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Nail-patella syndrome: “nailing” the diagnosis in three generations

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Abstract

Nail-patella syndrome (NPS) is a hereditary disorder characterized by fingernail changes, elbow dysplasia, hypoplastic patellae, and presence of iliac horns. Clinical presentation can be subtle, and the spectrum of presentation often makes NPS a challenging diagnosis. Herein, we describe three family members with nail-patella syndrome who presented with different features and varying severity. The opportunity to recognize this rare syndrome in three linear generations provided a unique insight into NPS, and a moment to appreciate the random and unpredictable clinical presentation.

Keywords: nail-patella syndrome, hereditary osteo-onychodysplasia, Fong disease

Introduction

Nail-patella syndrome (NPS) is an autosomal dominant disorder characterized by the tetrad of dysplasia of the fingernails and elbow, hypoplastic patellae, and iliac horns [1]. Nail-patella syndrome is considered fully penetrant, but genetic expressivity varies immensely, even within families [1]. Although more severe cases are easier to diagnose, referral to a geneticist may be necessary diagnoses in mild cases. Many patients initially present to a dermatologist for nail changes, giving them an essential role for early detection and diagnosis. With such an extreme variability seen in NPS, diagnosis and management may require an interdisciplinary team for optimal management and the prevention of complications.

We present a family, in which we evaluated and diagnosed three relatives with NPS. The ability to compare clinical presentations within a single family are rarely reported in the literature. With this unique opportunity, we describe the classic presentation of NPS and emphasize the wide variability and severity that can be seen in a single family. By describing and comparing the presentations side by side, it will help clinicians to diagnose NPS in patients with both mild and severe symptoms.

Case Synopsis

A 72-year-old man presented to the clinic with a lifelong history of fingernail changes. His medical history was significant for osteoarthritis, mild hypertension, and cataracts. Physical examination findings were notable for hypoplastic fingernails with triangular-shaped lunulae and increased dysplasia on the ulnar border of each thumbnail (**Figure 1**). Each thumbnail was separated into two-halves by a longitudinal cleft. Further questioning about family history revealed that both his daughter and granddaughter had similar signs and the patient agreed to bring them in at his next visit.

He returned a month later, accompanied by his 42-year-old daughter and 15-year-old granddaughter for evaluation. Physical examination of his daughter showed mildly hypoplastic fingernails. Similar longitudinal clefts were noted on both thumbnails, although the nails remained intact (**Figure 2**). The most severe features were seen in the granddaughter, who displayed anonychia of the thumbnails bilaterally, and severely hypoplastic changes on each of her fingernails. Additionally, her



Figure 1. Patient's thumbnails were significantly hypoplastic and a prominent longitudinal cleft can be seen splitting the nail at the center.

knees had a flattened appearance, secondary to patellar hypoplasia (**Figure 3**).

The patient's clinical presentation and similar features identified in his family was consistent with the diagnosis of nail-patella syndrome. We discussed the likely diagnosis of NPS with the family and reassured the patient's benign nail findings. Recommendation was to return for routine annual skin examination, and to establish care with the departments of nephrology and ophthalmology for routine screening. The patient was then referred for genetic testing for confirmation of diagnosis. Sequence analysis revealed a previously known single-nucleotide variant in the LIM homeobox



Figure 2. The patient's daughter presented with similar, but much milder findings. A longitudinal ridge was also noted, although her nailbeds remain intact with minor hypoplasia.

transcription factor 1-beta (*LMX1B*) on chromosome 9, a gene variant located within the homeodomain region. Thus, the patient's diagnosis of NPS was confirmed, and was a result of a heterozygous loss-of-function and haploinsufficiency of *LMX1B*.

Case Discussion

The classic tetrad of NPS involves changes in the nails, knees, and elbows. Iliac horns, described as bony projections from the pelvis, are pathognomonic for NPS, although they are present in only 70% of patients [3]. Thumb nail changes are almost always observed. Complications involving the eye and kidneys are most concerning and require surveillance. Eye findings include open-angle glaucoma, ocular hypertension, and Lester sign. Severity of nephropathy varies, and only one-third of patients present with proteinuria. Progression to chronic kidney disease occurs in 3% to 15% of cases. End-stage renal disease is a rare complication [4]. In addition to renal involvement, gastrointestinal and neurological symptoms are commonly reported in NPS [5].

