CASE REPORT

Constellation of signs and symptoms revealed a diagnosis of "Comel - Netherton Syndrome" in a case previously treated as Atopic Dermatitis: a case report

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ABSTRACT

Netherton Syndrome is a rare autosomal recessive (AR) inherited congenital disorder caused by a mutation in the SPINK5 gene (Serine Peptidase Inhibitor Kazal Type 5) found on Chromosome 5. It is a clinical diagnosis consisting of a triad: Widespread ichthyosiform erythroderma which may develop into 'ichthyosis linearis circumflexa, abnormal-looking scalp hair -Trichorrhexis Invaginata and Atopic dermatitis. Patients are born encased in a skin membrane (collodion baby). One-third of the babies have fatal complications such as failure to thrive, bronchopneumonia and sepsis. Laboratory investigation shows high levels of IgE in addition to eosinophilia. There is no cure for Netherton Syndrome unless applying emollients, topical antibiotics and topical steroids that help prevent exacerbations and fatal complications.

We are presenting a case of a 6-year-old female who was being treated as a case of atopic dermatitis since birth. She fulfilled the criteria to diagnose Netherton Syndrome: Ichthyosis linearis circumflexa, Trichorrhexis Invaginata and Atopic dermatitis with markedly elevated IgE levels.

KEYWORDS: Netherton syndrome; Trichorrhexis invaginata; Ichthyosiform erythroderma

INTRODUCTION

Comel, an Italian dermatologist, first described the clinical features of ichthyosis linearis circumflexa in 1949. Netherton, an American dermatologist discovered a hair shaft abnormality that he termed "bamboo hair "and later defined as Trichorrhexis Invaginata in 1958. Wilkinson et al delineated the triad of congenital ichthyosis, Trichorrhexis Invaginata and Atopy as "Netherton Syndrome" in 1964.[1]

Netherton syndrome(NTS) is a rare inherited autosomal recessive disorder of cornification that occurs worldwide, with a higher prevalence in inbred populations. The incidence of NTS reaches as high as 1 in 100,000 to 200,000 live births. It was later recognized that NTS include different cutaneous presentations and manifestations such as continuous skin peeling, ichthyosiform erythroderma and localized Ichthyosis linearis circumflexa.

NTS is caused by biallelic mutations in the SPINK5 gene (Serine Peptidase Inhibitor Kazal Type 5) that is found on chromosome 5.

NTS presents in most of the cases in the neonatal or early infantile period with generalized scaling erythroderma, but not a true collodion-baby phenotype. Neonates with NTS are usually born prematurely and develop the eruption in utero or during the first weeks of life.

About 20% of neonates develop potentially fa-

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tal complications such as failure to thrive which is often profound, perturbed thermoregulation, pneumonia and sepsis. The associated electrolyte imbalance and hypernatremic dehydration that usually require hospitalization for nutritional support and correction are often seen.

NTS presents with the three following characteristics:

Ichthyosiform erythroderma which is described as inflamed, red, scaly skin

Trichorrhexis invaginata ("bamboo hair") is characterized by short, brittle, lustreless hair.

Atopic diathesis that the patient is prone to allergic manifestations and flares.

Individuals with Netherton syndrome may show some or all of these features with varying degrees of severity of their symptoms.

Skin biopsy and DNA testing may also be performed to confirm diagnosis.

Treatment is symptomatic and should be adjusted to the patient's specific needs.

CASE REPORT

We report a six-year-old girl referred to our dermatology clinic with a diagnosis of atopic dermatitis that had been treated since birth.

The patient was treated intensively for severe atopic dermatitis with a variety of topical applications (corticosteroids, TCI, antibiotics and emollients) in addition to several courses of systemic antibiotics during the flare-ups with minimal improvement that kept the patient suffering and interfered with her daily activity.

She presented to her parents who reported a history of intractable pruritus and generalized eczematous lesions resistant to atopic dermatitis therapy.

