Fingernail Abnormalities in an Adolescent With a History of Toe Walking

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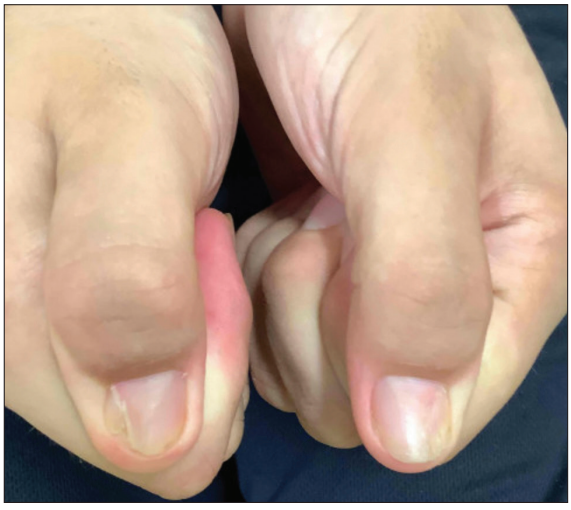

A 14-year-old boy with a history of toe walking, attention-deficit/hyperactivity disorder, and mixed receptive expressive language disorder presented to our pediatric dermatology clinic with fingernail abnormalities that had been present since birth. Physical examination revealed narrowing and longitudinal splitting of the nail plates with triangular lacunae and progressive improvement appreciated toward the fifth digits. The nail changes were most prominent on the first digits. A review of the patient's medical record revealed incidental bilateral iliac horns of the pelvis on radiographs taken at age 18 months. The patient reported waxing and waning knee pain that worsened with prolonged activity and when climbing stairs. Urinalysis demonstrated mild hematuria without proteinuria. The patient was normotensive. There was no evidence of glaucoma, cataracts, or hyperpigmentation of the pupillary margin (Lester iris) on ophthalmologic examination. Genetic testing was performed.

WHAT'S YOUR **DIAGNOSIS?**

a. hypohidrotic ectodermal dysplasia
b. leukonychia
c. nail-patella syndrome
d. onychomycosis
e. psoriasis

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Alexandra Hoffman and Dr. Ophaug have no relevant financial disclosures to report. Dr. Funk has received research support and/or honoraria from AbbVie, Amgen, Arcutis Biotherapeutics, Incyte, LEO Pharma, Medimetriks, Palvella Therapeutics, Sanofi, and Regeneron.
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Cutis. 2025 February;115(2):E11-E13. doi:10.12788/cutis.1177

THE **DIAGNOSIS:** Nail-Patella Syndrome

Nail-patella syndrome (NPS) is an autosomal-dominant disorder that is present in approximately 1 in 50,000 live births worldwide.[1,2] It manifests with a spectrum of clinical findings affecting the nails, skeletal system, kidneys, and eyes.[3] Most cases of NPS are caused by loss-of-function mutations in *LMX1B*,[1] a gene encoding the LIM homeobox transcription factor.[4] The *LMX1B* gene plays a critical role in the dorsoventral patterning of developing limbs.[5] Mutations of this gene impair the development and function of podocytes and glomerular filtration slits[6] and have been found to affect the development of the dopaminergic and mesencephalic serotoninergic neurons.[2] Approximately 5% of patients with NPS have an unexplained genetic cause, suggesting an alternate mechanism for disease.[1] Loss-of-function mutations also were observed in the Wnt inhibitory factor 1 gene (*WIF1*) in a family with an NPS-like presentation and could represent a novel cause of the condition.[1] Regardless, NPS may be diagnosed clinically based on characteristic medical history, imaging, and physical examination findings.

