Visual Diagnosis: Abnormal Nails in an Infant
Natalie P. Cunningham and Peter J. Green
Pediatrics in Review 2012;33:e72
DOI: 10.1542/pir.33-11-e72

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pedsinreview.aappublications.org/content/33/11/e72
Abnormal Nails in an Infant

Natalie P. Cunningham,* Peter J. Green, FRCP †

Presentation
A dermatologist has been following a 3-year-old girl for unusually shaped fingernails noted at birth. Her history is as follows.

At age 6 months, the patient’s primary care physician referred her to the dermatology service after the child’s adoptive mother expressed concern about her daughter’s small, misshapen fingernails. The infant was born after a pregnancy complicated by maternal smoking. She was induced at term due to failure to progress and eventually required vacuum extraction, weighing 2.405 kg at birth with Apgar scores of 9 and 9 at 1 and 5 minutes, respectively. There had been no concerns with her growth or development, and she was an active and happy child. She took no medications and had no known allergies. Her family history included a biological mother with attention-deficit/hyperactivity disorder and substance abuse and a healthy maternal half-brother. Little was known about the biological father, but the biological mother indicated that the father had abnormal nails.

Physical examination at 6 months revealed an alert, well-appearing infant in no acute distress. Vital signs were within normal limits for her age, and she was growing between the

Figure 1. Nail dystrophy, most pronounced on thumbnails and less so on the nails of the fifth digits.

Figure 2. Fingernails display triangular shaped lunulae.
50th and 75th percentiles for height, weight, and head circumference. She was normal in appearance. There were no dysmorphic features on her head, face, or torso. Her fingers were slightly tapered with normal creases. The nails of her fingers on both hands were small and unusually shaped with longitudinal grooving, most pronounced on her thumbnails and less so on the nails of the fifth digits. Her toenails were unaffected. Given the nonspecific nail features, the dermatologist recommended seeing the infant 1 year later.

At age 17 months, the child was re-evaluated. The fingernails remained misshapen (Fig 1) but now had triangular shaped lunulae (Fig 2). Because a clinical diagnosis was suspected, plain radiographs of the pelvis and knees were performed. However, the radiographs were inconclusive, and the patient was asked to return 1 year later.

The patient is seen now at age 31 months. This time, repeat radiographs of the knees and pelvis display decreased ossification of the patellae (Fig 3) and a subtle horn on the right iliac wing of the pelvis (Fig 4). Further laboratory examination reveals persistent hematuria and proteinuria on urinalysis.

A clinical diagnosis is made.

**Diagnosis: Nail Patella Syndrome**

The clinical presentation and radiographic findings are consistent with nail patella syndrome (NPS). Genetic testing confirmed the diagnosis, demonstrating a mutation in the LMX1B gene.

**Discussion**

NPS is a rare autosomal dominant disorder due to mutations in the gene LMX1B and heralded by a tetrad of dermatologic and musculoskeletal features that include dystrophic nails, hypoplastic or abnormal patellae, elbow dysplasia, and iliac horns. NPS is referred to also as hereditary osteo-onychodysplasia (HOOD syndrome), Turner-Kieser syndrome, Österreicher syndrome, or Fong disease. The incidence of NPS has been estimated historically at 1:50,000 (1); however, the incidence may be much lower. One half of patients born with NPS have renal involvement demonstrated by hematuria, loss of filtration with proteinuria, and nephrotic range proteinuria.

The mutation connected with NPS involves LMX1B, an LIM homeodomain transcription factor gene mapped to chromosome 9q34.1 and specifically linked to the ABO blood group locus. (1) Studies by Chen et al using homozygous knockout mice suggested LMX1B’s roles in dorsoventral patterning of limb development and renal cellular differentiation. (2) LMX1B has since been associated with the development of the anterior chamber of the eye and the central nervous system. Over 150 different mutations causing loss of function of LMX1B have been described to date, according to the Human Gene Mutation Database 2003 update. This genotype is highly penetrant; most patients with the NPS genotype present with symptoms or signs of the disease. Disease severity

**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>NPS</td>
<td>nail patella syndrome</td>
</tr>
</tbody>
</table>
has unpredictable individual, inter- and intrafamilial variability. The mechanism underlying phenotypic variation remains unknown.

Nail abnormalities, present at birth in 80% to 90% of affected individuals, include absence but more commonly hypoplasia or dysplasia in the form of nail ridging, splitting, spooning, fragility, and discoloration. Although a single triangular lunula can be due to trauma, involvement of multiple nails is more specific for NPS. (3) Nail lesions are symmetric and often most severe at the thumb, with decreasing severity as the nails become more ulnar; toenail involvement is less common.

Hypoplastic or absent patellae are noted in 74% to 93% of cases. Knee dysplasia and hypoplasia of the lateral femoral condyle can lead to dislocation, pain, and arthritis at the knee. Elbow dysplasia is present in 93% with hypoplasia of the radial heads and capitellum, potentially causing posterolateral subluxation and dislocation. (4) Iliac horns, which are asymptomatic bony pyramidal protuberances arising from the dorsolateral aspect of the iliac crests, are considered pathognomonic for NPS but are present in only 30% to 70% of individuals with NPS.

