Angle Closure Glaucoma in a Patient with MFRP Gene-Related Nanophthalmos: A Case Report*

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ABSTRACT

This is a case of a 27-year old female who presented with sudden left eye pain associated with blurring of vision and redness. At a consult done at another institution, patient was given analgesics and underwent plain cranial CT scan with unremarkable results. Worsening of the symptoms prompted patient to seek second opinion at this institution. Ophthalmologic examination showed best corrected visual acuity (BCVA) of 20/40 on the right eye and light perception on the left eye. Intraocular pressure (IOP) was 24 mmHg on the right eye and 42 mmHg after 1 dose of Acetazolamide 250mg. Ocular findings of the left eye revealed narrow palpebral fissure, 6mm pupil non-reactive to light, convex iris, elevated intraocular pressure, and synechial closure on all angles. More than the clinical picture of angle closure glaucoma, the discovery that the patient's parents were first cousins and her history of high hyperopia since early childhood prompted clinical suspicion of nanophthalmos. Fundus photography, keratometry, ultrasound biomicroscopy, ocular A-scan and B-scan ultrasonography, and optical coherence tomography were all consistent with the diagnosis of angle closure glaucoma secondary to nanophthalmos. Despite being subjected to pressure-lowering agents, the IOP remained uncontrolled and trabeculectomy was done to the left eye. Postoperatively, patient's IOP was 14 mmHg on the right eye and 18 mmHg on the left. BCVA was noted at 20/40 on the right and 15/400 on the left eye. Having taken into account that history of consanguinity increases risk for genetic disease, especially autosomal recessive diseases, genetic investigation was done. A Microphthalmia/Anophthalmia panel was requested and showed a mutation in the Membrane-type Frizzled-Related Protein (MFRP) gene.

Key words: Angle closure glaucoma, nanophthalmos, macular edema

Nanophthalmos is a small-eye disorder derived from the Greek word nano, meaning, "dwarf."[3] In this condition, both eyes are usually affected.[8] The anterior and posterior segments of the nanophthalmic eye are both reduced in size, but are structurally and functionally normal. It has a global prevalence estimated to be less than 1 out of 2,000.[9] The presence of nanophthalmos has also been observed among consanguineous populations in some studies.[9,11,17] To date, the only local report on the same ophthalmic entity was that of Bromeo, et al.[2] Due to its rarity, this ocular disease may frequently go undiagnosed or misdiagnosed, and if inappropriately treated, may result in blindness.

Relhan and colleagues noted that diagnosis may be overlooked because individuals with nanophthalmos often manifest with high hyperopia during childhood, which can initially be improved with glasses.[11] Later in life, visual acuity may be compromised as these individuals become highly susceptible to angle closure glaucoma due to the disproportion between the normal increase in lens thickness relative to an eye with a very small intraocular volume.[5] Yalvac,

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et al. explain that the mechanism of angle closure in the setting of a nanophthalmic eye may be multifactorial. The lens can push the iris towards the crowded anterior chamber, causing a pupillary block and eventually leading to the formation of peripheral anterior synechia. The anterior chamber angle can also be closed by physical displacement of the peripheral iris by anteriorly-rotated ciliary processes when nanophthalmos presents with ciliochoroidal effusion and ciliary body detachment.[17]

To the best of our knowledge, this is the first paper to report a positive genetic test in a patient diagnosed with nanophthalmos in the Philippines. This paper aimed to discuss a case of nanophthalmos which presented with angle closure glaucoma. This report highlights the importance of a holistic approach to history taking and examination, early recognition, and management of such rare disease.

THE CASE

This is a case of a 27-year-old Filipino, female, Roman Catholic, currently residing in Caloocan City, who came in with a chief complaint of left eye pain.

The history of present illness started two weeks prior to consult when the patient experienced sudden left eye pain, boring in character, radiating to her left parietal area associated with redness and blurring of vision of the left eye. Patient self-medicated with Paracetamol 500mg as needed for the pain. However, this afforded no relief of the symptoms. The progression of symptoms prompted her to consult at another institution where she was given a dose of intravenous analgesics, which provided temporary relief of symptoms. The assessment was not disclosed. Patient was discharged stable and advised plain cranial CT scan as outpatient basis, which revealed unremarkable results.

During the interim, patient still reported persistence of the severe left eye pain, eye redness, and blurring of vision. However, she opted to tolerate these symptoms due to the enhanced community quarantine brought about by the COVID-19 pandemic.

Two days prior to consult, persistence of the symptoms prompted patient to seek a second opinion with a private ophthalmologist. At the time of examination, BCVA of the right eye was 20/40 and light perception on the left eye despite the use of very thick corrective spectacles. IOP of the right eye was 26 mmHg and 60mmHg on the left eye, which decreased to 42mmHg after 1 dose of 250mg Acetazolamide. Gonioscopy revealed appositional closure and synechial closure on the right eye and left eye, respectively. At this juncture, working impression of angle closure glaucoma secondary to nanophthalmos of the left eye was considered with suggestion for further work-up. Patient was started on Acetazolamide 250mg 1 tablet 3 times a day, Prednisolone acetate eye drops 4 times a day, and Timolol + Brimonidine eye drops 3 times a day. The patient was then advised Glaucoma service consult at this institution.

Past Medical History

Patient is a non-hypertensive, non-diabetic, non-asthmatic with no history of previous surgeries. She had one prior hospitalization due to Amoebiasis in 2006. She is known to be allergic to seafood.

Family History

Patient's paternal and maternal grandparents were all hypertensive. Her paternal grandmother died due to stroke, while her father died due to cardiac arrest. Further probing led to the discovery of a history of consanguinity in the family (Figure 12). The parents of the patient are first-degree cousins. The patient reported no other family members who made use of spectacles. There was no history of any form of ocular surgery, blinding or glaucomatous disease in her family.

Personal and Social History

Patient is a non-smoker, non-alcoholic beverage drinker, who denies any illicit drug use. Patient works as a hardware shop saleslady.

Ocular History

Patient was diagnosed with hyperopia at 6 years of age and was prescribed full correction by an optometrist that same year. No history of consult with an ophthalmologist nor any previous eye medications. No previous ocular trauma nor surgeries.

Ophthalmologic Examination

The patient was conscious, coherent, oriented to three spheres, and not in cardiorespiratory distress with stable vital signs. Physical examination was

unremarkable. Ocular examination findings are summarized in Table 1. The patient's visual acuity on the right eye was 20/400 without correction (SC) which improved with correction (CC) to 20/40, while the left eye had a BCVA of light perception. Neither retinoscopy nor automated refraction could be performed due to the compromised media of the patient. Her spectacle correction, measured through a lensometer, was +13.50D sph on both eyes. External eye examination (Figure 1) showed a deep-set left eye and exotropia demonstrated by the nasal displacement of the corneal light reflex of the left eye. The interpalpebral fissure of the patient's right eye measured 9mm vertically (Marginal Reflex Distance 1 or MRD 1 of 3mm, Marginal Reflex Distance 2 or MRD 2 of 5mm) and 27mm horizontally. Whereas the patient was noted to have a narrow interpalpebral fissure on the left eye, measuring 7mm vertically (MRD 1 of 3mm, MRD 2 of 4mm) and 25mm horizontally. Slit-lamp examination of the right eye (Figure 2A) showed a 2-3mm pupil that was reactive to light, clear cornea, a shallow (deeper compared to the left eye) but quiet anterior chamber, convex iris configuration, and clear lens. The pupils were examined prior to constriction of the right pupil (Figure 2A) for laser peripheral iridoplasty and laser peripheral iridotomy of the right eye. The left eye (Figure 2B) showed a 6mm pupil not reactive to

