

## Two siblings with Netherton syndrome

Selma EMRE<sup>1</sup>, Ahmet METİN<sup>1</sup>, D. Deniz DEMİR SEREN<sup>1</sup>, Ahu YORULMAZ<sup>1</sup>, Aykut ONURSEVER<sup>2</sup>,  
Burçin KAFTAN<sup>1</sup>

**Aim:** Netherton syndrome (NS) is a rare genodermatosis characterized by autosomal recessive inheritance pattern, unknown etiology, ichthyosiform cutaneous changes, atopic diathesis, and alterations in the hair shaft. As a result of aging coupled with immune deficiency, clinical symptoms may vary. Herein, we present 2 siblings with the characteristic cutaneous symptoms of NS, albeit with some differences between the siblings.

**Materials and methods:** Two sisters presented to our clinic with sparse and brittle hair along with pruritic, erythematous, and scaling cutaneous lesions. Both patients underwent a clinical examination and laboratory analyses.

**Results:** Based on the clinical and laboratory findings, both patients were diagnosed with Netherton syndrome.

**Conclusion:** The cases were reported because of the rarity of the disorder and simultaneous occurrence in 2 siblings, while aiming to highlight the variable nature of the clinical manifestations

**Key words:** Netherton syndrome, atopic diathesis, siblings, ichthyosis linearis circumflexa, trichorrhhexis invaginata

### Netherton sendromlu kardeş olgular

**Amaç:** Netherton sendromu (NS), iktiyoziform deri değişiklikleri, kıl shaftı anomalileri ve atopik diatez ile karakterize, nadir görülen otozomal resesif geçişli bir hastalıktır. Yaşın ilerlemesi ile birlikte özellikle immün yetmezliğin de etkisi ile klinik bulgularında değişiklikler olmaktadır. Burada farklı klinik özelliklere sahip NS lu 2 kardeş hastanın sunulması amaçlandı.

**Yöntem ve gereç:** Yaşları 13 ve 14 olan 2 kız kardeş polikliniğimize, seyrek kırılğan saçlar, kaşıntılı, kepekli, eritemli cilt lezyonları ile başvurdu. Her 2 kız kardeşe, klinik muayene ve laboratuvar incelemeleri yapıldı.

**Bulgular:** Klinik ve laboratuvar incelemeler sonucunda her 2 hastaya da Netherton sendromu tanısı konuldu.

**Sonuç:** NS nun aynı anda 2 kardeşte birden görülmesinin nadir olması nedeniyle ve farklı klinik özelliklerinin de olabileceğini vurgulamak amacıyla bildirilmesi uygun görüldü.

**Anahtar sözcükler:** Netherton sendromu, atopi, akrabalık, iktiyozis linearis sirkumflexa, trikoreksis invajinata

### Introduction

Netherton syndrome (NS) is a rare disorder characterized by autosomal recessive inheritance pattern, unknown etiology, ichthyosiform cutaneous changes, atopic diathesis, and alterations in the hair shaft. Its incidence is estimated to be 1/200,000. It has been reported that 18% of all congenital erythrodermas might represent NS (1). The disease was first described by Comel (2) in 1949 as double-edged desquamation in the periphery of erythematous and squamous lesions with

Received: 30.04.2009 – Accepted: 15.10.2009

<sup>1</sup> Department of Dermatology, Atatürk Training and Research Hospital, Ankara - TURKEY

<sup>2</sup> Department of Pathology, Atatürk Training and Research Hospital, Ankara - TURKEY

**Correspondence:** Selma EMRE, Mehmet Akif Ersoy Mah., Urankent Sitesi E 2 Blok Daire:13, Yenimahalle, Ankara - TURKEY  
E-mail: dr\_sembre@yahoo.com

serpiginous and polycyclic margins and called ichthyosis linearis circumflexa (ILS). Later, in 1958, Netherton (3) reported an association of hair shaft anomalies and congenital ichthyosiform erythroderma (CIE) in a 4-year-old female patient. Wilkinson et al. (4) described this hair shaft anomaly as trichorrhexis invaginata in 1964.

