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Case Report

Failure to grow and infections in a baby with Netherton syndrome

鱗樣紅皮病—竹髮—遺傳過敏（Netherton）綜合症嬰兒有生長遲緩及感染問題一例

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We report a Nepalese girl with Netherton syndrome, presenting as erythroderma. The child developed recurrent episodes of infection in her first year of life accompanied by poor physical development and failure to thrive. Gastroenterological studies did not show significant problems. The red skin continued to remain a challenge in management as it was raw and healed poorly except for the ankles and groins. The use of a ceramide-dominant barrier-repair emollient improved the skin condition. The skin barrier dysfunction highlights this child as a more difficult problem in skin dysfunction amongst the ichthyoses.

我們報告一名患有魚鱗樣紅皮病 — 竹髮 — 遺傳過敏綜合症的尼泊爾裔紅皮症女童。女童在首年嬰兒期有著頻繁的感染問題，同時伴有身體發展欠佳及生長遲緩；但腸臟檢查則一切正常。其幼嫩易損的紅皮為治理帶來很大挑戰，除腳踝及腹股溝外，其他的皮損皆不易自然復原。在使用神經醯胺為主的角質層修復潤膚劑後，皮膚情況終得以改善。以上女童的皮膚屏障功能障礙正反映出此病的皮膚失衡為魚鱗症中較為棘手的一類。

Keywords: Failure to thrive, infections, LEKTI, Netherton syndrome, *SPINK5*

關鍵詞：生長遲緩，感染，淋巴 Kazal 型相關的抑製劑，鱗樣紅皮病—竹髮—遺傳過敏綜合症，第五號 Kazal 型絲胺酸蛋白胨抑制因子

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Case report

We report a Nepalese child with Netherton syndrome confirmed by DNA mutation analysis. A newborn girl who was a firstborn was found to have erythroderma at birth. The neonate, who weighed 2578 g, was born by spontaneous vaginal delivery at 37 weeks' gestation. Her parents are of a non-consanguineous marriage.

She had generalised erythematous macular lesions on face, trunk and limbs. Coarse scaling was found at the margins of the lesions (Figure 1). There were no erosions, blisters or pustules. Her mother developed varicella zoster infection in the first trimester. There was no family history of atopy or dermatitis. Foetal scan done at 20 weeks of gestation showed no abnormality.

Renal panel on day 1 showed increased levels of sodium 152 mmol/L (normal 135-145 mmol/L), potassium 6.1 mmol/L (normal 3.9-5.9 mmol/L), urea 11.9 mmol/L (normal 1.4-7.7 mmol/L), chloride 126 mmol/L (normal 101-112 mmol/L) and creatinine 129 µmol/L (normal 27-80 µmol/L). The TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and HIV) screen was negative. She was suspected to be suffering from Netherton syndrome. Trichorrhexis invaginata was present in the hair shaft (Figure 2). Histology from skin biopsy showed compact parakeratosis, psoriasiform epidermal hyperplasia with loss of the granular layer and mild perivascular inflammatory lymphocytic infiltrates in the dermis. Mutation analysis revealed a homozygous 1048 C>T mutation (R350X) on exon 12 in the Serine Protease Inhibitor Kazal type 5 (*SPINK5*) gene. Lymphoepithelial Kazal type-related inhibitor (LEKTI) staining on skin was negative (Figure 3). This confirmed the diagnosis of Netherton syndrome.

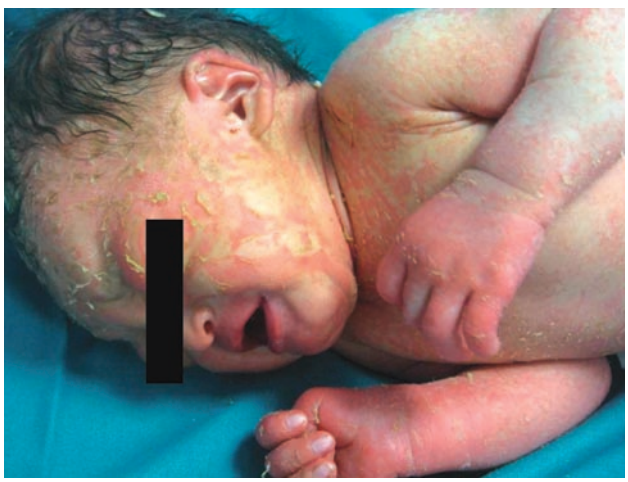

Figure 1. Erythematous patches with coarse scales on face, trunk and limbs found at birth.

