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Case Report

A 6-Month-Old Boy with Reddish, Scaly Skin: Netherton Syndrome

Fatma Derya Bulut[1], Deniz Kör[1], Berna Şeker Yılmaz[1], Mustafa Yılmaz[2], Derya Ufuk Altıntaş[2], Serdar Ceylaner[3], Sebile Kılavuz[1], Neslihan Önenli Mungan[1]

[1]Çukurova University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Metabolism and Nutrition, Adana, Turkey
[2]Çukurova University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Allergy and Immunology, Adana, Turkey
[3]Intergen Genetic Laboratory, Ankara, Turkey

ABSTRACT

Typical features of Netherton syndrome are congenital ichthyosiform erythroderma, atopic diathesis and trichorrhexis nodosa. Here in this report, we present a case with congenital ichthyosis with atopy presenting later. We wanted to discuss the importance of whole exome sequencing to diagnose the atypical presentations of common syndromes.

Keywords: Ichthyosis, erythroderma, Netherton syndrome, atopy, whole exome sequencing

Introduction

Netherton syndrome (OMIM #256500) is an autosomal recessively inherited syndrome, first described by Netherton (1). Netherton syndrome is caused by homozygous or compound heterozygous mutations in the *SPINK5* gene, which encodes the serine protease inhibitor LEKTI (lympho-epithelial Kazal-type-related inhibitor), on chromosome 5q32 (2). Clinical features are congenital ichthyosiform erythroderma, atopic diathesis and specific bamboo hair appearance (3). Less than a hundred cases have been reported so far. However, atypical cases make the diagnosis difficult. We present a case of Netherton syndrome with congenital ichthyosis with atopy presenting later.

Case Report

A six-month-old boy was admitted to our hospital due to dry, reddish, scaly skin and failure to thrive. He was born by caesarean section at 38 weeks gestational age to a 26-year-old, G1P1, healthy woman. He weighed 2900 gr (appropriate for gestational age). He had respiratory distress soon after birth, was diagnosed with neonatal pneumonia and stayed at the neonatal intensive care unit for 15 days. His skin findings started when he was 1 week old and became worse in time, although the family applied some skin ointments and zinc suspensions. He was breastfed supplemented with infant formula. He had loose stools but did not have chronic diarrhea. The patient's parents were first degree cousins, other than this, his family history was unremarkable.

On physical examination, weight, height and head circumference were 3500 gr, 52 cm and 39 cm respectively (all below the third percentile for his age). His general appearance was well, he had normal motor and mental development. He had generalized, scaly erythroderma (Figure 1, informed consent was taken from patient's legal guardians). On auscultation, he had normal respiratory sounds, normal heart rate and no murmur. He had mild

Address for Correspondence
Fatma Derya Bulut MD, Çukurova University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Metabolism and Nutrition, Adana, Turkey
Phone: +90 532 743 27 18 E-mail: dozduran@cu.edu.tr ORCID ID: orcid.org/0000-0003-0529-2404
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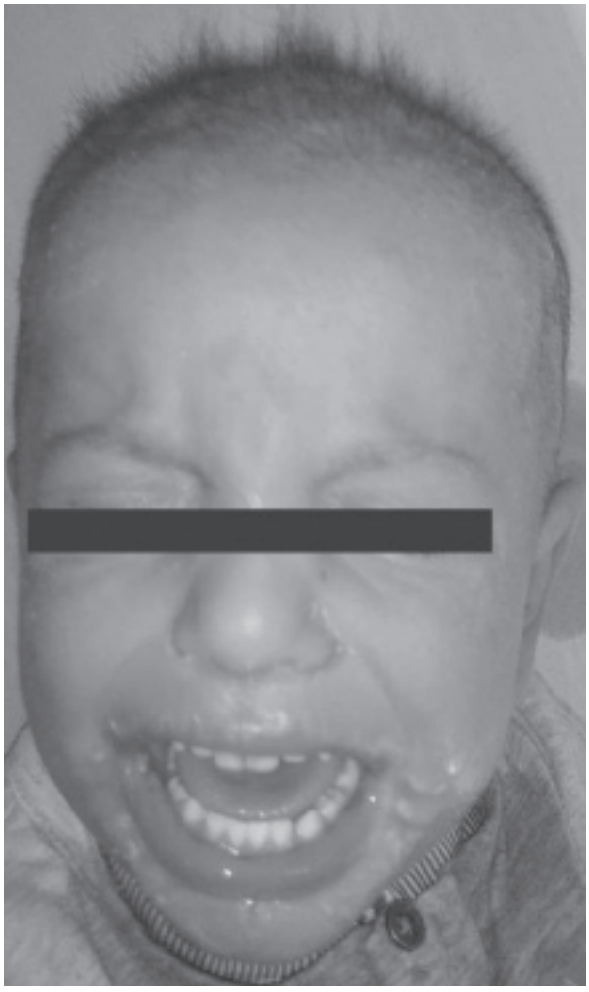

Figure 1. Scaly ichthyosiform erythroderma of patient's face, without apparent bamboo hair appearance

hepatosplenomegaly. He had no limb anomaly. He had sparse eyebrows and sparse scalp hair.

