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Case Report

Nail-Patella Syndrome and Glaucoma: A Case Report and Review of the Literature

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Abstract
Nail-patella syndrome (NPS) is a rare autosomal dominant disease characterized by nail dysplasia, aplastic or hypoplastic patellae, elbow dysplasia, and presence of iliac horns. Renal or ocular abnormalities are also associated with the disease. We report the case of a 57-year-old woman affected by NPS and having haploinsufficiency of the LMX1B gene who experienced severe bilateral chronic angle-closure glaucoma in both eyes and that was successfully managed with a flap-express procedure in the right eye. The left eye had no light perception, and medical treatment was considered. Glaucoma is the most frequent ocular abnormalities observed in association with NPS and usually presents with an open angle. Glaucoma associated with NPS typically has an early onset open-angle phenotype. In fewer cases, it may present with an angle-closure phenotype. Therefore, we emphasize the need for glaucoma case-finding protocols comprehensive of gonioscopy in NPS patients and their relatives.

Introduction

Nail-patella syndrome (NPS) is an autosomal dominant disorder characterized by a classical clinical tetrad involving nail dysplasia, aplastic or hypoplastic patellae, elbow dysplasia, and the presence of iliac horns [1]. Besides nails and osteoarticular defects, a significant proportion of patients present with multisystemic involvement, namely, renal

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anomalies extending from asymptomatic proteinuria to end-stage renal failure [2]. Among other involved organs, ocular anomalies and ocular sight-threatening diseases have been consistently reported in patients affected by NPS [1, 3–10]. NPS was first described in the 1800s, and more recently, in 1998, the LMX1B mutations (9q33.3) leading to loss of function of the LMX1B protein were identified as responsible for NPS [11]. LMX1B gene encodes a transcription factor that belongs to the LIM-homeodomain family of proteins. These proteins are essential for the normal development of dorsal limb structures in vertebrates, the renal glomerular filtration barrier components, and the anterior segment of the eye [2, 12]. Therefore, the haploinsufficiency of this transcription factor has been implicated in the pathogenesis of NPS multisystemic disease. Ocular anomalies have been initially described among people affected by NPS, with phenotypes varying from ocular hypertension (OHT) to pigmentary glaucoma and bilateral congenital glaucoma [3]. In cases where glaucoma was clinically indistinguishable from typical primary open-angle glaucoma (OAG), a relatively young age at diagnosis (median: 38, interquartile range 30–43 years) was observed [3, 11]. Of note, no manifest gonioscopic signs of angle dysgenesis were observed in these cases. In other studies on NPS patients, glaucoma or OHT was found in 20–33% of patients aged 40 years or more, significantly more than the prevalence expected in an age-matched population without NPS [1, 4, 7]. Other ocular abnormalities reported in NPS patients included microcornea, sclerocornea, congenital cataract, and the presence of the Lester's sign [2, 13]. Lester's sign consists of a zone of darker pigmentation around the central part of the iris, but this sign is not specific since it is also frequently observed in the normal population [1, 13]. Recently, a case of NPS associated with bilateral symptomatic angle closure caused by plateau syndrome was described [10]. We report another case of NPS associated with angle-closure glaucoma.

Case Report

A 57-year-old woman of African descent was referred in February 2021 to the glaucoma unit of Clinica Oculistica San Martino Polyclinic Hospital, Genoa, Italy, to manage a medically uncontrolled bilateral glaucoma. At the first evaluation, the patient complained about progressively decreased vision in both eyes. Carefully interviewed, she reported a history of glaucoma for about 5 years, currently on therapy with brinzolamide/timolol b.i.d. (Azarga, Novartis Farma SpA, Italy) and latanoprost q.d. (Xalatan, Medifarm Srl, Italy). Best-corrected visual acuity was logMAR 0.5 in the right eye and no light perception in the left eye. In the right and left eyes, the intraocular pressure (IOP) was 48 mm Hg and 60 mm Hg, respectively.

Besides a subtle microcystic corneal oedema in the left eye, the slit-lamp examination revealed a within anterior limit anterior segment and a trace of lens nuclear sclerosis for both eyes. Furthermore, corneal dynamic gonioscopy showed bilateral peripheral anterior synechiae extending almost entirely over the circumference. In addition, the neuroretinal rim of the right optic disk was very thin, whereas the left eye papilla was atrophic. Then, acetazolamide 250 mg per os q.i.d was prescribed, and gentle decompression was performed, via an inferotemporal paracentesis, in both eyes. The day after, IOP decreased to 18 and 30 mm Hg in the right and left eyes, respectively. Despite maximum tolerated medical therapy, IOP remained above the target, and a surgical procedure was scheduled for the right eye. Trabeculectomy with Ex-PRESS implantation was performed, and after a year of follow-up, IOP was stable in the mid-teens (Figs. 1, 2).

