgE levels and the patients were put on an elimination diet. No clinical response was obtained. At 3 years of age they were examined by gastroduodenal endoscopy due to growth retardation and constipation. The endoscopic and histological findings were non-specific.

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On physical examination, their skin was xerotic, and there were erythematous scaly patches on the scalp, face and especially on the extremities (Fig. 1). The localization of the eczematous lesions was not typical for atopic dermatitis. They had dry and short scalp hair, especially in the occipital and temporal areas. The eyebrows and eyelashes were sparse, and their nails, teeth, palms, soles and mucosal surfaces were intact. Their height and weight were below the third percentile. They had no psychomotor retardation and the remaining physical examination was normal.

Histological examination of their skin biopsy specimens showed superficial dermatitis with minimal hyperkeratosis, hypergranulosis and acanthosis. Light microscopic examination of their hair and eyebrows showed trichorrhexis invaginata (TI) (Fig. 2).

Biochemical tests and serum folate, iron, vitamin B12 and zinc levels were normal as were the urinary amino acid analysis and serum biotinidase level. Serum levels of immunoglobulins (IgA, IgG, IgM, IgG subclasses) and complements (C3, C4) lymphocyte subset counts (CD3, CD4, CD8, CD14, CD19, CD56) were within normal limits. Neutrophil functions (nitroblue tetrazolium test, chemotaxis, phagocytosis and respiratory burst) were intact. Serum anti-gliadin IgA and IgG, anti-endomysium IgA, ANA, anti-dsDNA and anti-HIV tests were negative. Thyroid hormone levels and autoantibodies were within normal limits.

The patients had serum eosinophilia and high serum total IgE levels (27,247 IU/ml and 24,300 IU/ml, respectively). Specific cow's milk and hen's egg IgE levels were above normal values.

Genomic DNA was extracted from the peripheral blood of the patients with informed consent. Exons 1–33 and the exon-intron boundaries of the *SPINK5* gene were amplified from the submitted genomic DNA by PCR. A bi-directional sequence was obtained and analyzed until a disease-causing mutation was identified. The homozygous mutation c581_82delGT in exon 7 of the *SPINK5* gene was detected in both patients. At the protein level the mutation is denoted p.Cys194fsX4 (GeneDx, Gaithersburg, Md.).



Fig. 1 Facial appearance, hair and cutaneous findings of the twins



Fig. 2 Light microscopic examination of the children's hair and eyebrows showing trichorrhexis invaginata

Discussion

Netherton syndrome is the only disorder of ichthyosis that presents with elevated serum IgE levels [19]. The syndrome consists of ichthyosiform dermatosis, hair shaft defects and atopic manifestations [7, 8, 21]. Because of atopic-like skin involvement and mildly elevated IgE levels at the beginning of the disease, NS can be misdiagnosed as atopic dermatitis, which can lead to inappropriate treatments. Misdiagnosis is very common, especially when specific features, such as the short hair, are not yet evident.

There are two clinical variants based on the skin manifestations; these are known as the CIE-type and ILC-type [19]. Most patients present at birth or soon thereafter with generalized erythroderma and scaling resembling CIE. The other presentation, polycyclic migrating plaques with characteristic double-edged scales [7], denoted as ILC, is one of the pathognomonic features of NS. It often does not become evident until after the first year of life [4]. The CIE pattern may later evolve into ILC [3]. ILC did not develop in our two patients in the 4 years since birth.

Patients with NS have short, brittle hairs, and their scalp usually has a thick scale. The diagnostic hair defect is TI; however, it is not always present and, if suspected, it is important to repeat light microscopic examinations of the hair to confirm the diagnosis [7]. As the hairs in the eyebrows are more frequently affected than scalp hairs, examination of eyebrow samples will be more useful [7]. In addition to TI, trichorexis nodosa and/or pili torti can also be seen [7, 8].

Various atopic manifestations and imbalance of the immune system, such as elevated serum IgE levels, eosinophilia or allergic reactions to various foods (e.g. eggs, fish, nuts), can be found in patients with NS [19, 25]. In 30% of the patients atopic manifestations, such as atopic dermatitis-like skin lesions [25], allergic rhinitis, urticaria, angioedema and asthma, are present [22, 24]. To our knowledge, our patients have the highest IgE levels among NS cases previously published.