On laboratory investigation, the patient had mild anaemia (hemoglobin: 9.64 g/dL, hematocrit: 29.9%), normal liver transaminases (aspartate aminotransferase: 26 IU/L, alanine aminotransferase: 17 IU/L) and hypoalbuminemia (albumin: 2.3 g/dL). Thyroid function tests, anti-tissue transglutaminase and anti-endomysial antibodies were within normal limits for age. Serum immunoglobulin E (IgE) level was 841 IU/mL (normal: 10-180). Other Ig levels were within reference range for age (IgG: 1315 IU/mL, IgA: 127 IU/mL, IgM: 351 IU/mL). In order to investigate the underlying atopy, a skin prick test was done and revealed negative. The peripheral blood smear showed the prominence of eosinophilia (absolute eosinophil count: 12%). Differential diagnoses for this infant were autosomal recessive lamellar ichthyosis and harlequin ichthyosis. For autosomal recessive congenital ichthyosis and harlequin ichthyosis, molecular analyses of *TGM1*, *NIPAL4* and *ABCA12* genes were all normal. Since he had mild hepatosplenomegaly along with the skin findings, Gaucher disease Type II was suspected but molecular analysis of the *GBA* gene was normal. For a definite diagnosis, a whole exome sequencing was performed and detected a known, disease causing homozygous mutation in *SPINK5* gene [IVS2+5G>T (c.81+5G>T)]. The diagnosis was Netherton syndrome. Although the patient had a negative skin prick test, food specific IgE panel revealed that plasma levels of egg white specific IgE, milk specific IgE and wheat specific IgE were all high (65.5, 8.51 and 38.7 kUA/L respectively). Milk, wheat and egg white were all eliminated from his diet and his skin condition improved in the course of time. Food challenge tests for milk, wheat and egg white were all positive and these three foods were permanently eliminated from the diet. Concurrently, microscopically, his hair exhibited the typical bamboo hair appearance gradually and erythroderma resolved with the restricted diet. Netherton syndrome (OMIM #256500) is an autosomal recessive disorder, characterized by congenital ichthyosiform erythroderma, atopic diathesis and trichorrhexis nodosa (3). Rarely collodion babies are seen. The disorder is commonly confused with atopic dermatitis but does not respond to topical corticosteroid treatment (4). In the beginning, our patient was suspected of atopy but he had a negative skin prick test. Subsequently, food specific IgE panel and food challenge tests revealed the atopy. The false negative skin prick test was attributed to ichthyosis. Rarely, progressive and fatal hypernatremic dehydration may be seen in infants. In our patient, due to a coincidental neonatal pneumonia, our patient was well-hydrated in the neonatal intensive care unit and hypernatremic dehydration was not seen. His malnutrition, hypoalbuminemia and iron deficiency anaemia were attributed to enteropathy which is consistent with the syndrome (5). Diagnosis may be delayed beyond the neonatal period until the appearance of the pathognomonic bamboo hair anomaly which may also be recognized along the disease course (5). Under a light microscope, hair showing nodular trichorrhexis is diagnostic (the distal area of hair invaginates toward its proximal area). The histological findings of skin biopsy are frequently non-characteristic thinning of the granular layer and stratum corneum, psoriasiform hyperplasia and less common compact parakeratosis with large nuclei, subcorneum or intracorneum splitting, presence of clear cells in the upper epidermis or stratum corneum, dyskeratosis, dermal infiltrate with neutrophils and/or eosinophils and dilated blood vessels in the superficial dermis (6). On transmission electron microscopy, immature lamellar granules are observed between keratinocytes (7). Another non-invasive diagnostic method is molecular analysis of the *SPINK5* gene, this provides a genetic counselling opportunity to the family. Treatment is symptomatic and requires prompt management of the neonatal complications such as fluid and electrolyte management, an elimination diet to prevent atopic dermatitis and long-term use of emollients and/or topical immunomodulators for amelioration of the skin disorder (7,8). Some patients responded to ammonium lactate lotion, the per oral retinoid and psoralen plus ultraviolet A therapy. The prognosis may be severe in neonates with life-threatening complications like recurrent dermal infections, fluid and

electrolyte abnormalities and postnatal lethality is high. The skin manifestations and hair anomalies persist throughout life, but the disease usually improves with age and most patients begin to thrive during the second year of life (6,7).

Discussion

More than a hundred conditions are described relating to ichthyosis. It is important to make the specific diagnosis by detecting features other than skin findings in order to establish proper treatment, predict the prognosis and also provide genetic counselling for the family. Molecular studies can be helpful in making an accurate diagnosis and are also non-invasive.

Ethics

Informed Consent: Informed consent was taken from patient's legal guardians.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.D.B., N.Ö.M., Concept: F.D.B., N.Ö.M., Design: F.D.B., M.Y., D.U.A., N.Ö.M., Data Collection and Processing: F.D.B., Analysis and Interpretation: S.C., Literature Search: S.K., D.K., B.Ş.Y., Writing: F.D.B., S.K., D.K., B.Ş.Y., M.Y., D.U.A., S.C., N.Ö.M.

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