Table 1. Ocular examination

	OD	OS
Visual Acuity	SC: 20/400 CC: 20/40	SC: Light perception CC: No improvement
Pupils	2-3mm pupil RTL	6mm mid-dilated pupil NRTL
External Exam	Palpebral fissure (9mm vertically, 27mm horizontally) Nonhyperemic conjunctiva	Nasal displacement of corneal light reflex Deep set eye Narrow palpebral fissure (7mm vertically, 25mm horizontally) Slightly hyperemic conjunctiva
Anterior Segment	Clear cornea No cells/flare Convex iris plane White-to-white corneal diameter: 10.5mm <1/4x 1x <1/4x	Hazy cornea No cells/flare Convex iris plane White-to-white corneal diameter: 9.5mm (+) Glaucomflecken <1/4x 1x <1/4x
Funduscopic Exam	(+) ROR, clear media, 2:3 AVR, 0.3 CDR, no exudates or hemorrhages, distinct disc borders	Could not be appreciated
Tonometry	18mmHg	40mmHg
Gonioscopy	SL→TM SL→TM SL→TM SL→TM	SL SL SL PAS 360° SL
Extraocular Movements	0 0 0 0 0 0	0 0 0 0 0 0

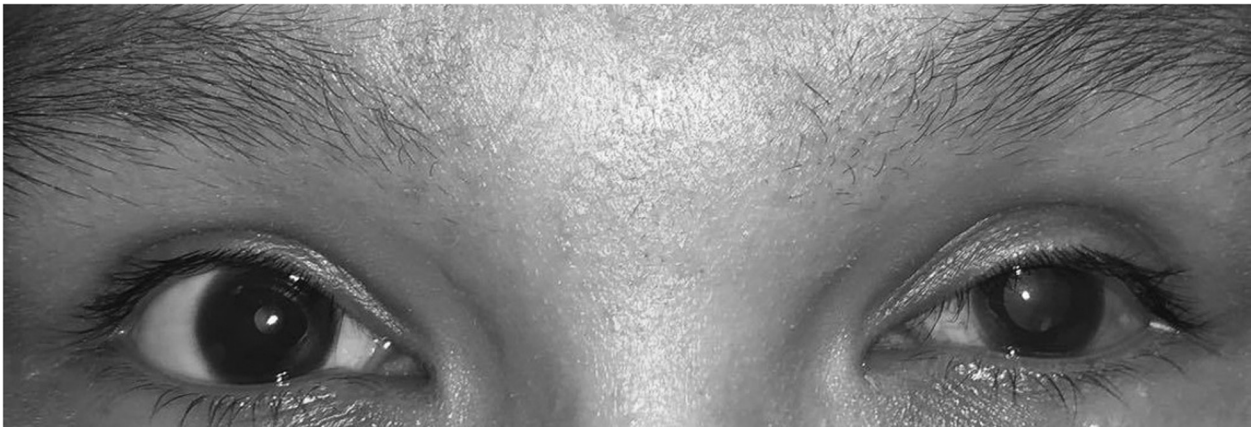

Figure 1. External eye examination. A deep-set left eye with narrow interpalpebral fissure, measuring 7mm vertically and 25mm horizontally, and exotropia demonstrated by the nasal displacement of the corneal light reflex.

Figure 2. Slit-lamp microscopy photographs. A) The right eye showing a 2-3mm pupil equally reactive to light (constricted in the photo), a clear cornea, convex iris plane, and shallow anterior chamber B) The left eye showing a 6mm mid-dilated pupil, hazy cornea, shallow anterior chamber, and glaucomflecken.

light, hazy cornea, shallow anterior chamber (narrow centrally), no cells or flare, a likewise convex iris configuration, and presence of a glaucomflecken at the 7 to 8 o'clock area of the lens. Horizontal corneal diameters, measured using a Castroviejo caliper, were noted to be 10.5mm on the right eye and 9.5mm on the left eye. Funduscopy of the right eye revealed presence of red orange reflex (ROR), clear media, 0.3 cup-disc ratio (CDR), 2:3 arteriolar-to-venular ratio (AVR), no exudates or hemorrhages, distinct disc borders. However, the left fundus could not be appreciated at the time of examination due to the edematous cornea. On Goldmann applanation tonometry, IOP were 18mmHg on the right eye and 42mmHg on the left eye. On gonioscopy, the right eye was closed, showing Schwabe's line with iris strands throughout all angles, but on indentation gonioscopy, part of the trabecular meshwork could be appreciated – denoting an appositional angle closure. In contrast, synechial angle closure was present in the left eye as it was closed on angles with a 360 degree peripheral anterior synechiae (PAS).

Ancillary tests were done to confirm the diagnosis. The keratometry reading revealed a central corneal thickness (CCT) 566µm and 602µm on the right and left eye, respectively. The mean corneal curvature of the both eyes were very steep, measuring 50.12D on the right and 50.22D on the left. White-to-white dimensions or horizontal corneal diameter of right eye and left eye were recorded to be 11.5mm and 11.6mm, respectively (Figure 3). A-Scan ocular ultrasound of both eyes showed short axial lengths measuring 18.36mm and 18.26mm on the right and left, respectively. Ultrasound biomicroscopy of the right eye (Figure 4A) revealed a shallow anterior chamber (AC) depth measuring 1.29mm, increased iris thickness measuring 0.47mm,