Besides the glaucoma diagnosis, the patient was diagnosed in 1990, at the age of 26 years old with NPS based on clinical criteria (Fig. 3). No renal involvement was noted during the course of the disease, and glaucoma was not investigated at the time of NPS diagnosis. Later, in 2016 genetic analysis confirmed the diagnosis of NPS, revealing haploinsufficiency of the

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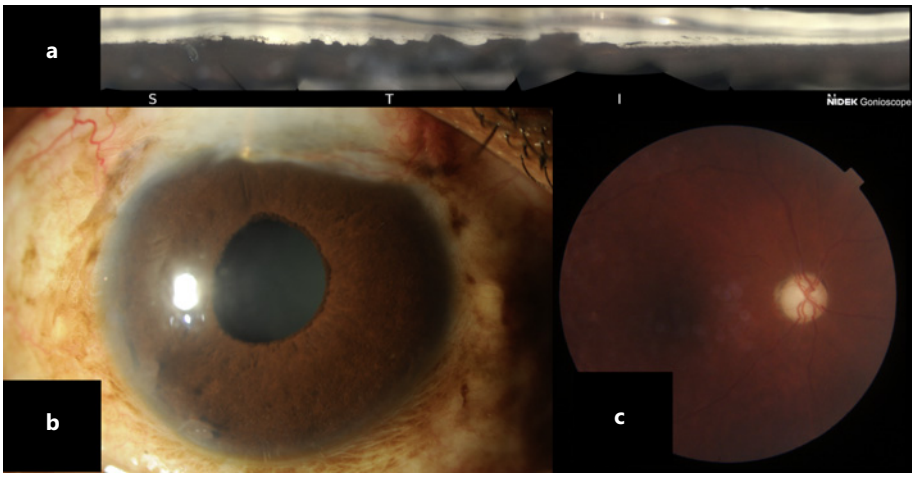

Fig. 1. Right eye: gonioscopic view (**a**), slit-lamp photo (**b**), fundus photo (**c**).

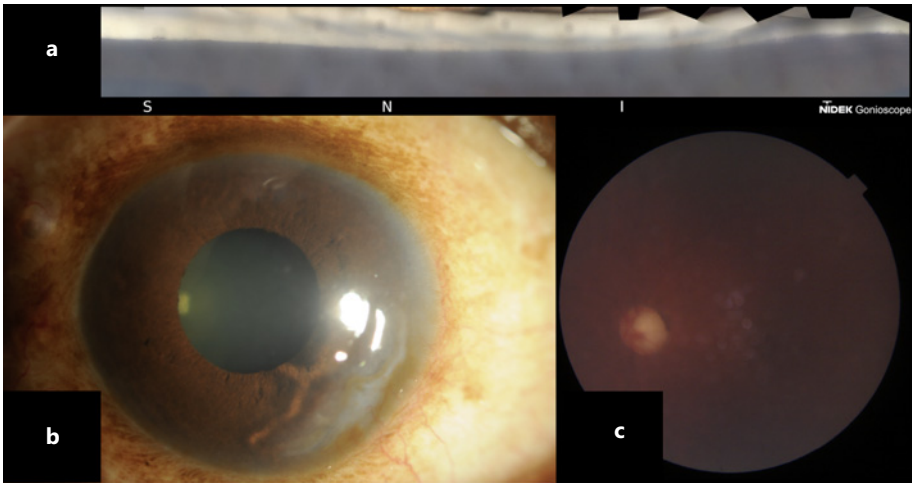

Fig. 2. Left eye: gonioscopic view (**a**), slit-lamp photo (**b**), fundus photo (**c**).

LMX1B gene (c.312dup> [p.Gln105Thr/s*43]), described in the literature as causative of the NPS. Clinical features of NPS were hypoplastic nails with absent lunulae and loss of distal interphalangeal skin creases (Fig. 1), and bilateral patellar hypoplasia (Fig. 2). She reported the diagnosis of NPS also in her only daughter with mild renal involvement and no ocular disease. Unfortunately, no access to detailed medical records was possible.

Discussion

Since the initial description of NPS more than a century ago, several involved organ anomalies have been associated with the condition in the last two decades [7, 13, 14]. Renal and ocular involvements are the most severe comorbidities related to NPS and may represent a significant part of the disease burden [4, 14]. Our work presented a case of bilateral chronic angle-closure glaucoma unresponsive to medical treatment and treated by a filtering

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Fig. 3. Clinical features of nail-patella syndrome. Hypoplastic nails with absent lunulae and loss of distal interphalangeal skin creases on fingers of right hand (**a**) and left hand (**c**). X-ray scan of the knees showing a bilateral hypoplastic patella in right (**b**) and left leg (**d**).

procedure. Previous studies have described a broad spectrum of glaucomas or OHT associated with NPS encompassing congenital glaucoma, pigmentary glaucoma, OAG, normal-pressure glaucoma, and plateau iris syndrome [3, 5, 6, 10]. Table 1 summarizes the studies reporting association between glaucoma and NPS. Even if glaucoma is a relatively common eye disease and its co-existence with other ocular or systemic diseases is not surprising, several clues link NPS and glaucoma pathogenesis. First, since the early reports by Litcher et al. [3], the onset of glaucoma in NPS patients was observed at a younger age than what is expected with primary OAG. Even if the gonioscopic features of NPS glaucoma patients described by Litcher were not suggestive of angle dysgenesis, nowadays, optical coherence tomography scans of the anterior chamber angle have shown abnormalities in the trabecular meshwork and Schlemm's canal that are otherwise undetected by standard angle examination techniques [15]. Thus, it is impossible to rule out that some form of angle dysgenesis could exist even in a normal-appearing angle.