Nail changes are the most consistent feature of NPS. The nails may be absent, hypoplastic, dystrophic, ridged (horizontally or vertically), or pitted or may demonstrate characteristic triangular lacunae. Nail findings often are congenital, bilateral, and symmetrical. The first digits typically are most severely affected, with progressive improvement appreciated toward the fifth fingers, as seen in our patient. The nail changes can be subtle, sometimes manifesting only as a single triangular lacuna on both thumbnails. Toenail involvement is less common and, when present, tends to be even more discreet. In contrast to the fingernails, the fifth toenails are most commonly affected.[7]

There are many skeletal manifestations of NPS. Patellae may be absent, hypoplastic, or irregularly shaped on physical examination or imaging, and changes may involve one or both knees. The Figure shows plain radiographs of the knees with bilateral patellar subluxation. Elbow dysplasia or radial head subluxation may result in physical limitations in extension, pronation, or supination of the joint.[7] In approximately 70% of patients seen with the disorder, imaging may reveal symmetric posterior and lateral bony projections from the iliac crests, known as iliac horns; when present, these are considered pathognomonic.[8]

Open-angle glaucoma is the most common ocular finding in NPS. Other less commonly associated eye abnormalities include hyperpigmentation of the pupillary margin (Lester iris).[6] Renal involvement occurs in 30% to 50% of patients with NPS and is the main predictor of mortality, with percentages as high as 5% to 14%.[7] Defects occur in the glomerular basement membrane and manifest clinically with hematuria and/or proteinuria. The course of proteinuria is unpredictable. Some cases remit spontaneously, while others remain asymptomatic, progress to nephrotic syndrome, or, although rare, advance to renal failure.[7,9]

Bowel symptoms, neurologic problems, vasomotor concerns, thin dental enamel, attention-deficit disorder or attention-deficit/hyperactivity disorder, and major depressive disorder all have been reported in association with NPS.[2,7]

Nail psoriasis typically exhibits nail pitting and onycholysis. Other manifestations include subungual hyperkeratosis, oil drop discoloration, and splinter hemorrhages. Topical and intralesional treatments are used to manage symptoms of the disease, as it can become debilitating if left untreated, unlike the nail disease seen in NPS.[10] Onychomycosis can have a similar manifestation to psoriasis with sublingual hyperkeratosis of the nail, but it usually is caused by dermatophytes or yeasts such as *Candida albicans*. Onycholysis and thickening of the subungual region also can be seen. Diagnosis relies on direct microscopy and fungal culture, and a thorough patient history will help distinguish fungal vs nonfungal etiology. New-generation antifungals are used to eradicate the infection.[11] Leukonychia manifests with white-appearing nails due to nail-plate or nail-bed abnormalities. Leukonychia can have multisystem involvement, but nails demonstrate a white discoloration rather than the other abnormalities discussed here.[12] Hypohidrotic ectodermal dysplasia is a rare hereditary congenital disease that affects ectodermal structures and manifests with a triad of symptoms: hypotrichosis, hypohidrosis, and hypodontia. The condition often manifests in childhood with characteristic features such as light-pigmented sparse and fine hair. Physical growth as well as psychomotor development are within normal limits. Neither bone nor renal involvement is typical for hypohidrotic ectodermal dysplasia.[13]

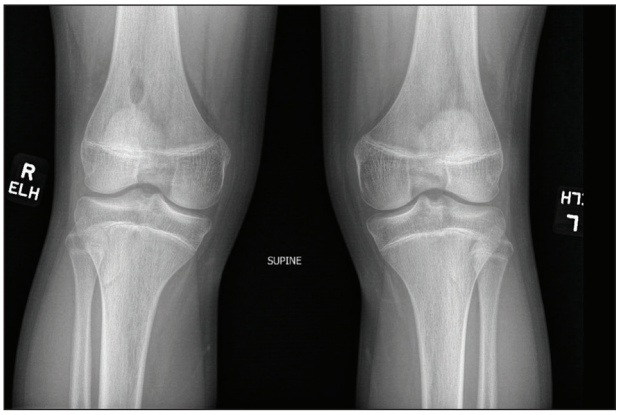

FIGURE. Plain radiograph of knees showing bilateral patella subluxation.

Our case highlights the typical manifestation of NPS with multisystem involvement, demonstrating the complexity of the disease. For cases in which a clinical diagnosis of NPS is uncertain, gene-targeted or comprehensive genomic testing is recommended, as well as genetic counseling. Given the broad spectrum of clinical manifestations, it is imperative that patients undergo screening for musculoskeletal, renal, and ophthalmologic involvement. Treatment is targeted at symptom management and prevention of long-term complications, reliant on clinical presentation, and specific to each patient.

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