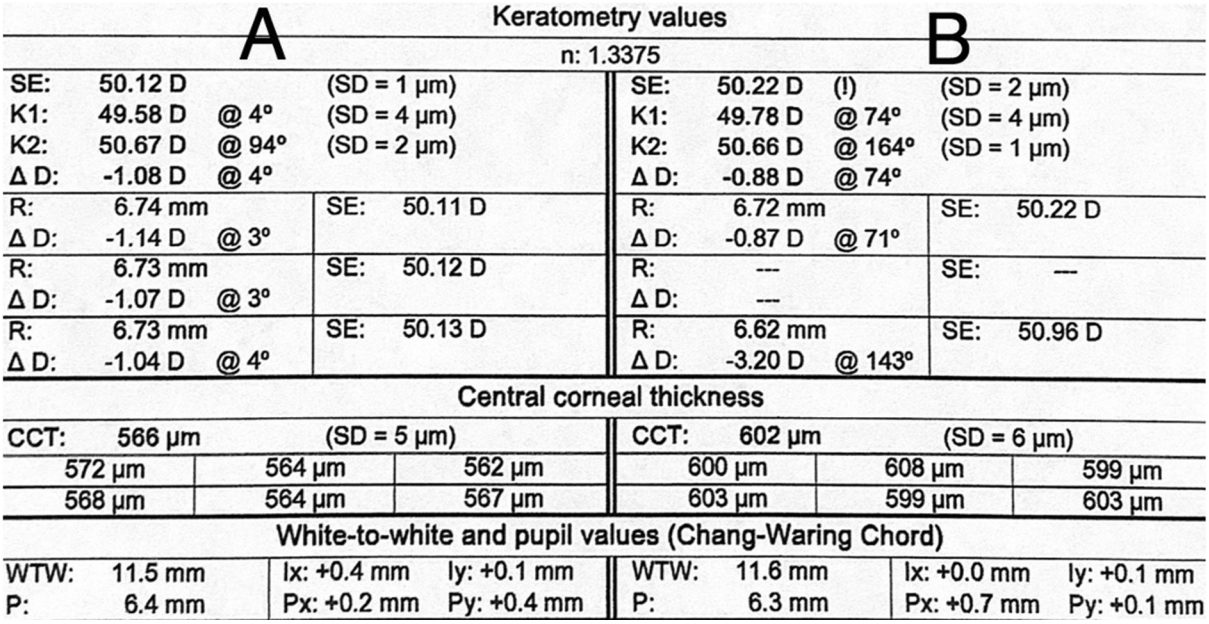

Figure 3. Keratometry. Keratometry readings (A, right eye; B, left eye) revealed very steep mean corneal curvatures, measuring 50.12 D on the right eye and 50.22 on the left eye, a central corneal thickness (CCT) 566µm and 602µm on the right and left eye, respectively.
White-to-white (WTW) values were recorded to be 11.5mm on the right eye and 11.6mm on the left eye.

normal lens thickness measuring 4.43mm, and the lens eye-volume ratio (LEVR) was calculated to be 24%. The lens-eye volume ratio parameter was derived by dividing the lens anterior-posterior diameter by the axial length. The left eye (Figure 4B) also showed a shallow anterior chamber depth measuring 1.67mm, increased iris thickness measuring 0.57mm, normal lens thickness measuring 4.22mm, and a likewise high lens-eye volume ratio of 23%. Both eyes were noted to have narrow angular widths, though the right eye (19.5°, 18.1°) was closer to the normal range in comparison to the left eye (15.7°, 11.1°). On B-scan ocular ultrasound (Figure 5A, 5B). the posterior segment was measured to be 14.22mm on the right eye and 13.61mm on the left eye. Scleral thickness was notably increased in the right and left eyes measuring 2.04mm and 2.50mm, respectively. The choroids were also thickened measuring 1.52mm on the right eye and1.39mm on the left eye. No choroidal effusion or retinal detachment was noted. Optical coherence tomography (OCT) of the right eye showed macular edema (Figure 6) as depicted by the intraretinal and subretinal hyporeflective spaces. Retinal thickness on all subfields, particularly the central thickness, were above normal values. There was also notable loss of the foveal depression. Color fundus photograph of the right eye (Figure 7A) showed a clear media with distinct disc borders, with a CDR of 0.3, there was no rim thinning, peripapillary atrophy, hemorrhages or exudates. There were signs of macular edema due to a petalloid pattern of abnormal reflex in the central macula, consistent with the OCT findings. On the left eye (Figure 7B), there was hazy media, a pale disc with CDR of 0.8, and neuroretinal rim thinning on the temporal side. Macular edema nor cellophane maculopathy could not be completely ruled out on the left eye. Retinal nerve fiber layer loss could not be determined. Also noted was a large drusen located at the nasal retina of both the right (Figure 7C) and left (Figure 7D) eyes. Fundus autofluorescence photographs of both eyes (Figures 8A & 8B) showed intensity signals found in the peripheral retina, corresponding with the yellow spots in the color fundus photographs.

Given these findings, the clinical diagnosis of nanophthalmos of both eyes with secondary angle closure glaucoma on the left eye was confirmed. Prophylactic laser peripheral iridoplasty and laser peripheral iridotomy were performed on the right eye. After securing clearance, she then underwent trabeculectomy of the left eye the following week (Figure 9).

Ultrasound Biomicroscopy

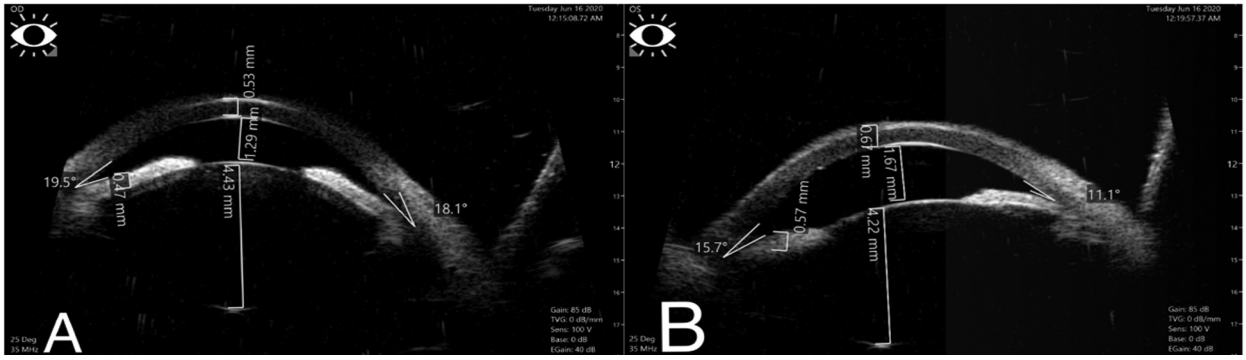

Figure 4. Ultrasound biomicroscopy. (A) The right eye showing a shallow anterior chamber depth, increased iris thickness, normal lens thickness, and high lens-eye volume ratio (B) The left eye showing shallow anterior chamber depth, increased iris thickness, normal lens thickness, and high lens-eye volume ratio. Both eyes had narrow angles (left eye more than the right)

B-Scan Ocular Ultrasound

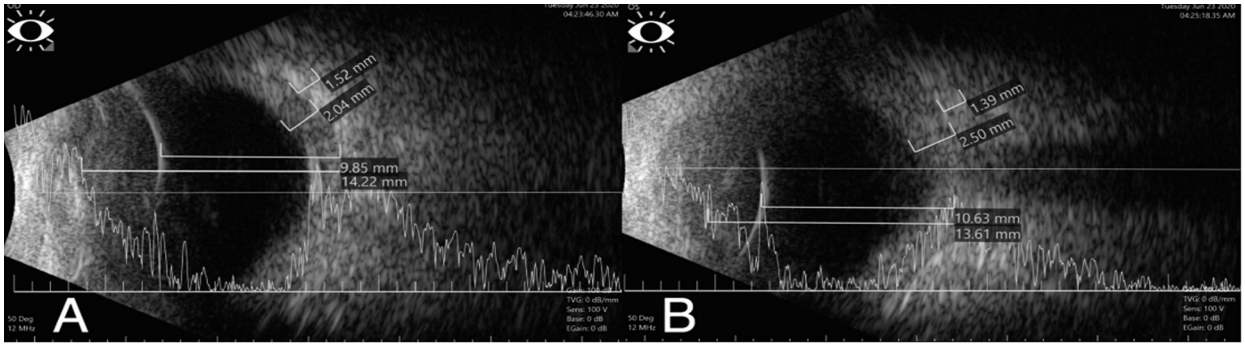

Figure 5. B-scan ocular ultrasound. (A) The right and (B) the left eye both noted to have short posterior segments with clear vitreous as well as thickened sclera and choroid.

