Nail-Patella Syndrome: Optical Coherence Tomography Angiography Findings

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Keywords
Nail-patella syndrome · Glaucoma · Ocular hypertension · Optical coherence tomography angiography

Abstract
We describe a 51-year-old Hispanic female with nail-patella syndrome (NPS), a rare genetic disease with a wide range of systemic features such as nail dysplasia and finger abnormalities, elbow webbing, iliac horn, patellar subluxation, and proteinuria. Some patients additionally have a history of glaucoma and other ocular features such as thick central corneal thickness, Lester’s sign, prominent iris processes, and optic nerve cupping. Our patient had a history of glaucoma suspicion, prominent iris processes, increased cup to disc ratios, tilted optic discs, and tigroid fundi. In addition, we report optical coherence tomography angiography (OCTA) findings of focal areas of poor vessel densities in the macular and circumpapillary regions of both eyes, suggesting early compromised vascular supplies to these areas. Our OCTA findings (which include both structural and vascular details of retina and optic nerve) lend support to the use of this technology in patients with NPS.
Introduction

Nail-patella syndrome (NPS), also known as hereditary osteo-onychodysplasia or Fong disease, is a rare disorder of autosomal dominant inheritance with a reported incidence of approximately 1 in 50,000 live births [1]. It is believed to be caused by a mutation in the LMX1B gene, whose protein is a transcription factor that is necessary for normal embryonic development of eyes, limbs, and kidneys [2]. Animal studies have found that LMX1B is expressed in the periocular mesenchyme, extraocular muscles, corneal stroma and endothelium, trabecular meshwork, and iris and ciliary body stroma [3]. The LMX1B transcription factor is essential for development of the cornea, iris, and ciliary body during embryogenesis, and its mutation contributes to glaucoma and anterior segment dysgenesis observed in NPS patients [3]. Systemic features of NPS include nail abnormalities (absent or underdeveloped nails with triangular lunulae), skeletal irregularities (iliac horns and irregularly shaped elbows and patellae), and renal manifestations (proteinuria, hematuria, glomerulonephropathies) [4–6].

Ocular manifestations of NPS range from mild to severe and may include microcornea, sclerocornea, congenital cataract, abnormal iris processes, pigmentation of the inner margin of the pupil (Lester’s sign), congenital glaucoma, ptosis, hypertelorism, epicanthal folds, keratoconus, microphakia, anisocoria, or pupillary ectopia [5, 7]. In addition, these patients may also present with early onset ocular hypertension (OHT) and/or primary open-angle glaucoma. This is believed to be due to cosegregation of a “glaucoma gene” and the NPS-causing gene LMX1B on chromosome 9q34 [8]. Because of this association, NPS patients are screened for glaucoma as early as childhood.

Previous studies have focused on ocular findings, visual field (VF) results, and optical coherence tomography (OCT) data (Table 1). As seen in Table 1, relevant OCT findings for NPS patients include retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) thinning. This report, in addition to the previously described parameters, focuses on OCT angiography (OCTA) which provides both structural and vascular measurements and adds new dimension to early detection of glaucoma in these patients.

Case Report

A 51-year-old female of Mexican descent who was diagnosed with NPS in 2003 at age 33 presented to the university eye clinic for glaucoma screening. She was diagnosed as a glaucoma suspect 4 years prior to the visit.

At this visit, she had no ocular complaints, and her best corrected visual acuity was 20/20 in both eyes. Her refraction was −3.25 diopters in the right eye (OD) and −1.25 diopters in the left eye (OS). Intraocular pressure (IOP), measured by Goldmann applanation tonometry (Haag-Streit, Inc., Koeniz, Switzerland), was 16 mm Hg OD and 15 mm Hg OS. Central corneal thickness measured by Sonogage pachymeter (Cleveland, OH, USA) was 570 μm OD and 600 μm OS, which are thicker than normal range. Fundus photographs (shown in Fig. 1a and Fig. 1b) showed tigroid fundii and tilted optic discs with a cup to disc ratio of 0.5 OD and 0.45 OS. There was no evidence of retinal myopic degeneration. Gonioscopy revealed slightly narrow angles with anterior insertion of the base of the iris and prominent iris processes, and only a thin strip of the ciliary body visible bilaterally (Grade 3 Schafer). Slit-lamp examination of the anterior segment revealed no other abnormalities. Humphrey VF analyzer (Carl Zeiss Meditec AG, Dublin, CA, USA) results showed early inferior arcuate depression OD (shown in Fig. 1i) and early superior para-central depression OS (shown in Fig. 1j). Repeat VFs may show stability or progression of these changes, as previous VF results were not available. OCTA imaging utilizing Optovue AvantiXR AngioVueHD Software Version 2018.0.0.18 scanner (Optovue®, Freemont, CA, USA) was also
performed (shown in Fig. 1c–h. Values for OD and OS (our own calculated normative values in parentheses), respectively, were as follows: average RNFL thickness 106 μm and 94 μm (≥95 μm); average GCC thickness 95 μm and 94 μm (≥95 μm); vessel density (VD) macula 49.75% and 49.5% (≥50%); circumpapillary (peripapillary) VD 57% and 56% (≥55%). Perifoveal VDs are calculated as averages of the values shown in Fig. 1c–d, while RNFL and GCC values were obtained from the Optovue machine. Although these values were within normal ranges, the patient exhibited focal areas of reduced VD in both perifoveal and circumpapillary areas.