Although no curative treatment exists, screening and early intervention can prevent long-term morbidity. Current recommendations include annual urinalysis for renal disease, eye examination for glaucoma, and dental examination every six months. A thorough history and physical is essential to detect neurologic, gastrointestinal, and orthopedic abnormalities [5].

A geneticist should be consulted in patients with suspected NPS owing to the wide variety of clinical presentations [4]. DNA testing for mutations in the *LMX1B* gene is the gold standard for diagnosis. Nail-patella syndrome results from a heterozygous loss-of-function mutation of this gene, which encodes for a transcription factor expressed in several tissue types. *LMX1B* plays a crucial role in limb formation and in development of podocytes and glomerular basement membranes, anterior eye segments, and the nervous system [4].

The unique opportunity to compare NPS within a family makes it distinct from other reports in the

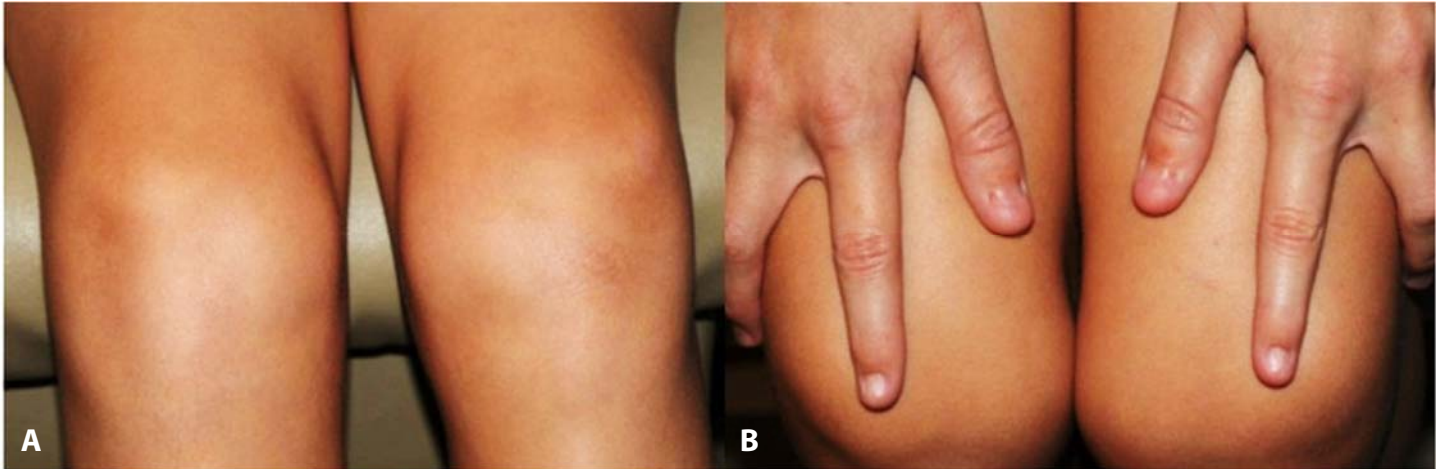


Figure 3. A) A flattened appearance of the knee, secondary to marked hypoplasia of the patellae in in nail-patella syndrome. **B)** Nail changes in the granddaughter, described as complete anonychia of the thumbnails bilaterally. Significant hypoplastic nails, depicted on her index fingers, were seen on all fingernails

literature. The different presentations and severity in one family further supports previous findings [5-7]. By emphasizing the extreme variability and severity of NPS we hope that readers will be more likely to make an early diagnosis and initiate screening to prevent kidney and other complications.

Conclusion

Nail-patella syndrome is a complex genetic condition that should be evaluated and managed by an interdisciplinary team. The majority of patients

will also have an affected parent, although clinical symptoms vary so dramatically that mild cases can be easily missed. When the diagnosis is uncertain, referral to a geneticist is necessary. Our case of three individuals in the same family emphasizes the clinical variability and severity of NPS. Although kidney involvement is common, progression to end-stage renal disease rarely occurs.

Potential conflicts of interest

The authors declare no conflicts of interests.

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