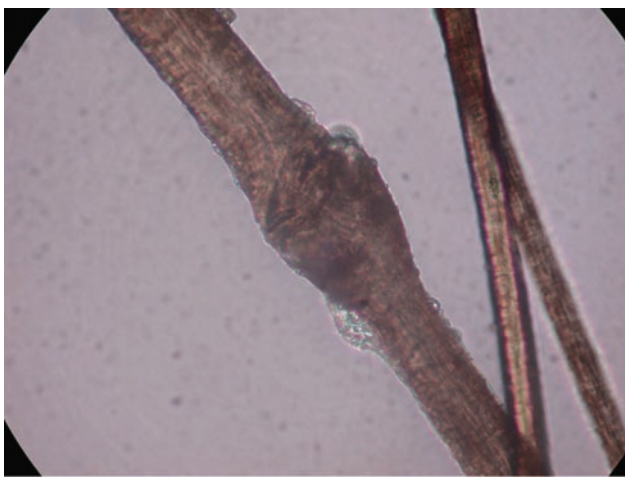

Figure 2. Trichorrhexis invaginata with ball-and-socket appearance in the hair shaft.

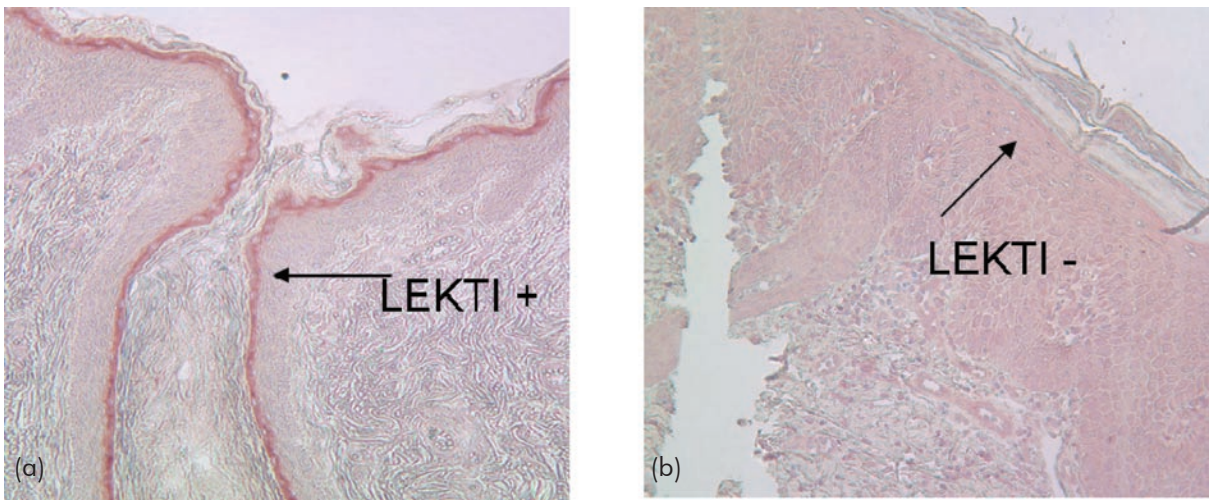

Figure 3. (a) LEKTI present in the control (b) LEKTI absent in the patient's specimen.

The neonate suffered from recurrent infections requiring multiple courses of antibiotics. These included *Klebsiella* pneumonia, MRSA bacteraemia, *Candida* sepsis, *Enterococcus* and extended-spectrum beta-lactamase (ESBL) – producing *Klebsiella* and long line infections caused by *Pseudomonas aeruginosa* and *Enterobacter aerogenes*. However, work-up for immune deficiency for B and T cell subsets did not reveal any immunodeficiency. Except for a raised IgE 162 IU/ml (normal range: 18-100 IU/ml), the immunoglobulin levels were normal.