Table 1. Ocular features in patients with Nail patella Syndrome

| Study                | Sample size; gender; age range | Family history | G or OHT  | Ocular features and exam findings                                      | OCT/OCTA findings          | Systemic features                                                                 |
|----------------------|--------------------------------|----------------|-----------|------------------------------------------------------------------------|-----------------------------|----------------------------------------------------------------------------------|
| Sawamura et al. [5]  | 1; 1F; 29                      | 1; N           | 1; OHT    | Lester’s sign, thick CCT, prominent iris processes, myopic optic disc changes, normal VF | OCT: RNFL and GCC thinning  | Nail dysplasia, triangular lunulae, patellar hypoplasia, iliac horns              |
| Romero et al. [6]    | 5; 3F, 2M; 19–63                | 5; Y           | 3; G      | optic disc cupping, neuroretinal rim loss, and VF loss                 | OCT: RNFL thinning          | Nail hypoplasia, nail discoloration, patellar hypoplasia, iliac horns, depression, drug/alcohol addiction |
| Mimiwati et al. [4]  | 33; 21F, 12M; 10–77             | 43; Y          | 2; G      | optic disc cupping, VF loss                                            | N/A                         | Nail dysplasia, triangular lunulae, patellar hypoplasia, absent patellae, elbow/webbing |
| Milla et al. [9]     | 10; 7F, 3M; 7–90                | 10; Y          | 1; G      | Thick CCT, cataracts, diabetic retinopathy, macular edema, optic disc asymmetry | OCT: normal or thickened RNFL | Nail dysplasia, patellar hypoplasia, hip subluxation, glomerulonephritis, spasmodic colitis |
| Sweeney et al. [1]   | 123; 70F, 53M; 0.33–80          | 105; Y         | 8; G      | Lester’s sign                                                         | N/A                         | Nail dysplasia, triangular lunulae, dystrophic toenails, patellar hypoplasia, elbow webbing, iliac horns, pes planus, proteinuria, IBS |
| Our Study            | 1; 1F; 51                       | 1; Y           | 1; G      | Tigroid fundus, tilted optic discs, thick CCT, increased CDR, prominent iris processes | OCTA: Reduced focal areas of VD | Nail dysplasia, triangular lunulae, patellar dysplasia and subluxation, elbow webbing, iliac horn, proteinuria, IBS |

CCT, central corneal thickness; CDR, cup disc ratio; F, female; G, glaucoma; GCC, ganglion cell complex; IBS: irritable bowel syndrome; M, male; N, no; OHT, ocular hypertension; U, unknown; VD, vessel density; VF, visual field; Y, yes.
Our patient's systemic manifestations included bilateral thumb hypoplasia, triangular lunulae over the ring fingers, absence of top knuckles on all fingers, and left elbow pterygium with limited range of motion and cubitus valgus (Fig. 2a–c). Knee x-ray showed left mild lateral patellar subluxation with inferior tilting, and hip x-ray showed iliac horn (shown in Fig. 2d–e). In addition, she had mild proteinuria with a prior history of renal cyst, as well as a history of diverticulitis of the large intestine and systemic hypotension.

Notably, our patient's mother had developed a de novo case of NPS with more severe symptoms and features than our patient, including difficulty straightening both arms, increased spinal curvature, inability to walk until age 6, and bilateral knee replacements due to severe patellar hypoplasia. Our patient underwent genetic testing and the results showed heterozygous variant c.731C>G (p. Pro244Arg) in exon 4 of gene LMX1B. This novel missense mutation replaces proline with arginine at codon 244, yielding a moderate physicochemical difference. The rest of the patient's family do not demonstrate clinical signs of NPS as noted in the pedigree presented in Figure 3.