She complained of generalized migratory serpiginous scaly dry patches over most of the body areas - scalp, face, trunk and extremities. The eczematous lesions were not typical of atopic dermatitis. The napkin area was involved with similar lesions. She had a dry, short, sparse and lustreless scalp hair.

A review of the patient's medical history showed that she was born at term to a 25-year-old mother at 38 weeks gestation following an uncomplicated pregnancy and normal vaginal delivery. Parents were non-consanguinous. Directly after birth, the patient got her first treatment for desquamative skin lesions. During the following months, the desquamation resolved, but the patient developed generalized, pruritic, erythematous lesions. The eruption waxed and waned, but never completely cleared. There was no family history of skin disorders or similar conditions. Allergy tests were negative. There was no history of recurrent infections of the skin, upper respiratory tract, or gastrointestinal tract.

On physical examination, the vitals were stable. The height and weight were normal for her age. Her skin was dry, and there were widespread serpiginous erythematous patches with double-edged peripheral scaling typical of ichthyosis linearis circumflexa on the face, trunk, napkin area and extremities (Fig 1).

The scalp hairs were short, brittle, and sparse. The eyelashes and eyebrows were sparse (Fig 2). The nails looked dry and atrophied with no signs of pitting. The palms, sole and mucosal surfaces were spared. Examination of abnormal hair under the microscope showed defects of the hair shafts with bamboo hair (trichorrhexis invaginata) (Fig 3).

Upon laboratory investigations, blood indices

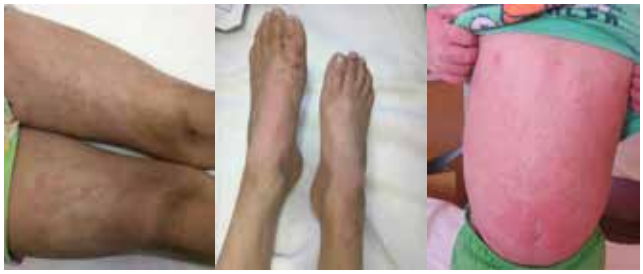

Fig. 1 Widespread serpiginous, erythematous patches with double-edged peripheral scaling typical of ichthyosis linearis circumflexa over multiple sites of the body.

Fig. 2 The scalp hair was short, brittle, and sparse. The eyelashes and eyebrows were sparse

Fig. 3 Trichoscopic examination of the scalp hair showing trichorrhexis invaginata (bamboo hair)

showed marked eosinophilia (absolute eosinophil count of 22,000/mm^3). Biochemical, vitamins, immunoglobulins, and complements were normal. Urinary analysis, thyroid hormone and thyroid autoantibodies were within normal.

The serum IgE levels were extremely high 1780 IU/ml. Serum levels of IgG, IgA, and IgM were normal. Antinuclear antibody (ANA), anti-dsDNA and anti-HIV tests were negative.

A skin biopsy showed psoriasiform epidermal hyperplasia with irregular acanthosis, compact parakeratosis, large nuclei, subcorneal splitting, presence of clear cells in the upper epidermis, dyskeratosis, dermal infiltrate with neutrophils and eosinophils, and dilated blood vessels in the superficial dermis.

The patient received treatment with topical corticosteroids and skin moisturizers. The family was counselled about the diagnosis.

DISCUSSION

Netherton syndrome is an autosomal recessive condition characterized by the triad of congenital ichthyosis linearis circumflexa, trichorrhexis invaginata ("bamboo hair" or "ball and socket" hair shaft deformity), and an atopic diathesis.