Approximately 50% of patients with NPS have renal disease, including proteinuria, hematuria, and frank renal failure. Lemley (3) proposed two patterns of renal involvement: 1) asymptomatic, accelerated, age-related loss of filtration function and 2) nephrotic range proteinuria, occurring in 5% to 10% of patients, with onset in childhood or early adulthood, a predictor of progression to end-stage renal disease. Urinalysis often is done when a diagnosis of NPS is suspected to screen for kidney involvement. Renal biopsy is unnecessary for patients with NPS unless urinary signs and symptoms suggest another form of kidney disease. (3)

Other findings associated with NPS have been described. Ocular hypertension is present in 7% of individuals who have NPS, and primary open angle glaucoma occurs in 10%. Lester sign, or darker pigmentation of the iris at the pupillary margin, appears in the general population but is more common in individuals with NPS (~50%). Patients with NPS also can have 8% to 20% lower bone mineral density compared with normal controls, thereby increasing their risk for fracture and scoliosis. Disrupted development of the mesencephallic dopaminergic and hindbrain serotoninergic neurons may account for the association of NPS with major depressive disorder and attention deficit disorder. Up to 25% of patients with NPS experience numbness, paresthesia, decreased pain, and reduced temperature sensation, which may be related to disrupted development of dorsal horn neurons.

**Diagnosis**

Diagnosis often can be made clinically at birth or thereafter by history and physical examination, assisted by ancillary investigations that include urinalysis, diagnostic imaging, and ophthalmologic examination. NPS may not be considered, given the subtle phenotype and the relative unfamiliarity of physicians with the disease. With clinical suspicion, patients often undergo radiographic imaging first. The most common radiographic findings in NPS include iliac horns, hypoplasia or absence of the patella, elongated radius, and hypoplasia of the radius and capitellum. Genetic consultation may be appropriate to confirm the diagnosis, but genetic sequencing (85% sensitive) is not always necessary.

**Management**

The care of patients with NPS involves a multidisciplinary approach by clinicians in primary care, dermatology, nephrology, orthopedics, and ophthalmology. Care generally is symptomatic. Annual urinalysis is recommended to screen for proteinuria and hematuria. However, there is little evidence to indicate that intervention will affect progression of kidney disease. (3) Despite decreased bone density and increased risk for fracture, it is unclear whether patients with NPS should undergo early bone mineral density screening. Patients should have annual ophthalmologic screening for early detection of ocular hypertension and glaucoma. Genetic counseling is appropriate, and parents of an affected individual with NPS should be examined closely for subtle features of NPS. Surgical intervention for chronic orthopedic problems of elbows, knees, and feet is reserved for significant functional impairment.

The ultimate prognostic feature for NPS is the extent of renal disease. Because angiotensin-converting enzyme (ACE) inhibitors slow progression of other nondiabetic proteinuric glomerular diseases, they may have a similar impact in NPS nephropathy. Although ACE inhibitors have been effective anecdotally, this therapy has yet to be studied rigorously in NPS. In one case report, combination therapy with ACE inhibitors and angiotensin receptor blockers has resulted in complete remission of proteinuria in a patient with NPS nephropathy. (5) Corticosteroid-responsive, frequently relapsing nephrotic syndrome in a patient with NPS suggests that corticosteroid therapy might be worthwhile. Cyclosporin, used with some success in the treatment of Alport syndrome, another genetic kidney disease, may be an alternative treatment when ACE inhibitors are contraindicated. Renal transplant has been anecdotally
successful without recurrence of disease or development of anti-glomerular basement membrane antibodies in individuals with end-stage renal disease.

**Patient Course**
The patient underwent renal biopsy, which revealed a histologic pattern similar to minimal change disease. She is followed by ophthalmology and to date has normal intraocular pressure and no signs of glaucoma. She has reduced extension at the elbows by 10 to 15 degrees and has difficulty with supination. She was referred to medical genetics for counseling.

**Summary**
- **Nail patella syndrome (NPS)** is an autosomal dominant disorder due to mutations in the gene LMX1B.
- The clinical tetrad of NPS includes dystrophic nails with triangular lunulae, hypoplastic or abnormal patellae, elbow dysplasia, and iliac horns.
- When NPS is suspected, plain radiographs of the pelvis and knees are appropriate initial diagnostic examinations.

**References**

**Suggested Reading**

*The ultimate prognostic feature for NPS is presence of renal disease. One half of NPS patients have renal disease, including proteinuria, hematuria, and frank renal failure.*
**Visual Diagnosis: Abnormal Nails in an Infant**

Natalie P. Cunningham and Peter J. Green

*Pediatrics in Review* 2012;33;e72

DOI: 10.1542/pir.33-11-e72

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at: <a href="http://pedsinreview.aappublications.org/content/33/11/e72">http://pedsinreview.aappublications.org/content/33/11/e72</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>References</td>
<td>This article cites 5 articles, 2 of which you can access for free at: <a href="http://pedsinreview.aappublications.org/content/33/11/e72#BIBL">http://pedsinreview.aappublications.org/content/33/11/e72#BIBL</a></td>
</tr>
<tr>
<td>Subspecialty Collections</td>
<td>This article, along with others on similar topics, appears in the following collection(s):</td>
</tr>
<tr>
<td></td>
<td>Dermatology <a href="http://pedsinreview.aappublications.org/cgi/collection/dermatology_sub">http://pedsinreview.aappublications.org/cgi/collection/dermatology_sub</a></td>
</tr>
<tr>
<td></td>
<td>Genetics <a href="http://pedsinreview.aappublications.org/cgi/collection/genetics_sub">http://pedsinreview.aappublications.org/cgi/collection/genetics_sub</a></td>
</tr>
<tr>
<td></td>
<td>Dysmorphology <a href="http://pedsinreview.aappublications.org/cgi/collection/dysmorphology_sub">http://pedsinreview.aappublications.org/cgi/collection/dysmorphology_sub</a></td>
</tr>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: /site/misc/Permissions.xhtml</td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online: /site/misc/reprints.xhtml</td>
</tr>
</tbody>
</table>