Other common features of the disease are enteropathy, hypoalbuminemia, aminoaciduria, mental retardation, growth retardation, and immunologic abnormalities. While ichthyosiform erythroderma presents as ILS in the majority of NS cases, rarely it may be in CIE form. Hair shaft anomalies comprise trichorrhexis invaginata, pili torti, and/or trichorrhexis nodosa (5).

Herein we present 2 siblings with the characteristic cutaneous symptoms of NS, albeit with some differences between the siblings.

### Case 1

A 14-year-old girl presented to our polyclinic with pruritus of the face and feet, skin desquamation, and sparse and thin hair. Dermatological examination demonstrated brittleness and scaling of the hairs, eyebrows, and eyelashes; erythema and desquamation of the cheeks; pinkish-red macules with scales; hypopigmented macular lesions on the ichthyosiform skin involving the area beginning from the patella and extending to the distal part of the leg; and lichenified, erythematous plaques with patchy fissures in both antecubital and popliteal regions. Subungual hyperkeratosis, discoloration, and destruction were noted in the toe nails (Figure 1). Microscopic examination of the material collected from the nails showed no fungal components.

Laboratory analyses yielded normal results except for a leukocyte count of 11,300/ $\mu$ L and a total IgE of 467 IU/mL. The patient, who was complaining of ear pain, was diagnosed with otitis media following a pediatric examination and antibiotic therapy (amoxicillin-clavulanic acid 2  $\times$  675 mg/day) was started.

### Case 2

A 13-year-old girl presented to us with pruritus of the face and feet, skin desquamation and lack of hair growth and sparse hair. Dermatological examination revealed thinning and sparseness of the hair and eyebrows, erythema and patchy scaling in the perioral area and face, and pinkish-red macular lesions with white scales on the dorsa of both feet. Both legs had diffuse ichthyosis; patchy, hypopigmented, 1-2 cm macules; and lichenified, erythematous plaques with patchy fissures in both antecubital and popliteal areas (Figure 2). Ocular examination of the patient was normal and she had no dental anomaly other than an orthodontic problem.

Laboratory results showed an IgE value of 720 IU/mL and cow's milk allergy was detected in the specific IgE studies. Urinalysis, performed because of polyuria, revealed 149/hpf leukocyte, +3 leukocyte esterase count. Systemic antibiotic therapy (ceftriaxone 1 g/day) was initiated with a diagnosis of urinary tract infection. Bone age and chronological age were found to be consistent in the bone radiography. A pediatric psychiatry consultation revealed mild mental retardation and attention deficit and hyperactivity disorder.

Cutaneous lesions in both patients had started within the first month following birth. Both siblings had growth retardation (below the 3rd percentile). Histopathological evaluation of skin biopsies collected from the patients demonstrated severe hyperkeratosis, psoriasiform-type acanthosis, and focal spongiosis in the epidermis; and perivascular lymphocyte infiltration in the dermis (Figure 3). A trichogram test displayed trichorrhexis nodosa and whisk hair abnormalities (Figure 4).

In light of those findings, the patients were diagnosed with Netherton syndrome. Cutaneous lesions were treated with topical moisturizers and topical corticosteroid ointments. Keratolytic agents were prescribed for the hyperkeratotic areas.



Figure 1. First patient: Perioral erythema, scaling, sparse hair, eye lashes, and eye brows (A). Erythematous, fissured, lichenified plaques on the ankle and dorsum of the feet (B,C). Nail dystrophy and subungual hyperkeratosis of the toes (D).



Figure 2. Image of the second patient showing the hair, eye brows, and eye lashes; also perioral region (A), erythematous and squamous plaques on the legs (B), elbows (C), and hands (D,E).

