Original Article

Ten-year Follow-up of Familial Nanophthalmos in Three Siblings

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Abstract

Purpose: Nanophthalmos is a rare congenital disorder associated with a high incidence of angle-closure glaucoma. We followed the clinical manifestations of three siblings to evaluate their responses to various treatments.

Methods: Three sisters with nanophthalmos were followed from 2000 to 2013. Glaucoma and cataract treatments were performed whenever indicated.

Results: The oldest sister had chronic elevation of intraocular pressure(IOP) and underwent laser peripheral iridotomy (LPI) on both eyes, followed by uneventful phacoemulsification with intraocular lens (IOL) implantation on the left eye and phacotrabeculectomy with IOL implantation on the right eye. The middle sister had acute elevation of IOP and initially underwent phacoemulsification combined with implantation of two IOLs on her left eye and LPI on her right eye. Severe uveal effusion occurred when phacoemulsification was performed on her right eye 6 years later, but ultimately was completely resolved. In both sisters, stable IOP and visual results were achieved after lensectomy. The youngest sister, who had suspected angle-closure, achieved a stable IOP and visual results with prophylactic LPI alone.

Conclusion: In nanophthalmic eyes, the severity of the disease may foreshadow the severity of surgical complications and responses to therapy.(***Eye Science 2013; 28:113-118***)

Keywords: nanophthalmos; angle-closure glaucoma; laser peripheral iridotomy; phacoemulsification

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Introduction

Nanophthalmos, or microphthalmos without intraocular malformations, is a rare congenital disorder characterized by short axial length (less than 17–20 mm), high hyperopia, elevated lens-to-eye volume ratio, and thickened sclera[1-3]. These anatomical aberrations lead to a high incidence of angle-closure glaucoma[4], whose management may require a combination of medications, laser peripheral iridotomy, trabeculectomy, and cataract extraction[4-7]. Intraocular surgery for nanophthalmic eyes can be challenging due to the small anterior chamber as well as the propensity for sudden uveal effusion and increased pressure from the posterior segment[3-6,8].

Nanophthalmos occurs sporadically or in familial aggregates. Very few reports of long term follow-up have appeared for the management of hereditary nanophthalmos. In this report, we describe three affected sisters with 9–12 years of follow-up.

Materials and methods

In nine siblings, three sisters were diagnosed with nanophthalmos. Along with their immediate relatives, the three sisters were evaluated in Zhongshan Ophthalmic Center, Guangzhou, China. The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board. Informed consent was obtained from all subjects, including consent for publication of the clinical information and associated images presented in this study.

Each patient underwent a best corrected visual acuity (BCVA) test, slit lamp and fundus examination, and Goldmann applanation tonometry. Anterior

chamber depths (ACD) were measured with a ultrasound biomicroscope (UBM), while the anterior chamber angles were evaluated by UBM and classified by Scheie's grading system with gonioscopy. Corneal thicknesses and axial lengths were measured by A-type ultrasonography, while scleral thicknesses were determined by B-type ultrasonography. Lens opacity was graded by the lens opacity classification system III (LOCSIII).

Glaucoma treatments, including medications, laser peripheral iridotomy, lensectomy, and trabeculectomy with mitomycin C, were performed whenever indicated, using the usual established techniques. The intraocular operations were performed under a retrobulbar anesthetic block. Mannitol 250 ml (20%) was administered intravenously thirty minutes before intraocular surgeries.

Results

The siblings' father, who has died some years previously, reportedly had glaucoma but his ocular history could not be verified. The genetic map is shown in Figure 1. The demographic information of the three sisters and some of their ocular findings on initial examination are summarized in Table 1. All three patients showed normal attachments of the vitreous bodies and the retinas on initial evaluation.

Case 1

The oldest of the three sisters was first diagnosed with nanophthalmos in December 2000. Due to chronically elevated intraocular pressure (IOP) and the risk of progressive angle closure glaucoma, she underwent bilateral laser peripheral iridotomy (LPI). One month after LPI, shallow anterior chambers were noted in both eyes (OU). The peripheral iridotomy site had closed in the left eye (OS), necessitating a second LPI. The anterior chamber of the right eye (OD) deepened 2 days later, but the ACD of OS remained 0.90–1.03 mm at several follow-up visits. Because IOP was controlled (around 18~20 mmHg) medically with timolol alone, no further treatment was performed at that time.