The other inconsistent features associated with NS are delayed growth and development, amino aciduria, mental retardation, hypoalbuminemia, non-specific immune ab-

Table 1 Diagnostic features of erythrodermas (adapted from [12, 18, 19]) (N normal)

	Alopecia	Total IgE (IU/ml)	Atopic diathesis	Mental retardation	Recurrent infection	Failure to thrive	Amino aciduria	Zn	Biotinidase	Response to steroids
NS	+ ^a	100 to >10,000	+	Sometimes	+	+	+	N	N	–
Severe atopic dermatitis	+	Less than NS	+	–	–	–	–	N	N	+
Acrodermatitis enteropathica	+	N	–	–	+	+	–	Low	N	–
Biotinidase deficiency	+	N	–	–	+	+	–	N	Low	–
Leiner's disease	–	N	–	–	+	+	–	N	N	–
Hyper IgE syndrome	–	>2,000	Rarely	–	+	+	–	N	N	–
Secretory IgA deficiency	–	High	+	–	+	+	–	N	N	–
Wiscott-Aldrich	–	High	+	–	+	+	–	N	N	–
Omenn syndrome	+	High	–	–	+	+	–	N	N	%50 +

^aWith TI by microscopic examination under polarized light

normalities and enteropathy [7, 10, 27]. The common complications that can be seen at the neonatal period are a tendency to hypernatraemic dehydration and failure to thrive [27]. Delayed growth and development were the only additional features in our patients among those listed above.

The NS gene was assigned to chromosome 5q32 by linkage analysis and homozygosity in 20 families. NS has been identified as a disease caused by a mutation of the *SPINK5* gene that encodes lymphoepithelial Kazal-type-related inhibitor (LEKTI) (23). Chavanas et al. described 11 different mutations in *SPINK5* in 13 families with NS [5, 24]. Decreased LEKTI activity may also influence the development of allergic diseases [13, 16]. It has recently been reported that polymorphisms in exon 13 and exon 14 of *SPINK5* are associated with atopy, asthma and atopic dermatitis in adults [15, 20, 26] as well as asthma in children [13]. The frame shift mutation found in our cases has not been published previously.

The diagnostic features of NS are helpful in making a differential diagnosis with other types of erythrodermas (Table 1). Petechiae and purpura due to thrombocytopenia are typical signs in Wiskott-Aldrich syndrome; diarrhoea and vesiculobulbous lesions distributed in a periorificial and acral pattern on the face, the scalp, the hands, the feet and the anogenital areas are typical signs in acrodermatitis enteropathica; diarrhoea and periorificial eczematous eruption are typical signs in biotinidase deficiency. In contrast to these conditions, NS presents with hair shaft anomalies such as TI and others [18]. Although hyper-IgE syndrome had to be considered as one of the initial differential diagnosis of NS for our patients, it was excluded due to the absence of recurrent infections, especially cold abscesses, typical face appearance, defective neutrophil chemotaxis and dental or skeletal anomalies [11, 14].

Trichothiodystrophy (OMIM 601675) should also be considered in the differential diagnosis of NS. Clinical expression is variable, although abnormalities are generally noted from birth. The characteristic hair-shaft defect in trichothiodystrophy is a transverse fracture called trichoschisis. Other possible associated features in this syndrome that are not seen in NS include ungeal dysplasias, bilateral cataract, defective teeth and pulmonary bronchiectasis [2, 9].

The twins reported here, who were treated for atopic dermatitis for 4 years, had the characteristic clinical features of NS: the typical hair shaft defect characterized by TI, extremely high total IgE and food allergies as atopic features and ichthyosiform erythroderma with eczema resistant to atopic dermatitis therapy. They also received topical tacrolimus treatment, which is commonly used in atopic dermatitis. However, topical tacrolimus should be avoided in NS due to its increased absorption and toxicity [1].

In our opinion, NS should be considered in the differential diagnosis in children who have generalized erythema with intractable eczematous lesions and elevated levels of IgE, even though the characteristic features, such as TI and ILC, are not yet evident.

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