Netherton Syndrome in Association With Vitamin D Deficiency

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PRACTICE **POINTS**

- Netherton syndrome (NS) is characterized by severe atopic dermatitis, ichthyosis linearis circumflexa, and trichorrhexis invaginata.
- Children with NS are at increased risk for vitamin D deficiency.
- Consider screening patients with chronic severe dermatitis for vitamin D deficiency.

To the Editor:

Netherton syndrome (NS) is a rare genodermatosis that presents with erythroderma accompanied with failure to thrive in the neonatal period. Ichthyosis linearis circumflexa, or double-edged scale, is a typical skin finding. Chronic severe atopic dermatitis with diffuse generalized xerosis usually develops and often is associated with elevated IgE levels; however, a feature most associated with and crucial for the diagnosis of NS is trichorrhexis invaginata, or bamboo hair, that causes patchy hair thinning. The triad of ichthyosis linearis circumflexa, atopic dermatitis, and trichorrhexis invaginata is diagnostic of NS. Several other clinical features, including delayed growth, skeletal age delay, and short stature also can develop during its clinical course.[1]

Netherton syndrome is an autosomal-recessive disorder resulting from a mutation in the *SPINK5* gene, which encodes a serine protease inhibitor important in skin barrier formation and immunity.[2] Thus, frequent infections are common in these patients. Current treatment options include emollients and topical anti-inflammatory agents to minimize and control the classic manifestations of NS.

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A 10-year-old girl with a history of allergic rhinitis and multiple food allergies presented to the dermatology clinic with a long history of diffuse generalized xerosis and erythema with areas of lichenification and scaly patches on the face, trunk, and extremities. She was born prematurely at 34 weeks and developed scaling and erythema involving most of the body shortly after birth. She exhibited severe failure to thrive that necessitated placement of a gastrostomy feeding tube at 8 months of age, resulting in satisfactory weight gain and the tube was later removed. A liver biopsy obtained at that time revealed early intrahepatic duct obstruction and early cirrhosis. She continued to have severe atopic dermatitis, poor growth, milk intolerance, and frequent infections. She had a history of dysfunctional voiding, necessitating the use of oxybutynin. The patient also was taking desmopressin to help with insensible water losses. She had no family history of dermatologic disorders.

At presentation she had diffuse scaling and erythema around the nasal vestibule and bilateral oral commissures. She also was noted to have coarse, brittle, and sparse scalp hair and eyebrows. Her current medications included hydrocortisone cream 2.5%, loratadine 10 mg daily, desmopressin 0.1 mg twice daily, and oxybutynin. Laboratory DNA analysis revealed 2 deletion mutations involving the *SPINK5* gene that combined with physical findings led to the diagnosis of NS. Due to her severe growth retardation (approximately 6 SDs below the mean), she was referred to the pediatric endocrinology department.

Our patient's skeletal age was markedly delayed (6.5 years), and she was vitamin D deficient with a total vitamin D level of 16 ng/mL (reference range, 30–80 ng/mL). She is now under the care of a dietitian and taking a vitamin D supplement of 2000 IU of vitamin D_3 daily. Growth hormone therapy trials have not been helpful.

An important feature of NS is growth retardation, which is multifactorial, resulting from increased caloric requirements, percutaneous fluid loss, and food allergies. Komatsu et al[3] proposed that the *SPINK5* inhibitory domain in addition to its role in skin barrier function is involved in regulating proteolytic processing of growth hormone in the pituitary gland. Its dysfunction may lead to a decrease in human growth hormone levels, resulting in short stature.[3] This association suggested that our patient would be a good candidate for growth hormone therapy.

Furthermore, our patient was found to be vitamin D deficient, which was not surprising, as cholecalciferol (vitamin D_3) is synthesized in the epidermis with UV exposure. This finding suggests that vitamin D deficiency should be suspected in patients with an impaired skin barrier. In addition to calcium regulation and bone mineralization, vitamin D plays a preventative role in cardiovascular disease, autoimmune diseases such as Crohn disease and multiple sclerosis, type 2 diabetes mellitus, infectious diseases such as tuberculosis and influenza, and many cancers.[4]

Vitamin D has 2 primary derivatives: (1) vitamin D_3 from the skin and dietary animal sources, and (2) ergocalciferol (vitamin D_2), which is obtained primarily from dietary plant sources and fortified foods. The most common test for vitamin D sufficiency is an assay for serum 25-hydroxyvitamin D (25[OH]D) concentration; 25(OH)D is derived primarily from vitamin D_3, which is 3 times more potent than vitamin D_2 in the production of 25(OH)D.[5] The American Academy of Pediatrics recommends vitamin D replacement therapy for children with 25(OH)D levels less than 20 ng/mL (50 nmol/L) or in children who are clinically symptomatic.[6] The Endocrine Society Clinical Practice Guidelines suggest screening for vitamin D deficiency only in individuals at risk.[7] We suggest that serum vitamin D testing should be routine in children with NS and other atopic dermatitis conditions in which UV absorption may be impaired.

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