Apart from sepsis, she also suffered from anaemia requiring packed cell transfusions and metabolic and electrolyte derangements including hypernatraemic dehydration, hyperkalaemia, hypocalcaemia, hypophosphataemia, hypoalbuminaemia and low zinc levels.

Failure to thrive with poor weight gain and developmental delay were noted. Feed intolerance and poor suck were present. Therefore, she was put on nasogastric tube feeding and nutritional supplements were given. A ceramide dominant barrier repair emollient was employed for use on the skin liberally and topical antibiotics were prescribed for skin erosions. To reduce the transepidermal water loss, dry wrapping technique with tubular bandage was used to cover the skin. The technique was demonstrated and taught to the mother. On the follow-up at 9 months of age, she was noted to have weight gain and the skin was found to be healing, less erythematous and had less scaling.

Discussion

Comel-Netherton syndrome (Online Mendelian Inheritance in Man 256500), NS, a rare autosomal recessive disorder, is characterised by congenital ichthyosiform erythroderma, hair shaft abnormalities and atopic manifestations. In 2000, Chavanas et al[1] identified that mutations in the *SPINK5* gene, located in chromosome 5q32, coding for the LEKTI caused the disease. The mutation in this girl was found to be homozygous 1048 C>T in exon 12 of *SPINK5* resulting in a direct stop codon (R350X).

There are 15 different serine protease inhibitory domains within the primary structure of LEKTI, which has a wide range of inhibitory functions towards trypsin, plasmin, cathepsin G, subtilisin A and neutrophil elastase. They are co-localised with human tissue kallikreins (KLKs) in skin and both of them are secreted together in lamellar bodies. LEKTI inhibits KLKs while KLKs, in turn, degrade LEKTI.[2]

In NS patients, pathogenic mutations might lead to LEKTI deficiency and truncated LEKTI with fewer domains. The length of the truncated LEKTI and the number of domains depend on the location and type of mutations. Komatsu et al[2] showed that there was genotype/phenotype correlation in cutaneous severity, growth retardation, skin infection, stratum corneum protease activities and KLK levels in the stratum corneum. Hachem et al[3] showed that the magnitude of serine protease activation correlated with phenotypic variation but was inversely correlated with residual LEKTI expression. Therefore, the complete absence of LEKTI protein in our case aptly predicted a severe clinical phenotype.

Atopy, a feature in up to 75% of patients with NS, might manifest as atopic dermatitis, asthma, urticaria, angioedema and allergic rhinitis. Commonly, the patients develop reactions to food allergens e.g. nuts, eggs and milk. It was found that in LEKTI-deficient epidermis, unregulated KLK 5 triggers atopic dermatitis-like lesions, independently of the environment and the adaptive immune system by directly activating proteinase-activated receptor 2 and induces nuclear factor κB-mediated overexpression of thymic stromal lymphopoietin, intercellular adhesion molecule 1, tumour necrosis factor-α, and IL8.[4]

There is broad skin barrier failure in NS patients. The permeability barrier and the antimicrobial barrier are compromised and this barrier failure

on the skin and in the gut leads to growth failure, electrolyte disturbance, dehydration, hypothermia and susceptibility to topical and systemic infections.[5,6] The mechanism affecting impairment of the permeability barrier involves the serine protease mediated loss of stratum corneum integrity and cohesion. This leads to a thinned stratum corneum. It also leads to unrestricted digestion of the enzymes, involved in the formation of lipids, which are essential in the lamellar membrane architecture.[3]