Ocular Coherence Tomography of the Macula

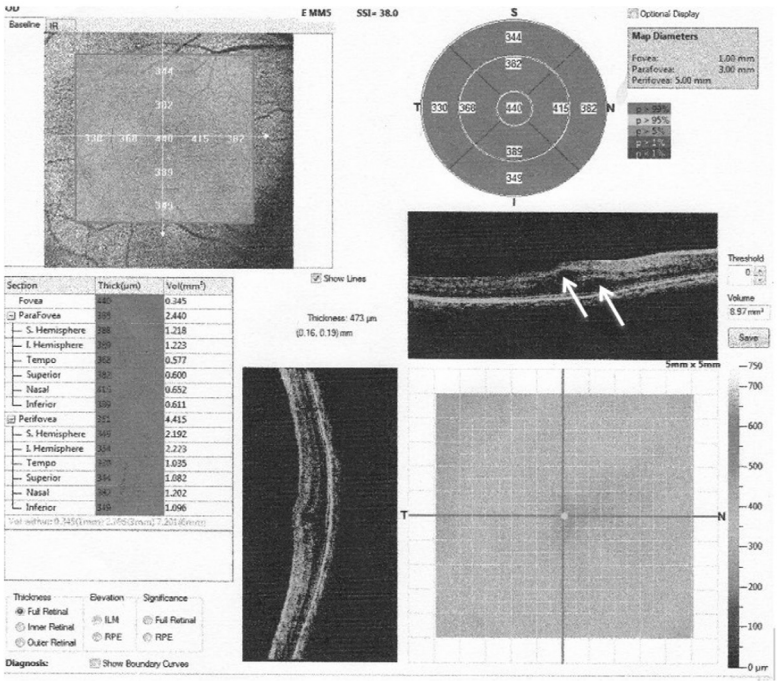

Figure 6. Ocular coherence tomography of the macula of the right eye. The macular thickness map showing increased retinal thickness on all subfields with central thickness above normal values. Horizontal and vertical scans through the fovea showing intraretinal and subretinal hyporeflective cystic spaces (white arrows). Loss of foveal depression was also noted.

Color Fundus Photographs

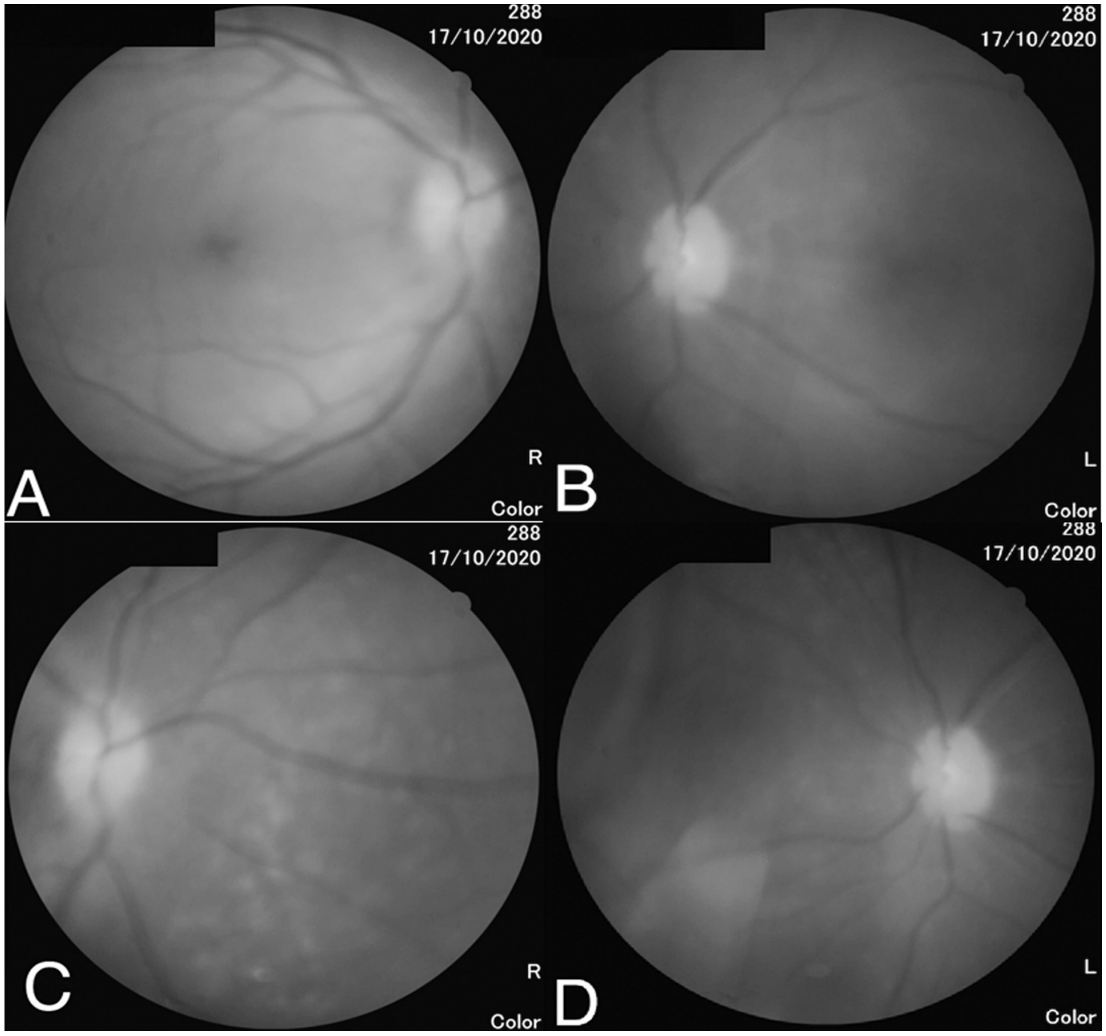

Figure 7. Color fundus photographs. The right eye showing (A) CDR of 0.3, no rim thinning, and signs of macular edema due to a petalloid pattern of abnormal reflex in the central macula consistent with the OCT findings. The left eye showing (B) hazy media, pale disc with CDR of 0.3, temporal neuroretinal rim thinning, and macular edema nor cellophane maculopathy could not be completely ruled out. Large drusen was also noted at the nasal retina of both the right (C) and left (D) eyes.

Fundus Photographs with Autofluorescence

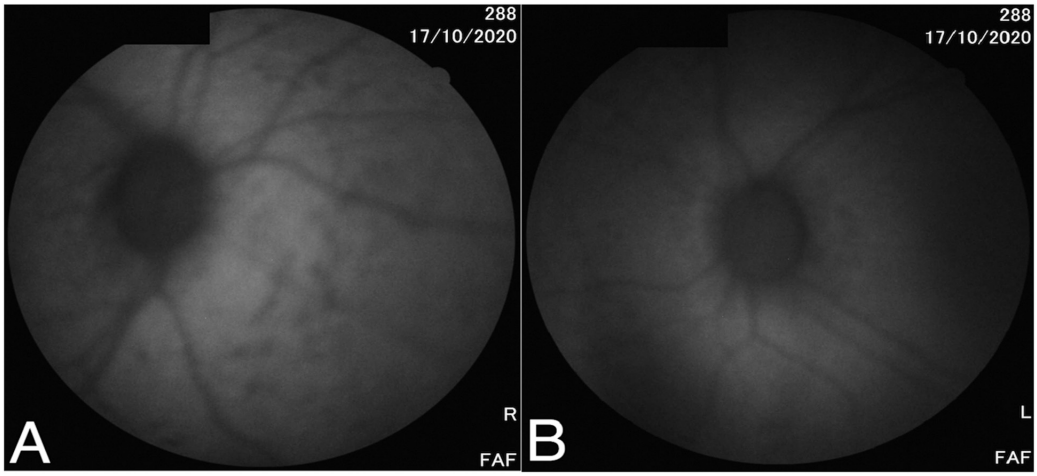

Figure 8. Fundus photographs with autofluorescence. Low intensity signals found in the peripheral retina corresponding with the yellow spots in the color fundus photographs.