It may first appear as severe congenital generalized exfoliative erythroderma at birth or during the first few weeks of infancy, which develops into serpiginous migratory annular and polycyclic patches surrounded by peripheral double-edged scale making the description of ichthyosis linearis circumflexa, generally seen after 2 years of age and occurs in about 70% of the patients. The lesions predominate over the trunk and extremities leaving no atrophy, scarring, or pigmentation. The lesions cause the newborn skin to lose heat, water and proteins, which are all essential for normal growth and development. The general condition manifests as widespread erythroderma and desquamation while some infants are born with a collodion membrane.[2] Pruritus and lichenification are common. The ichthyosiform erythroderma which is the typical manifes-

tation in the neonatal and infantile periods tends to improve with age.

The hair is typically lusterless, dry, sparse, short, spiky, beaded and brittle. Trichorrhexis invaginata of scalp hairs and eyebrows, due to invagination of the distal portion of the hair shaft into the proximal portion, which results from a defect in keratinization of the internal root sheath giving the classical "Bamboo hair" appearance. Which is described as ball and socket hair shaft deformity is pathognomonic for Netherton syndrome.[3] Hair shaft abnormalities usually develop later in infancy or early childhood and are best visualized on trichoscopy or trichogram which facilitates the visualization of the "matchstick" defect.[4] Older patients may suffer from complete or partial loss of eyebrows and eyelashes.

Atopic manifestations are characterized by atopic dermatitis, asthma, hay fever, allergic rhinitis, urticaria, angioedema and often anaphylaxis. NTS patients are prone to developing food allergies, especially to nuts.

Because of the defective skin barrier, recurrent bacterial skin infections are common. During the neonatal period, hypernatremic dehydration, pneumonia, sepsis and failure to thrive are common complications. NTS is often associated with delayed growth, mental retardation, hypoalbuminemia and enteropathies.

There is a positive related family history but in some cases, there is no family history of the trait and NTS is diagnosed when two unaffected parents who are both carriers of the mutated recessive gene have a child who receives both copies of the recessive gene.[5]

Netherton syndrome is caused by germline biallelic mutations in the SPINK5 gene located on chromosome 5q31-32.[6] The loss-of-function mutations in SPINK5 encode the multi-domain serine protease inhibitor (LETKI) which is a lymphoepithelial Kazal-type-related inhibitor. The increase in serine protease activity results in unopposed kallikrein-related peptidase 5(KLK5) and kallikrein-related peptidase 7(KLK7) activities leads to overactivity of elastase 2(ELA2) which ends in a decrease in the desmosomal proteins (desmoglein 1 and desmocollin 1) with premature degradation of corneocyte desmosomes and excessive desquamation.

It is estimated that the condition affects 1 in 100,000 to 200,000 live births. Patients have high levels of serum IgE and hypereosinophilia.[7] histologic examination of skin biopsy sections shows psoriasiform epidermal hyperplasia with irregular acanthosis, hyperkeratosis and parakeratosis.[8] The granular layer is typically absent and Immunohistochemistry using specific antibodies shows absent or reduced lymphoepithelial Kazal-type-related inhibitor (LEKTI).[9] Electron microscopic studies have revealed features that are specific to NTS.

Immunologic abnormalities have been described, suggesting that NTS should be considered a primary immunodeficiency disorder.

NTS should be distinguished from other differential diagnosis list in a newborn with erythroderma and abnormal-looking scalp hair, or in an older child with ichthyosis linearis circumflexa and sparse lustreless hair.[10] Misdiagnosis is usually due to atypical clinical features, absent characteristic cutaneous findings, no clear evidence of hair shaft abnormality and no related family history.

There is no specific or satisfactory treatment for Netherton syndrome. Treatment of NTS is supportive. Treatment aims to manage the symp-

toms and prevent skin infections and fatal complications. Keratolytic creams containing urea, lactic acid or salicylic acid in addition to skin moisturizers keep the skin moist and hydrated and prevent dryness and infection. Other treatment modalities such as topical corticosteroids, topical calcipotriene, topical calcineurin inhibitors, topical retinoids, topical and systemic antibiotics, NB-UVB, and PUVA are the available treatment options.