**Discussion**

Our patient presented with several classic clinical and radiographic manifestations of NPS including limited range of motion of the left elbow, bilateral hypoplastic thumbnails, mild proteinuria, and iliac horns. We classified her as being glaucoma suspect based on increased cup to disc ratios and VF changes.
A prevalent ocular sign of NPS is Lester’s sign, a darkly pigmented zone, similar in appearance to a cloverleaf or flower that is present around the pupil [1]. In a large study of patients with NPS, 54% (64/119) exhibited this trait [1]. Though this pathology is not specific to NPS, Lester’s sign appears at a significantly higher rate in NPS patients than in the general population [10].

Upon careful examination of the iris, our patient did not exhibit Lester’s sign.

To the best of our knowledge, this is the first report to document OCTA findings in an NPS patient with ocular manifestations. OCTA imaging offers three-dimensional, reliable, fast, objective measurements of both structural and vascular parameters of the optic nerve and retina. Although the exact underlying etiology of glaucoma is currently unknown, prominent theories include direct damage from elevated IOP (mechanical theory), inherently poor blood flow (vascular theory), or a combination of both [11]. Therefore, inclusion of OCTA data offers an avenue of exploration for both mechanical and vascular theories of glaucoma in patients with NPS.
Previously published reports of NPS patients with ocular findings record OCT results (Table 1). Sawamura et al. [5] report a case of juvenile onset OHT from de novo NPS. The patient’s OCT (RTVue FD-OCT) revealed thinning of both the circumpapillary RNFL and macular GCC in the superior temporal region of both eyes, suggestive of early glaucomatous damage versus high myopic changes. In a study by Romero et al. [6] of seven family members spanning five generations, OCT results showed RNFL loss in three of five subjects with NPS and open angle glaucoma. The pattern of RNFL loss included inferotemporal thinning and thinning of all quadrants. This pattern of RNFL in NPS patients with glaucoma is similar changes seen in other forms of glaucoma. Elevated IOP may directly damage the retinal nerve fibers at the level of lamina cribrosa and optic nerve head [12].

Previously reported gonioscopic findings in NPS patients include mostly open anterior chamber angles [5, 6]. Some patients were noted to have multiple iris processes and highly pigmented trabecular meshworks [5]. Furthermore, one family over multiple generations affected by NPS was shown to have a range of gonioscopic findings, including grade 3–4 trabecular pigment band with no iris processes, confluent anterior peripheral synechiae to operative sites superiorly and inferiorly to each angle, and open but narrow (Grade 1–2) angles [8].

Given the early onset of OHT and open angle glaucoma in NPS patients, early detection is imperative to prevent long-term visual impairment. NPS patients are screened for glaucoma as early as childhood due to this association. Thinning of RNFL has long been established as a key indicator of glaucomatous damage; however, the emergence of vascular analysis by OCTA has shown that VD values may also be of use for distinguishing glaucomatous eyes from healthy ones. Even though our patient’s average VD values appear in normal range, there were focal areas of decreased VD in both the macula and circumpapillary regions indicated by the blue zones in Figure 1 c–d and Figure 1 g–h, suggesting the importance of OCTA in earlier detection for borderline glaucoma cases [13]. The use of OCTA may provide insight on the retinal vasculature of patients who are at increased risk for glaucoma, including those with NPS, even if they have normal or borderline elevated IOP values. Data from OCTAs have shown that peripapillary VD, peripapillary flow index, and optic disc perfusion are reduced in glaucomatous eyes [14].

Acknowledgment

Special thanks to Emily Buchanan (The University of Texas at Dallas) for her invaluable assistance in preparing the figures and table.

Statement of Ethics

Ethical clinical practices were followed in this case report. Written informed consent was obtained from the patient for publication of this case report along with corresponding images. The study protocol was reviewed and the need for IRB approval was waived by University of Texas Southwestern IRB committee. The authors have no ethical conflicts to disclose and have followed the principles of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

Conflict of Interest Statement

The authors have no conflicts of interest in this material.
Funding Sources

This study was supported in part by an unrestricted grant from the Research to Prevent Blindness, New York, NY: Visual Sciences Core Grant EY 020799. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Contributions

Dr. Karanjit Singh Kooner treated the patient and collected clinical data. Hafsa Zehra Zuberi, Ashika Angirekula, and Muhammad Rubeel Akram drafted the manuscript and created accompanying figures. Dr. Karanjit Singh Kooner and Hafsa Zehra Zuberi provided critical revisions. Dr. Karanjit Singh Kooner, Hafsa Zehra Zuberi, Ashika Angirekula, and Muhammad Rubeel Akram approve of the final version of the manuscript and agree to be accountable for its content.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from Dr. Karanjit Kooner, MD PhD upon reasonable request.

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