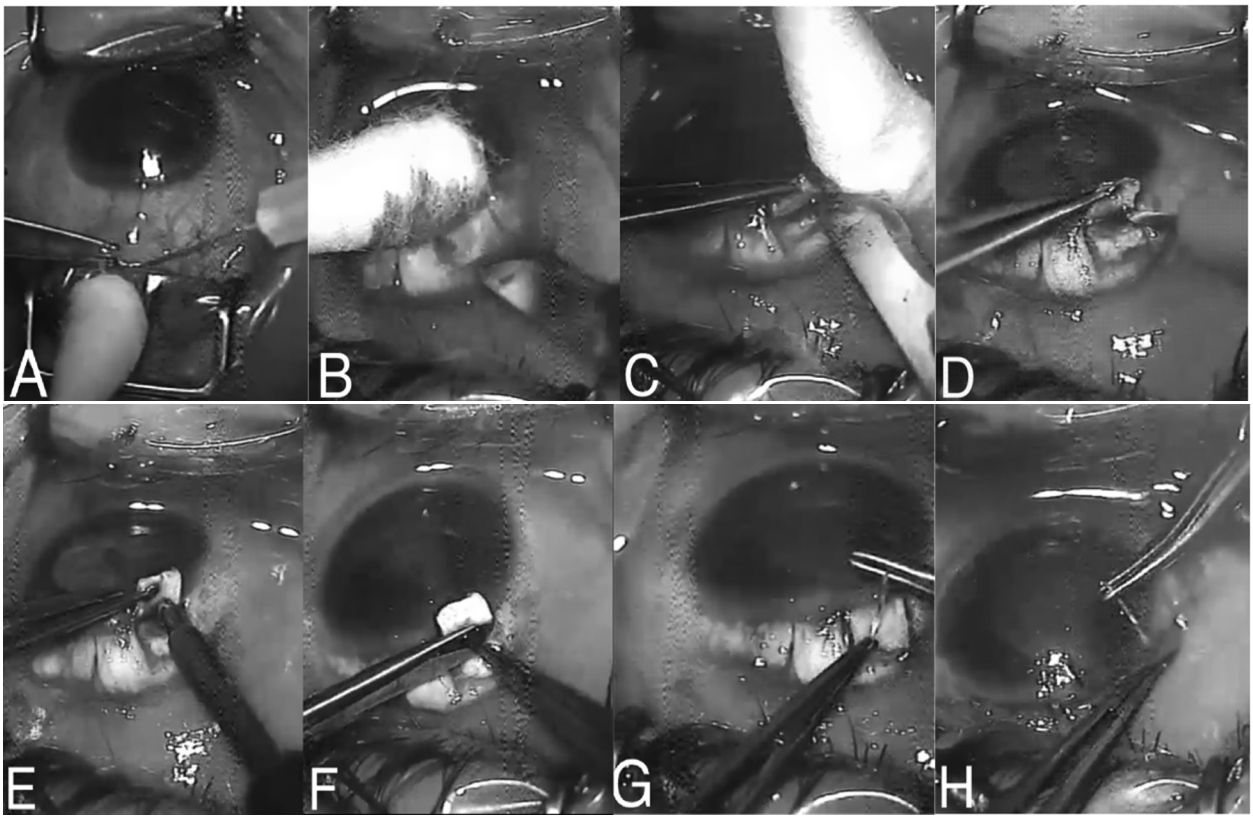

Figure 9. Trabeculectomy, left eye. Local anesthesia was instilled followed by asepsis and antisepsis, and lid retractor application. The surgeon then proceeded to give a subconjunctival injection of Mitomycin C (A). Formation of fornix-based conjunctival flap (B), hemostasis and cautery of bleeders, and dissection of scleral flap measuring 3.0 by 3.0 mm (C) were then performed. A sclerostomy was made (D, E). Peripheral iridectomy was successfully created (F). Finally, the scleral flap (G) and the conjunctival flap (H) were closed.

Table 2 summarizes the salient features seen in the patient in comparison with the differential diagnoses. Angle closure glaucoma (ACG) should be considered in any patient with presenting symptoms of severe ocular pain, eye redness, and decreased vision. It is sight-threatening and is considered an ophthalmic emergency. Angle closure glaucoma can be classified as either primary or secondary. A pupillary block commonly causes the former, while the latter occurs secondary to an ocular or systemic problem that led the iris to come in contact with the trabecular meshwork. Distinguishing the cause of angle closure is crucial as it will determine how the patient will be managed. The gender predilection, racial background, and hyperopia are all consistent with the patient's profile; however, it should be noted that the primary form of angle closure glaucoma (PACG) is rare in patients below 40 years old. Thus, whenever it is observed in this younger age group, one should suspect that the angle closure glaucoma is due to an underlying pathologic etiology or that the ACG is considered a secondary angle closure glaucoma (SACG).

Neovascular glaucoma (NVG) is a type of SACG wherein there is new vessel formation in the anterior chamber angle.[1] Patients with NVG often present with an acute or subacute glaucoma associated with reduced vision, ocular pain, conjunctival hyperemia, and corneal edema, which is why NVG (particularly its angle closure glaucoma stage) was considered. However, despite the similar presentation and the presence of an elevated IOP and PAS, the absence of iris and/or angle neovascularizations and the lack of any predisposing factor for NVG (e.g., retinal ischemic disease, carotid artery obstructive disease, diabetes mellitus, uveitis, trauma)[6], led the authors to rule out this disease entity.

Angle closure glaucoma secondary to nanophthalmos was also considered because SACG often occurs in nanophthalmic eyes. The patient's high hyperopia that began in childhood, findings of small anterior segment dimensions, the characteristic

Table 2. Differential Diagnosis. Salient features of angle closure glaucoma (red) and Salient feature of nanophthalmos (blue), OD (right eye), OS (left eye), OU (both eyes)