Oral acitretin and isotretinoin are limitly used but these medications may worsen the skin condition.[11] Understanding the basic pathophysiological changes of the disease will lead to more effective therapeutic modalities in the future.

In our case, the patient had erythroderma and desquamation shortly after birth in addition to classical ichthyosis linearis circumflexa and Trichorrhexis Invaginata, high serum IgE levels and marked hypereosinophilia which made the diagnosis of NTS clear even there was no family history of the syndrome.

The patient was treated with topical corticosteroids and skin moisturizers. The family was counselled about the diagnosis after multiple follow-up visits, her skin lesion showed good improvement over time but residual lesions were noticed on and off. We kept a close follow-up of the patient.

CONCLUSION

Netherton syndrome (NTS) is an autosomal recessive condition that combines ichthyosis, atopy, and hair shaft deformities. NTS is characterized by premature desquamation of the stratum corneum and impairment of the skin barrier. It can be misdiagnosed as atopic dermatitis due to the presence of eczematous lesions in Netherton syndrome and personal or family history of atopy, Skin biopsy and DNA testing may also be performed to confirm diagnosis.

Hair examination should be carried out early to make the correct diagnosis; the appearance of trichorrhexis invaginata is pathognomonic.[12]

There is no cure for Netherton Syndrome. Supportive and symptomatic treatment is highly helpful earlier in the patient's life.

REFERENCES

1. Rook's Textbook of Dermatology. Ed Rook A, Wilkinson DS, Ebling FJB, Champion RH, Burton JL. Fourth edition. Blackwell Scientific Publications.
2. Metze D. Disorders of keratinization. In: Calonje JE, Brenn T, Lazar AJ, et al. McKee's Pathology of the Skin. Elsevier Health Sciences; 2011:61-63.
3. Netherton EW. A unique case of trichorrexis invaginata; bamboo hairs. Arch Derm. 1958; 78:483-487.
4. I. Galadari, J. Al-Kaabi, and H. Galadari, "Netherton syndrome," SKINmed 2003; 2(6): 387-89.
5. Goujon E, Beer F, Fraitag S, et al. "Matchstick" eyebrow hairs: a dermoscopic clue to the diagnosis of Netherton syndrome. J Eur Acad Dermatol Venereol. 2010; 24:740-41.
6. Netherton syndrome: report of identical twins presenting with severe atopic dermatitis. Kilic G, Guler N, Ones U, Tamay Z, Guzel P. Eur J Pediatr. 2006; 165:594-97.
7. Leclerc-Mercier S, Hovnanian A, Fraitag S. Lekti immunochemistry for the diagnosis of netherton syndrome. Am J Dermatopathol. 2012; 34:853.
8. IgE allergen component-based profiling and atopic manifestations in patients with Netherton syndrome. Hannula-Jouppi K, Laasanen SL, Heikkilä H, et al. J Allergy Clin Immunol. 2014; 134:985-88.
9. Netherton syndrome mimicking pustular psoriasis clinical implications and response to intravenous immunoglobulin. Small AM, Cordoro KM. Pediatr Dermatol. 2016; 33:222-23.
10. Hovnanian A: Netherton syndrome. Cell Tissue Res 2013; 351:289.
11. De Felipe, F. J. Vázquez-Doval, and J. Vicente, "Comel-Netherton syndrome. A diagnostic challenge," British Journal of Dermatology 1997; 137(3): 468-69.

12. Lazaridou E, Apalla Z, Patsatsi A, Trigoni A, Ioannides D. Netherton's syndrome: successful treatment with isotretinoin. J Eur Acad Dermatol Venereol. 2009; 23:210-12.

13. Z. Meltem Akkurt, T. Tuncel, E. Ayhan, D. Uçmak, U. Uluca, and H. Uçak, "Rapid and easy diagnosis of Netherton syndrome with dermoscopy," J Cut Med Surg 2014; 18(4): 280-82.