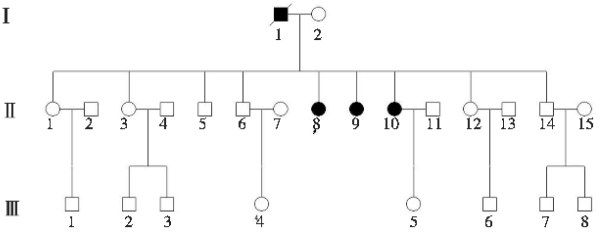

Figure 1 The genetic map of this nanophthalmos family

In July 2003, the patient's BCVA OS dropped to 20/300 due to progressing cataract (graded C1N1P1 with scattered pigmentation on the anterior capsule) and shallowing of the anterior chamber. In November 2003, uneventful phacoemulsification was performed OS with a 30D acrylic intraocular lens (IOL) implanted in the capsular bag.

When she presented again in March 2006, her BCVA OD had dropped to 20/200. Her IOP was

Table 1 Demographic information and ocular parameters at the initial visits

Case	Age at diagnosis	Eye	BCVA	IOP (mmHg)	Corneal diameter (mm)		Corneal thickness (μm)	ACD (mm)	Anterior chamber angle	Axial length (mm)	Scleral thickness (mm)	Lens	C/D
					horizontal	vertical							
1	48	od	20/100	23	10.5	10	542	1.551	NIV	15.64	2.31	clear	0.2
		os	20/100	23	10.5	10	545	1.500	NIV	15.78	2.22	clear	0.2
2	48	od	20/60	27	10	9	537	1.678	NIV	15.48	2.25	C1N2P1	0.2
		os	20/200	29	10	9	539*	1.458	NIV	15.19	2.32	C1N3P1	0.2*
3	46	od	20/60	18	11	10.5	553	1.700	NIV	17.32	2.10	clear	0.2
		os	20/60	18	11	10.5	548	1.732	NIV	17.56	2.12	clear	0.2

*: measured after resolution of corneal edema

BCVA: best-corrected visual acuity

IOP: intraocular pressure, measured by the Goldmann tonometer

ACD: anterior chamber depths, measured by ultrasound biomicroscopy (UBM)

Anterior chamber angles were graded by Scheie's grading system

Axial lengths were measured by A-type ultrasonography

Scleral thicknesses were measured by B-type ultrasonography

Lens opacity was graded by the lens opacity classification system III (LOCSIII)

23 mmHg on timolol and brimonidine, the opacity of the lens was graded $C_3N_2P_1$, and the cup-to-disc ratio enlarged to 0.4. Phacotrabeculectomy with 0.3 mg/ml mitomycin C (MMC) was performed with a 30D acrylic IOL implanted in the capsular bag. Her postoperative course was significant for severe anterior chamber inflammation and corneal edema, which eventually resolved with medical management.

At her last visit in March, 2013, BCVA remained 20/100, IOP was 14 mmHg without medications, and ACD had deepened to 3.5 mm in both eyes.

Case 2

This patient initially presented with redness and blurred vision OS for one day in July, 2003. Pigmented keratic precipitates (KP) and fibrin exudates were visible OS secondary to acute IOP elevation. Partial posterior synechiae were present OU. After pharmacological control of inflammation and IOP, phacoemulsification OS was performed with implantation of two IOLs. After gradual resolution of intraocular inflammation and corneal edema, BCVA OS was 20/60, while IOP improved to 16 to 18 mmHg without eye drops.