	Ocular Features of Patient	Neovascular Glaucoma	Angle Closure Glaucoma secondary to Nanophthalmos
Risk Factors	27/ F Filipino Hyperope (OU +13.50sph) Parents are 1st cousins	No age or gender predilection Retinal ischemic disease, Carotid artery obstructive disease, Uveitis, Trauma	< 40s/ F > M Asian Markedly hyperopic since childhood Consanguinity
Symptoms	Severe eye pain, OS BOV, OS Eye redness, OS Visibly smaller left eye	Ocular pain Reduced vision Conjunctival hyperemia Headache	Severe ocular pain Marked BOV (haloed vision) Congestion Eye normal in shape but small
Signs	Pupil 6mm NRTL, OS Corneal edema, OS Shallow AC, OU Glaucomflecken, OS Convex iris plane, OU Corneal diameter: OD 10.5mm, OS 9.5mm Interpalpebral fissure height: OD 9mm, OS 7mm	Vessels at pupil margin Corneal edema AC reaction Neovascularization	Fixed, mid-dilated pupil Corneal edema Shallow AC, Cells/flare Iris atrophy and/or glaucomflecken Convex iris or pupillary block Small corneal diameter Narrow palpebral fissure
Tonometry	IOP: OD 18mmHg OS 40mmHg	+/- elevated IOP	Markedly elevated IOP
Gonioscopy	OD Appositional closure on all angles OS Synechial closure on all angles, PAS	Open or closed angles	Closed angles +/- PAS, involved eye Shallow AC & narrow AC angle, fellow eye
Fundus	OD Clear media, CDR 0.8, thick neuroretinal rim OS Hazy media, CDR 0.8, neuroretinal rim thinning temporally	Neuroretinal rim thinning, RNFL defects, disc hemorrhages, vascular pattern changes	Neuroretinal rim thinning, RNFL defects, disc hemorrhages, vascular pattern changes
Ancillaries	Corneal curvature: OD 50.12D, 50.22D Axial length: OD 18.36, OS 18.26mm LEVR: OD 24%, OS 23% Scleral thickness: OD 2.04mm, OS 2.50mm Retinal thickening on all subfields: OD 330-415μm Central foveal thickness: OD 440μm		Steep cornea Short axial length High LEVR Increased thickness of sclera Increased retinal thickness, loss of foveal pit, macular thickening

high crystalline lens to total eye volume ratio despite a normal-size lens, choroidal-scleral thickening, and resulting macular edema all point to a nanophthalmic eye.

It is important to familiarize with the nomenclature of small eye-disorders as one may easily confuse one term with the other. Pertinent literature led to this schematic diagram (Figure 10) where small-eye disorders can be divided into subtypes under the umbrella term of microphthalmos.[3,6] A small eye warrants the term microphthalmos when the axial length is at least 2 standard deviations below the average relative to the age. It is classified as complex microphthalmos when associated with a congenital malformation (e.g., colobomas, anterior segment dysgenesis, lens abnormalities, posterior segment anomalies) or as part of a syndrome (e.g., Bosma arhinia microphthalmia syndrome and the Gorlin-Chaudhry-Moss syndrome).[18] Conversely, simple microphthalmos is when the small eye occurs as an isolated case. Simple microphthalmos is further subdivided into partial or complete microphthalmos, depending on the length of the anterior and posterior segments. When the overall reduction in the size of the eye is due to anterior segment shortening, it is termed relative anterior microphthalmos. In contrast, posterior microphthalmos is when only the posterior segment of the eye is undersized; the anterior segment is normal in depth and the angles between the iris and trabecular meshwork have normal configuration. Complete microphthalmos, or nanophthalmos, is a rare form of simple microphthalmos wherein both anterior and posterior segments are shortened with no other apparent ocular malformations.[3]

While the clinical presentations of a neovascular glaucoma and angle closure glaucoma secondary to nanophthalmos have similarities on presentation, they differ in the characteristic neovascularization of the anterior segment in the former. Apart from the clinical findings, the diagnosis of nanophthalmos was also strengthened by the parameters derived from the ancillaries done. With this, nanophthalmos was more likely than neovascular glaucoma to have precipitated the angle closure glaucoma attack in this case.

Post trabeculectomy of the left eye (Figure 11), best-corrected visual acuity was 20/40 on the right eye and was noted to have improved to 15/400 on the left eye. Slit-lamp examination showed a clear cornea with marked iris convexity and shallow anterior chamber that was narrow centrally in the right eye.

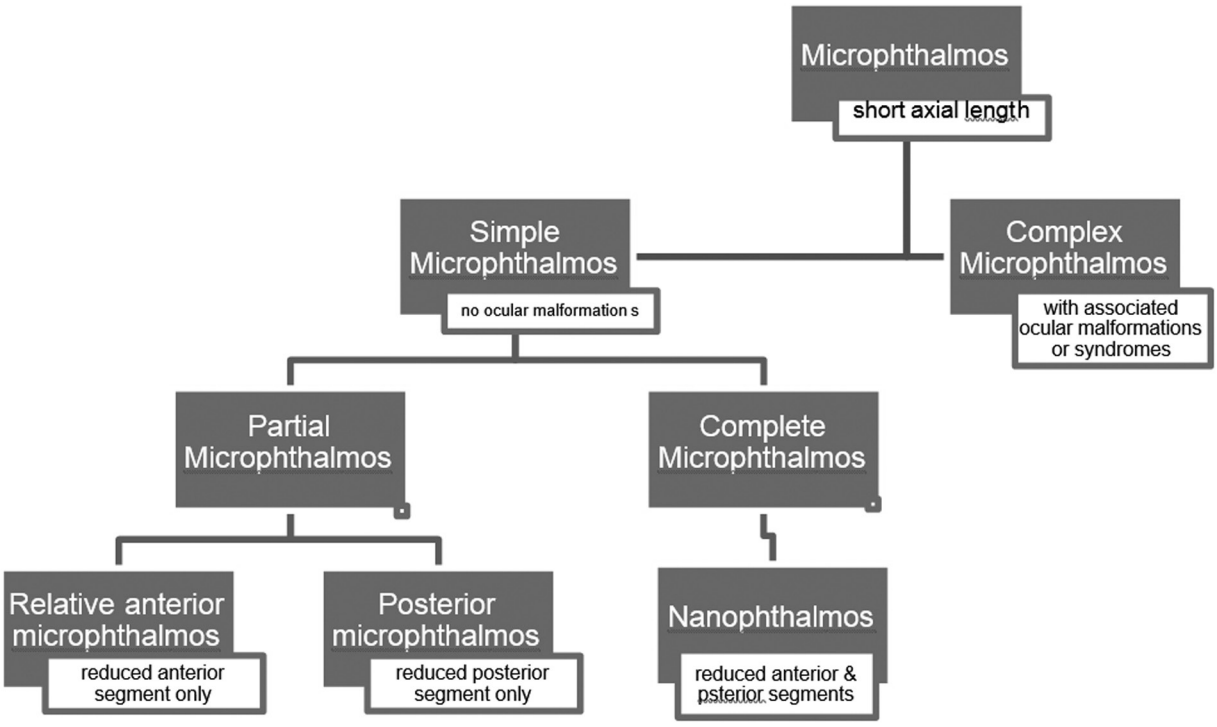

Figure 10. Schematic diagram of diagnosis of small-eye disorders

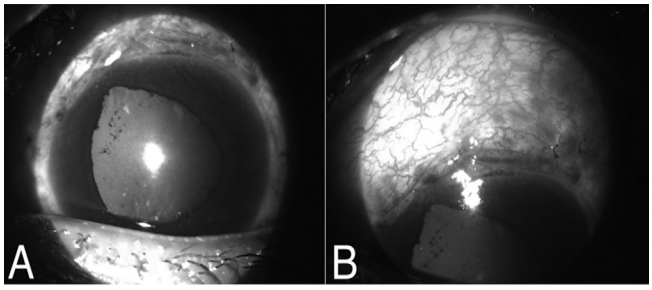

Figure 11. Two days post-operatively.

On the left eye, cornea was noted to be clearer post-operatively. Iris of the left eye still showed convex iris configuration and shallow anterior chamber that was narrow centrally. With the Indiana Bleb Grading System as reference, the bleb was graded low height (H1), extending to three limbal clock hours (E2), moderate vascularity (V3), and no seidel leakage (S0). The IOP on the right eye was 14 mmHg and 18 mmHg on the left eye.