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Table 1. Summary of studies reporting the association between glaucoma and NPS

First author (year)	Study design	NPS cases, *n*	Glaucoma diagnosis, *n*	Type of glaucoma	Age of diagnosis
Lichter et al. [3] (1997)	Case series	Family 1: 13 Family 2: 11	6 7	GL: 6 GL: 5 PG: 1 PDS: 1	Mean age family 1: 32 yo Mean age family 2: 24 yo (2 cases of congenital glaucoma)
Fröhlich et al. [9] (2002)	Case report	2	1	OAG	42
Sweeney [1] (2003)	Case series	83	14	GL: 8 OHT: 6	Mean age: 47.9 years (23–78 years)
Bongers [2] (2005)	Case series	51	17	OAG: 2 NTG: 4 OHT: 2 GL: 9	Mean age: 63.4 yo 1 case of OAG <40 yo 1 case of OHT <40 yo
Mimiwati et al. [4] (2006)	Case series	19	4	OAG: 1 NTG: 1 OHT: 2	33 63 14–24
Millá et al. [5] (2017)	Case series	10	7	OAG: 1 OHT: 6	
Romero et al. [6] (2011)	Case series	5	4	GL: 3 OHT: 1	57–53–42 21
Ghoumid et al. [7] (2016)	Case series	43	9	GL: 9	5 of them <40 yo
Nicolle et al. [8] (2017)	Case report	1	1	OAG	About 35 yo
Gardin et al. [10] (2020)	Case report	1	1	Plateau iris syndrome and angle-closure glaucoma	32 yo
Total		239 (only case series)	71 (29.7%)		

Only cases reporting an eye examination were included. GL, glaucoma; NL, normal; NPS, nail-patella syndrome; OHT, ocular hypertension; NTG, normal tension glaucoma; OAG, open-angle glaucoma; PG, pigmentary glaucoma; PDS, pigment dispersion syndrome; IOP, intraocular pressure; yo, years old.

The second clue that links NPS with glaucoma is represented by the protein coded by the role LMX1B gene, whose loss-of-function mutations cause NPS [11]. LIM homeobox transcription factor 1-beta is essential for the normal development of dorsal limb structures, the glomerular basement membrane, dopaminergic and serotonergic neurons, and the anterior segment of the eye [11]. Animal studies have shown that homozygous for a targeted mutation of LMX1B exhibits iris and ciliary body, hypoplasia, and cornea stromal abnormalities [16]. Moreover, by inducing different LMX1B mutations in mice, further research has demonstrated that different LMX1B mutations can result in elevated IOP and glaucomatous damage. LMX1B-mutated mice represent a rare animal model of human glaucoma caused by mutation of the same gene in humans and mice [17].

Lastly, a case-control genetic association study has shown that specific LMX1B haplotypes influence susceptibility to glaucoma in the general population and a genome-wide analyses also identify that some SNPs significantly associated with IOP in healthy population annotate near

LMX1B gene [18, 19]. Glaucoma is a progressive neurodegenerative eye condition caused by retinal ganglion cell apoptosis where IOP is the major modifiable risk factor for its onset and progression [20]. If untreated, glaucoma may lead to severe visual disability and irreversible blindness. Abnormalities in the anterior segment, particularly in the irido-corneal angle of the eye, may cause impaired aqueous humor reabsorption by the trabecular meshwork and hence IOP elevation. Since glaucoma is generally asymptomatic, progressive, and irreversible, early diagnosis and effective treatment by reducing IOP are of paramount importance. Whereas screening for glaucoma in the general population is not considered cost-effective, it is recommended in NPS because of the high prevalence of their association, early onset of the disease, and relatively few patients affected by NPS to be submitted for an ophthalmological examination [21].

Conclusion

Our study highlights the importance of screening for glaucoma comprehensive of gonioscopy in NPS patients. Moreover, we speculate that angle examination with modern technologies such as optical coherence tomography may show abnormalities of the trabecular meshwork or Schlemm's canal even in NPS patients with normal-appearing angles. This hypothesis should be tested in further studies.

Statement of Ethics

Ethics approval was not required in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. This report does not contain any personal information that could lead to the identification of the patient.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Nicola Pallozzi Lavorante, Michele Iester, Chiara Bonzano, Alessandro Bagnis, Carlo Enrico Traverso, and Carlo Alberto Cutolo: substantial contribution to conception and design of the case report and drafting the manuscript and gave final approval to be published.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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