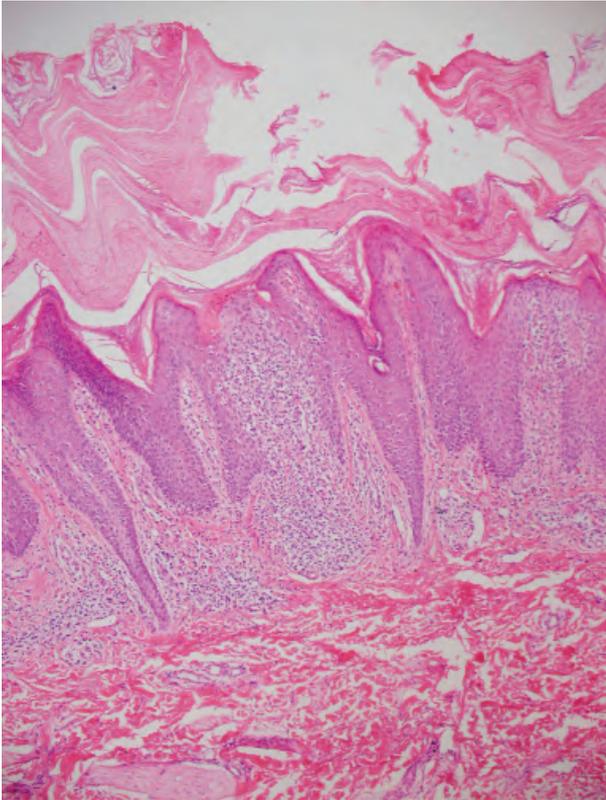


Figure 3. Severe hyperkeratosis, psoriasiform acanthosis, and focal spongiosis seen in the epidermis. (HE  $\times 100$ ).

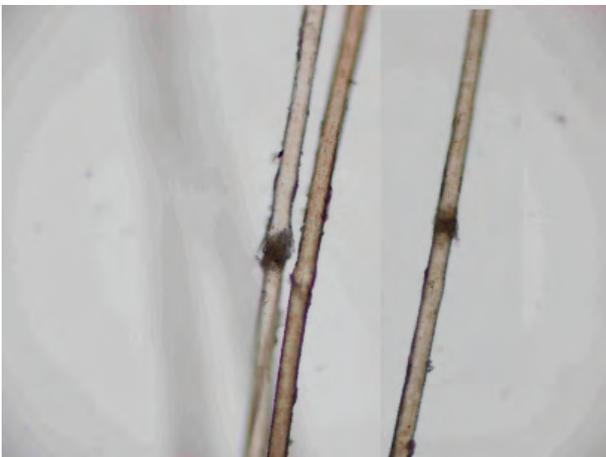


Figure 4. The trichogram; whisker hair abnormality.

## Discussion

NS is a rare type of ichthyosis with an autosomal recessive inheritance pattern. In the current report, we present 2 sisters with NS with a negative familial history and no parental consanguinity. The disease is characterized by the triad of ichthyosis, structural hair shaft anomalies, and atopy. In NS, while ichthyosiform erythroderma is seen as ILS, rarely it may occur as CIE. Hair shaft anomalies include trichorrhexis invaginata, pili torti, and/or trichorrhexis nodosa (5). Our patients had sparse, brittle, and markedly thin hair alongside trichorrhexis nodosa and bamboo-like growths in the hair shaft. At birth, erythroderma or collodion baby may be present. Our patients had no history of erythroderma or collodion baby. While ILS is the major diagnostic skin finding, these double-edged desquamative lesions appear from time to time and may not be present during the examination. Classical ILS lesions do not occur in infancy or early childhood. Erythroderma is usually present at birth, but characteristic hair symptoms may appear late due to delayed growth of hair (6). There was no history of previous NS diagnosis in the family; therefore there was a delayed diagnosis of NS. Shah and Marfatia (7) reported 2 NS sisters with similar characteristics in 2007. While our both patients had typical dermatologic symptoms of NS, in contrast to her sister, the second patient demonstrated mental retardation, attention deficit and hyperactivity disorder, and cow's milk allergy. Since NS is known to have a course with varying clinical symptoms, the presence of different clinical manifestations in 2 siblings was remarkable.