Patient was referred to Retina service where the patient was noted to have foveal cysts on the right eye with cystoid macular edema on both eyes. The patient was started on topical carbonic anhydrase inhibitor trial (Dorzolamide eye drops) to the right eye twice a day for a duration of four weeks. If there will be a favorable response on repeat OCT of the right eye, the plan is to suggest to do the same treatment on the left eye.

The patient's two children were also referred to Pediatric Ophthalmology service. Her first-born is a 6-year old male whose visual acuity was 20/25 on both eyes. Extraocular muscles were intact with full and equal movements. Pupils were 1-2mm equally reactive to light. The patient was evaluated to be orthophoric through the Krimsky prism test. White-to-white corneal diameter was measured to be 11mm. Cycloplegic refraction in the right eye was +1.75D sph () -0.25D cyl x 180 degrees and +2.00D sph () -0.50D cyl x 180 degrees in the left eye. Slit-lamp examination of both eyes showed clear corneas, deep anterior chambers, and clear lenses. Funduscopy examination of both eyes revealed the presence of ROR, clear media, CDR of 0.3, AVR of 2:3, no hemorrhages or exudates, distinct disc borders, and good foveal reflex. Assessment was essentially normal eye findings. Her second child is a 10-month old male whose visual acuity was predicted through the presence of central, steady, maintained fixation. Patient could follow a moving object or sound with both eyes. Pupils were 3-4mm equally reactive to light. The patient was also assessed to be orthophoric through the Krimsky prism

test. Cycloplegic refraction was performed and both eyes were measured to be +1.75D sphere. Funduscopy examination of both eyes revealed the presence of ROR, clear media, and CDR of 0.3. Assessment was essentially normal eye findings.

As mentioned, the patient reported that her father and mother are first-degree cousins (Figure 12). Considering the consanguineous union between her parents, the patient was referred to an Ocular Geneticist for genetic evaluation and genetic counseling. After a thorough history and physical examination, the patient was appraised regarding the relevance and possible implications of genetic testing, to which she consented to. A Microphthalmia/ Anophthalmia panel, which tests possible genes that cause the disease, was requested and results showed a pathogenic variant in the MFRP gene c.1150dup (p.His384Profs*8). Mutations in this gene are seen in individuals with microphthalmia/anophthalmia and retinal dystrophy.

DISCUSSION

Nanophthalmos is a rare subtype of microphthalmos that results from developmental arrest of the globe after closure of the embryonic fissure.[8] Carricondo, et al. point out that unlike other forms of microphthalmos, nanophthalmic eyes are reduced in volume, but otherwise normal in structure and function.[3] Most cases of nanophthalmos are sporadic, but it is also presumed to have a strong genetic basis, as there have been reports describing autosomal dominant and recessive forms of inheritance. Currently, five genes have been associated with the familial form of nanophthalmos: Membrane-type Frizzled-Related Protein (MFRP) Gene, Transmembrane Protein 98 Gene (TMEM98), Protease Serine 56 (PRSS56), Crumbs Homologue 1 Gene (CRB1), and Bestrophin 1 (BEST1). Genetic analysis of the patient revealed a mutation in the MRFP gene which is expressed in the retinal pigment epithelium and ciliary body.

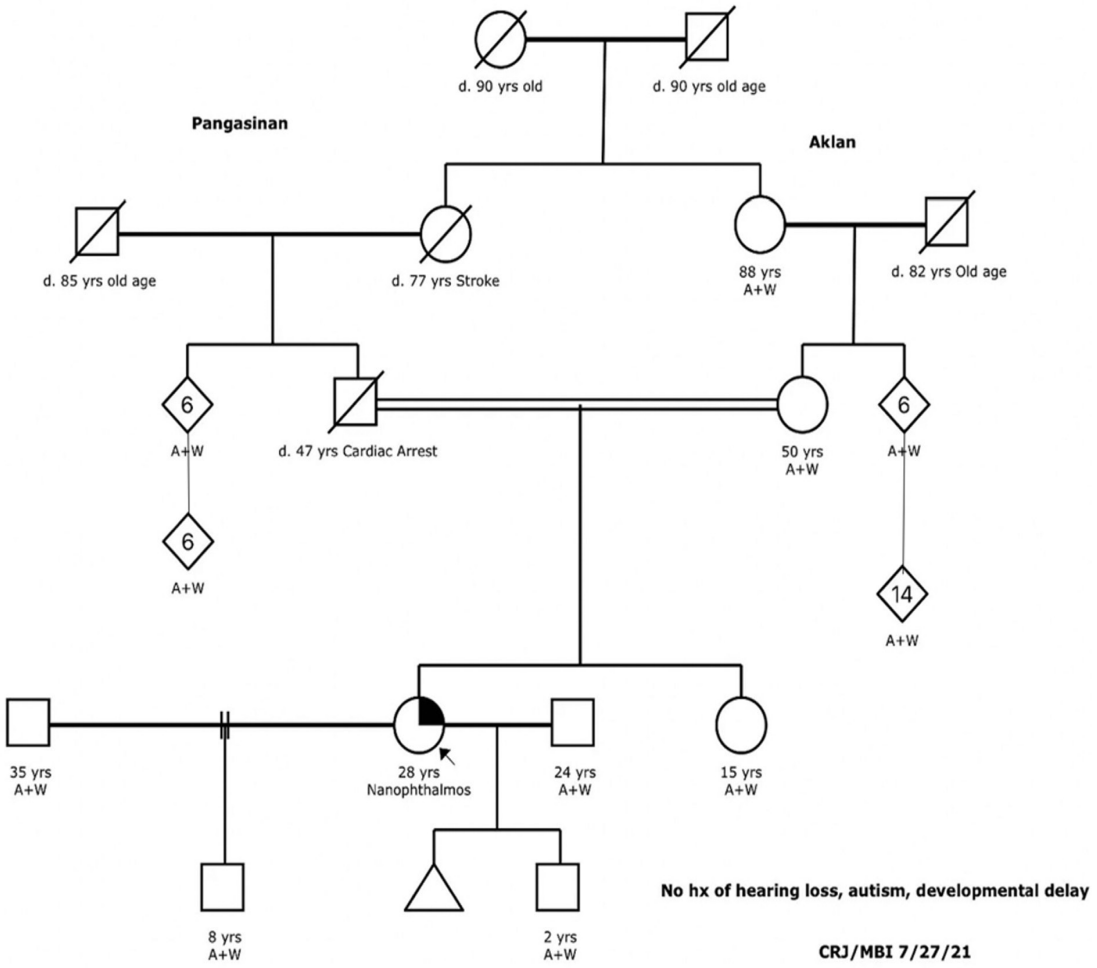

Figure 12. Family pedigree of the index patient with a history of consanguinity. The proband is marked with an arrow.