The girl was noted to have failure to thrive and poor physical development. Jejunal villous atrophy was demonstrated in a study of some infants with growth failure.[7] However, another study showed that nutritional deficiencies and gastrointestinal abnormalities were uncommon in children with failure to thrive and ichthyosis.[8] The growth failure could partly be due to the defective epidermal permeability barrier. As there is a significantly increased transepidermal water loss in NS patients, there will be an increased caloric drain through energy used in evaporation.[9] In addition, it was proposed that a lack of inhibition of proteases due to deficiency of LEKTI in the pituitary gland would lead to the over-processing of human growth hormone which might result in growth retardation.[2]

Bacterial infections involving the skin, respiratory, and gastrointestinal tracts often resulted in severe failure to thrive. Initially, our patient had a poor weight gain below the third percentile. She was placed on nasogastric tube feeding and given nutritional supplements. When reviewed in a subsequent visit at one year old, she weighed 6.4 kg, with improvement in weight gain but was still below 10th percentile.

Our patient suffered from multiple episodes of bacterial and fungal infections requiring multiple courses of antibiotics and antifungal agents. Most patients with NS suffer from recurrent respiratory, gastrointestinal, skin infections caused by *Staphylococcus aureus* predominantly, and sepsis. Defect in the skin and gut barrier in NS likely contributes to susceptibility to the infections and sepsis. However, there may be some underlying defect with the immune system. A decreased serum IgG levels,[10] in particular, the IgG2 subclass was found in one study.[7] The number and activity of NK cells were decreased and LEKTI deficiency might result in aberrant NK cell-epithelial cell interaction.[11] A decreased chemokine (C-C motif) ligand 5 (CCL-5), an elevated proinflammatory cytokine level, reduced memory B-cells and defective immune responses to vaccination in NS patients suggested that they might have cognate and innate immunodeficiency.[11] For our case, a raised IgE was found, 162 IU/ml (normal 18-100 IU/ml), but the B and T cell subsets were normal.

In the management of NS, it is important to identify and treat any of the following complications early, e.g. hypernatraemic dehydration, electrolyte abnormalities, infections, sepsis, feeding problems and failure to thrive. Ideally, the enlightened therapy of this condition should comprise a topical application of a barrier repair formulation and a serine protease inhibitor.[12] However, topical application of α-1-antitrypsin was not found to be effective in one study.[13] Topical steroids are inconsistently successful for accompanying eczema but there is a risk of increased percutaneous absorption. Ammonium lactate 12% lotion was reported to improve the condition.[14] Topical 0.05% calcipotriol ointment was reported to improve the erythema and scaling significantly.[15] Reports on the efficacy of topical tacrolimus in NS patients have been conflicting, with systemic absorption being the main problem.[16] Our experience shows that patients with NS respond well to tacrolimus (personal communication). Saif reported tacrolimus and pimecrolimus to be effective without any toxic effect in the treatment of skin condition in NS.[17] Tacrolimus blood levels were found to be undetectable or just detectable in the treated patients. The use of systemic retinoids including etretinate and actretin is controversial and they may aggravate the skin condition.

Recently, oral isotretinoin was reported to be effective and well tolerated in a boy with NS.[18] Renner et al reported that treatment with intravenous immunoglobulin (0.4 g/kg/month) resulted in remarkable clinical improvement and temporarily increased natural killer cell cytotoxicity.[11] The beneficial effect of intravenous immunoglobulin might be due to its high affinity neutralising and opsonising antibody required for phagocytosis and killing of bacteria, its ability to reduce inflammation in patients with chronic inflammatory disorders and an increase of NK cytotoxicity temporarily.

In practical terms, regular application of emollients is the mainstay of treatment. For our patient, a ceramide-dominant, barrier-repair emollient was employed to increase the hydration status of the epidermis. Furthermore, we tried to decrease the transepidermal water loss by the application of tubular bandage dressing. The condition of the skin improved on this simple but logical regimen. The importance of interdisciplinary management of NS is also highlighted in this case.

There is a high mortality and morbidity in the first year of life, especially in the neonatal period. Nevertheless, there is a tendency to improve after the neonatal period, and improvement usually occurs in the second year of life. It is hoped that in the future, targeted strategy to improve on the barrier dysfunction will make a substantial contribution to the treatment of NS.

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