LPI was performed OD. Despite worsening cataract and fluctuation of IOP, the patient chose not to have phacoemulsification until July 2009. By then, the

Table 2 Operations and long-term outcomes on the eyes of the three siblings with nanophthalmos

Case	Eye	Operations	Operation date	Indications	Outcomes		
					VA	IOP	Others
1	od	LPI	2000.12	Pupil block and elevated IOP	Gradually drop to 20/200	18–20 mmHg with Timolol but elevated (23 mmHg) later	Transient shallow AC
	os	LPI	2000.12	Pupil block and elevated IOP	Drop to 20/200	20mmHg with Timolol and Brimonidine but elevated (23 mmHg) later	Shallow AC, close of LPI site
	os	Second LPI	2001.1	Close of LPI site, shallow AC	Gradually drop to 20/300	18–20 mmHg with Timolol but elevated (29 mmHg) later	Continuous shallow AC (0.58–1.03 mm)
	os	Phaco+IOL	2003.11	Shallow AC, elevated IOP, 1/2 close of anterior chamber angle	Stable in 20/100	10–14 mmHg without eye drops	/
	od	Phaco+IOL +Trab+MMC	2006.3	Elevated IOP, 3/4 close of anterior chamber angle, enlargement of C/D, lens graded $C_3N_2P_1$	Stable in 20/100	12–14 mmHg without eye drops	/
2	os	Phaco+2IOLs	2003.7	Elevated IOP, funtional close of anterior chamber angle, lens graded $C_1N_3P_1$	Stable in 20/100	16–18 mmHg without eye drops	/
	od	LPI	2003.7	Pupil block and elevated IOP	Gradually drop to 20/200	Fluctuated in 18–25 mmHg with Timolol and Brinzolamide	/
	od	Phaco	2009.7	Elevated IOP,lens graded $C_2N_4P_1$	Stable in 20/200	18–20 mmHg with Brinzolamide	Choroidal effusion subsided completely after operation
3	od	LPI	2003.9	High risk of angle closure	Stable in 20/60	18–20 mmHg without eye drops	
	os	LPI	2003.9	High risk of angle closure	Stable in 20/60	18–20 mmHg without eye drops	

LPI: laser peripheral iridotomy
IOP: intraocular pressures
AC: anterior chamber
Phaco: phacoemulsification
IOL: intraocular lens implantation
VA: visual acuity
Trab+MMC: trabeculectomy with mitomycin C
C/D: cup disc ration
Lens opacity was graded by the lens opacities classification system III (LOCSIII)

lens was graded $C_2N_4P_1$. During phacoemulsification, the anterior chamber suddenly became shallowed, leading to rupture of the posterior capsule and choroidal effusion, preventing IOL implantation. Intravenous mannitol 250 ml (20%) and methylprednisolone 80 mg were administered immediately. The first day after surgery, funnel-shaped exudative retinal detachment and choroidal detachment were evident. One month later, BCVA had improved to 20/100, IOP was 19 mmHg on brinzolamide alone, ACD was 3.5 mm, and the retina and choroid had reattached. At the last visit in May, 2013, these findings had remained essentially unchanged.

Case 3

The youngest of the three sisters was diagnosed with nanophthalmos on routine eye exam in September, 2003. Bilateral LPI was performed prophylactically. Ten days later, IOP was 18 mmHg OU without eye drops. At the last visit in March 2013, all anatomical and visual parameters had returned to baseline levels.

A chronological summary of the operations and the outcomes on the eyes of the three sisters is shown in Table 2. The calculated IOL powers, the implanted IOLs, and the postoperative refractions for case 1 and case 2 are shown in Table 3.

Table 3 The calculated IOL powers, the implanted IOLs, and the postoperative refractions of the eyes of case 1 and case 2

Case	Eye	Calculated IOP powers		Implanted IOL	Postoperative refraction
		Holladay II	Hoffer Q		
Case 1	os	47.0D	55.5D	30D acrylic IOL in the capsular bag	16.5D
	od	49.5D	59.5D	30D acrylic IOL in the capsular bag	17.0D
Case 2	os	51.0D	64.5D	a 30D acrylic IOL in the capsular bag and a 12D acrylic IOL in the ciliary sulcus	13.0D
	od	49.5D	61.5D	/	34.0D

Discussion

Sporadic nanophthalmos is common, but nanophthalmos can also be inherited in an autosomal recessive or dominant fashion. Mutations in the MFRP and CHX10 genes have been associated with nanophthalmos[9-10]. Among four members with nanophthalmos in one sibship reported by Cross et al[1]., only one developed glaucoma. Neelakantan et al[3]. also described a brother and a sister with nanophthalmos, but only the sister developed angle-closure glaucoma (ACG). Three cases of familial nanophthalmos associated with ACG were reported by Martorina[2]. In the present study, two of three sisters developed ACG during the course of 9–12 years of follow up. The characteristically high lens/eye volume ratio, which contributes to the crowding of the anterior segment and shallowness of the anterior chamber[4], may predispose these patients to a high risk of developing ACG.