This gene has a central role in ocular growth and was also found to have a function in photoreceptor maintenance.[3] Evidence suggests that any mutation in the MFRP gene could lead to alterations in normal eye development with or without retinal changes. The patient presented with high hyperopia, reduced axial length, and with macular thickening, compatible with nanophthalmos and to previous MRFP-related reports.[21-23]

Given the findings on the hereditary transmission of nanophthalmos, eliciting a comprehensive patient history is paramount. The unexpected revelation of the patient's parents being first degree cousins, uncovered in her pedigree, prompted the authors to ask whether consanguinity played a significant role in the development of nanophthalmos. In two comparable studies by Relhan, et al. and Yalvac, et al. they observed that a history of consanguinity among the parents was present in approximately 60% of their participants with nanophthalmos. According to Hornby, et al., the highest prevalence of severe vision loss secondary to globe abnormalities is found in Asian countries where consanguineous marriages are common. Genetic counseling with health education was suggested to be a non-invasive, cost-effective method for preventing recessive diseases in these high-risk populations.[7]

To date, there is no established criteria to diagnose nanophthalmos. However, other related literature have proposed various parameters. One typical parameter is a short horizontal corneal diameter (below 11.0mm)[8,16,18], as measured in the patient using the Castroviejo caliper (10.5mm, right eye; 9.5mm, left eye) and keratometry (11.5m, right eye; 11.6mm, left eye). Another criterion is a topographically high corneal curvature (more than 46 D),[11] which coincides with the patient's steep cornea on both eyes (50.12 D, right eye; 50.22 D, left eye). Wu, et al. and Yalvac, et al. considered eyes nanophthalmic if axial length was reduced (21mm[16] and 20.5mm[17], respectively), which corresponds with the patient's shortened axial lengths (18.36mm, right eye; 18.26mm, left eye) on A-scan. A shallow anterior chamber (AC) was regarded by Relhan, et al. and Yalvac, et al. as another manifestation of nanophthalmic eyes (2.68±0.42[11] and 2.30±0.36mm[17], respectively), as seen in the patient who had shallow AC depths (1.29mm, right eye; 1.67mm, left eye) on ultrasound biomicroscopy. The high lens-to-eyeball volume ratio (LEVR) has been identified by most studies as a unique parameter of nanophthalmos, noted by Yalvac, et al. and Yang, et al. (2020), to be 10-32% in nanophthalmic eyes,[17,18] Both eyes of the patient were computed to be within this pathological range (24%, right eye; 23%, left eye). Additionally, Wu and colleagues were the first to include an abnormally thickened sclera (posterior scleral wall thickness more than 1.7mm) in the diagnostic criteria of nanophthalmos. On B-scan, the patient had thickening of both the sclera (2.04mm, right eye; 2.50mm, left eye) as well as the choroid (1.52mm, right eye; 1.39mm, left eye).

OCT studies conducted by Walsh, et al. and Demircan, et al., included findings of absence of normal foveal contour and macular thickening (average central macular thickness 331.90 ± 78.90μm)[5,15], as seen in the patient's OCT showing loss of foveal depression with retinal thickening on all subfields (330-415μm) and central foveal thickness (440μm), both of which were above the normative database (p>95%). Wu, et al. also cited macular edema as one of the comorbid ocular diagnoses in their review of nanophthalmos patients, which was consistent in the patient's OCT and fundus photographs.

Owing to its abnormal anatomy, a nanophthalmic eye may give rise to a number of complications such as retinal detachment, uveal effusion syndrome, and those which were present in the patient namely, high hyperopia and angle closure glaucoma (ACG).[8,18] The unusual use of a very thick corrective spectacles in the patient, who had no history of intraocular surgery, prompted the suspicion of a high hyperopic refractive error. It was stated by Krishnan, et al. that the nanophthalmic patient is often extremely hyperopic of early onset with a refraction ranging from +8.00D to more than +25.00D sphere, yet has good corrected visual acuity.[8] Similarly, the patient's refraction was +13.50D sphere for both eyes. During adulthood, nanophthalmic patients are prone to ACG due to lens growth in an eye that is already too small.[18] The relative shortening of the anterior segment of the eye with a normal-sized lens in nanophthalmos causes crowding of the anterior chamber angle, which becomes accentuated by increasing age and lens thickness. A case series on nanophthalmic glaucoma published last 2002 had similar presentations as the present case including eye pain, loss of vision, high level of hyperopia, with increased IOP and synechially closed angles.[20] More recently, a similar case reported in 2019 was that of a highly hyperopic patient presenting with one month history eye pain eventually accompanied by rapid blurring of vision in the right eye more than the left.[2] In addition, Sener, at

al. reported that strabismus may also be present among these individuals, which was seen in the incidental finding of exotropia of the left eye in the patient.[12]

The management of angle closure glaucoma in small eyes has proven to be a big challenge to ophthalmologists.[14] Medical therapy, laser peripheral iridotomy (LPI), and argon laser peripheral iridoplasty (ALPI) remain the safest ways to treat glaucoma in these patients.[6] But even when initiated early, medical treatment is known to have a high failure rate, reflected in the present case. Laser interventions are more beneficial in the early stage of glaucoma because these may not adequately regulate IOP once there is already formation of peripheral anterior synechiae (PAS), which were successfully done as prophylaxis in the patient's good, right eye. When all possible conservative treatments have been exhausted, intraocular surgery is considered a last resort due to the increased risk of potentially devastating complications intra- or postoperatively. Yalvac, et al. mentioned that glaucoma filtration surgery (i.e., trabeculectomy) may be required in cases when there is formation of PAS or elevated IOP is refractory to medical treatment. In line with this, trabeculectomy was done in the patient who had the same findings.

In addition to treating the patient's presenting problem, it is imperative that a physician manages the patient and her family holistically. Genetic counseling and testing are vital in the evaluation of patients with nanophthalmos. As advised by the Ocular Geneticist, since gene analysis yielded an autosomal-recessive disease, the patient's two children have a 25% chance of inheriting the mutation. Genetic counseling can also be done to future generations, so that they may be made aware of the possible implications of the genetic test result of the patient. This would entail close monitoring as it could provide an avenue for early detection and prevention of possible complications that could negatively impact their quality of life – the chance that the patient unfortunately did not have.

CONCLUSION

Nanophthalmos is an uncommon developmental ocular disease characterized by unusually small eyes with clinical features of a small cornea, reduced axial length, shallow anterior chamber, increased lens/eye volume ratio, and thickened sclera. It is primarily established through ophthalmologic and imaging examinations to quantify the eyeball's parameters. Apart from these ancillary tests, recognizing subtle clinical clues in the history may already lead the physician to entertain its diagnosis. Thus, having elicited a history of high hyperopia at an early age and a consanguineous family history in this patient who initially presented with signs and symptoms of angle closure glaucoma, was key to pointing to an underlying pathology of nanophthalmos.

Treatment of the high incidence of angle closure associated with nanophthalmos varies with the severity of the glaucoma. Conventional therapeutic methods are often ineffective, while surgery, when inevitable, must be proceeded with caution due to the serious complications it could entail in nanophthalmic eyes. Beyond this, the physician must counsel and share decisions with the patient in order to manage expectations. The identification of genetic mutations linked to nanophthalmos places emphasis on treating not only the affected individual, but examining her family members as well. Genetic counseling and testing could substantially aid in the timely diagnosis, close monitoring, and raising awareness of the disease to minimize possible sequelae.

Nanophthalmic eyes pose a great diagnostic and therapeutic challenge to ophthalmologists, yet the prognosis may be favorable if this disorder is correctly identified and treated without delay. This paper illustrates how a high index of suspicion is crucial in the prompt recognition of this potentially blinding condition. The optimal approach to arrive at a diagnosis of nanophthalmos is through a detailed history, comprehensive physical examination, and appropriate imaging with the advent of advanced ocular examination technologies. Best efforts in proper management and active surveillance can ultimately improve outcomes for individuals with such challenging eyes.

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