Aminoaciduria, growth retardation, and disorders in the cellular arm of the immune system may be observed in some patients with NS. Susceptibility to bacterial infections is increased in affected patients (8). Our patients had a history of frequent infections, while, on examination, we diagnosed otitis media in one sister and urinary infection in the other. Some immunological abnormalities have been reported in patients with NS. IgE level is usually raised. Stryk et al. (8) reported a selective antibody deficiency against bacterial polysaccharide antigens. Cytokine analyses performed with a limited number of patients with NS showed that IgE production is not dependent on only

one factor among those patients, but has a variable and complex pattern (6).

As pointed out in the pediatric psychology assessment of the younger sister, some patients may exhibit mild or moderate level mental retardation (4).

NS is associated with the mutation in the SPINK5 gene, which codes LEKTI (lymphoepithelial Kazal-type related inhibitor), a serine protease inhibitor. LEKTI is expressed in epithelium, mucosa, and thymus. It is localized in the stratum granulosum of normal skin. Ong et al. (9) conducted a study in 4 patients with NS and showed that LEKTI was either not present or stained at a considerably reduced level. However, LEKTI has been shown to stain positively in the skin of a control group comprising psoriasis,

atopic dermatitis, and nonbullous erythroderma cases.

Treatment alternatives include keratolytics, topical corticosteroids, retinoids, and PUVA. Since the barrier function of the skin is disrupted in NS, use of topical tacrolimus for atopic dermatitis should be carefully evaluated due to the significant systemic absorption risk (5,10). Both patients were treated with topical moisturizer and keratolytic ointments, barrier creams, and protein-rich diets, and they were treated for infectious diseases. At the end of a 1-month follow-up period, the patients' lesions were observed to have regressed due to the applied dermatologic treatment and skin care, while the infections were found to have healed.

## References

1. Bitoun E, Chavanas S, Irvine AD, Lonie L, Bodemer C, Paradisi M et al. Netherton syndrome: disease expression and spectrum of SPINK 5 mutations in 21 families. *J Invest Dermatol* 2002; 118: 352-361.
2. Comel M. Ichthyosis linearis circumflexa. *Dermatologica* 1949; 98: 133-6.
3. Netherton EW. A unique case of trichorrhexis nodosa – bamboo hairs. *Arch Dermatol* 1958; 78: 483-7.
4. Wilkinson RD, Curtis GH, Hawk WA. Netherton's disease: Trichorrhexis invaginata (bamboo hair), congenital ichthyosiform erythroderma and the atopic diathesis. A histopathologic study. *Arch Dermatol* 1964; 89: 46-52.
5. Erdoğan AG, Balaban D, Derviş E, Karaoğlu A. A case of Netherton syndrome associated with aminoaciduria. *Turkderm* 2006; 40: 108-10.
6. Gysel DV, Koning H, Baert MRM, Savelkoul HFJ, Neijens HJ, Oranje AP. Clinico-immunological heterogeneity in Comel-Netherton syndrome. *Dermatology* 2001; 202: 99-107.
7. Shah D, Marfatia YS. Netherton's syndrome in two sisters. *Indian J Pediatric Dermatol* 2007; 10: 54-55.
8. Stryk S, Sieghfried EC, Knutsen AP. Selective antibody deficiency to bacterial polysaccharide antigens in patients with Netherton syndrome. *Pediatric Dermatol* 1999; 16: 19-22.
9. Ong C, O'Toole EA, Ghali L. LEKTI demonstrable by immunohistochemistry of the skin: a potential diagnostic skin test for Netherton syndrome. *Br J Dermatol* 2004; 151: 1253-57.
10. Allen A, Siegfried E, Silverman R, Williams ML, Elias PM, Szabo SK et al. Significant absorption of topical tacrolimus in 3 patients with Netherton syndrome. *Arch Dermatol* 2001; 137: 747-50.