Most reports indicate the typical manifestation of ACG secondary to nanophthalmos to be a slow, painless, and progressive elevation of intraocular pressure in middle age[1-7]. The poor visual acuities and foveal abnormalities (such as absent or rudimentary foveal avascular zone and diminished foveal pit) in nanophthalmic patients[11] typically render the results of visual field examinations unreliable. In addition, due to the proportional abnormalities of intraocular contents and of the optic papilla, the cup-to-disc ratio can underestimate the extent of optic nerve damage. Prominent glaucomatous cupping usually suggests late stage disease[7,12]. The use of other diagnostic modalities such as optical coherence tomography has not been well established in the management of glaucoma in nanophthalmos. Therefore, glaucoma in nanophthalmic patients may need earlier and more aggressive treatment.

LPI, lensectomy, and trabeculectomy have been traditionally used to manage glaucoma in nanophthalmos. Most reports in the literature have fewer than two years of follow-up[2-6,8]. LPI is considered safe because it maintains the integrity of the eyeball and avoids many of the risks associated with intraocular surgery[4]. LPI relieves pupillary block, but in the present study, it seemed insufficient for two out of three patients in the long term, similar to the case reported by Sharan et al[13]. The main cause of the ele-

vated IOP with narrow angles in nanophthalmos is not simply pupillary block, but also involves the relatively large lens volume and the consequent forward displacement of the lens-iris diaphragm[3]. LPI does not fully address the underlying pathophysiology. In case 3, LPI appears to be effective, probably because her axial lengths and anterior chamber depths were greater than those of her sisters. Therefore, the severity of nanophthalmos may determine the response to LPI.

Uveal effusion may occur spontaneously, during or after intraocular procedures in nanophthalmos[3-5,8], probably as a result of choroidal congestion secondary to obstruction of the vortex veins by the abnormally thickened sclera[2]. Sudden decompression of the globe during intraocular surgery appears to aggravate the degree of uveal effusion. In 1975, Calhoun described lens extraction to manage glaucoma in nanophthalmos[6] despite the high incidence of serious posterior segment complications. Large-incision extracapsular cataract extraction could improve IOP control[14], but choroidal effusion and non-rhegmatogenous retinal detachments were common[4,6]. The introduction of small-incision phacoemulsification improved the surgical results in patients with nanophthalmos[14,15]. While few reports have described the success of phacoemulsification alone in managing nanophthalmic glaucoma[13], increasingly more data show favorable results for phacoemulsification as a treatment for primary angle closure glaucoma[16-20]. The current study indicates that, in select cases (left eyes of cases 1 and 2), lens extraction by phacoemulsification can achieve good visual and IOP results in nanophthalmic patients with ACG in the long run.

Calhoun suggested that "ordinary glaucoma surgery was to be avoided"[6] in 1975, and severe complications have been periodically reported[4,5,8]. With some modifications, such as prophylactic sclerotomy, trabeculectomy remains an important procedure to manage glaucoma in nanophthalmos[7]. The right eye of case 1, which underwent phacotrabeculectomy with MMC, achieved long-term visual and IOP results similar to eyes with primary angle closure glaucoma[21].

IOL power calculation and selection can be challenging in nanophthalmic eyes due to the shorter axial lengths and greater corneal curvatures. The Holladay II and Hoffer Q formulas have been shown to be adequate in microphthalmos[22,23]. Because nanophthalmic eyes usually require IOL powers that are not commonly available, implantation of two or more IOLs in the posterior chamber of the same eye has been successfully attempted[24,25]. In the current study, it is difficult to determine which formula is better.

In summary, glaucoma management in nanophthalmos is challenging. Lensectomy, with or without trabeculectomy, appears effective in lowering IOP, while iridotomy alone may be insufficient. However, intraocular surgeries can be complicated by uveal effusion and a significant inflammatory response. Nanophthalmos should be stratified according to severity, which may predict the need and response to treatment.

Disclosure statement

There is no conflict of interest to declare.

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