Nanophthalmos and Glaucoma

Selim DOGANAY[1], Derya DOGANAY[2]

ABSTRACT

Nanophthalmos is an uncommon, bilateral and developmental ocular disease and is usually genetic. The patients may experience serious ocular problems such as glaucoma and uveal effusion syndrome, especially in the third–fifth decades of their lives. Surgical management of glaucoma in patients with nanophthalmos is quite difficult. Serious complications can occur during or after the glaucoma surgery in patients with nanophthalmic eyes. In this study, the clinical and therapeutic approaches of glaucoma-nanophthalmos will be reviewed in the light of the literature.

Keywords: Nanophthalmos, Glaucoma.

DEFINITION AND EPIDEMYOLOGY

Nanophthalmos means "dwarf eye" in Latin. It is one of the subtype of microphthalmia (Table 1). It is a clinical entity characterized by short anterior and posterior segment (axial length <20.5 mm), normal and/or micro-cornea (corneal diameter<11 mm) and thick sclera and choroid. Its incidence range from 1to 20 case per 100,000 birth (1-20/100,000).[1] It may be either unilateral or bilateral.

There may be sporadic cases although it is inherited in autosomal dominant manner (MFRP, TMEM98, PRSS56 and NNO3 genes).[1]

CLINICAL PRESENTATION OF NANOPHTHALMOS

Nanophthalmos is a development eye disorder characterized by shorter anterior-posterior diameter of eye (2 SD) according to age.[2]

There are 2 types including simple and complex nanophthalmos. No ocular abnormality is seen simple type whereas coloboma, anterior dysgenesis, lens abnormalities and posterior segment abnormalities are seen in the complex type.[2]

Although anterior-posterior diameter of eye is small in

Table 1. *Microphthalmia phenotypes*

Anophthalmia	Absence of eye
Simple Microphthalmia	Shorter axial length, no additional anomaly
Complex Microphthalmia	Shorter axial length and ocular malformations (coloboma, PHPV, retinal dysplasia)
Relative Ant. Microphthalmia	Short AL due to shortness of anterior segment alone, normal posterior segment and scleral thickness
Posterior Microphthalmia	Short AL due to shortness of posterior segment alone, normal anterior segment
Nanophthalmos	Short AL due to shortness of anterior and posterior segments and thick choroid and sclera, normal lens size

AL: Axial length, **PHPV:** Persistent Hyperplastic Primary Vitreous

1- Prof. MD., Ophthalmology Department of Uludag University, Medicine School, Bursa, Turkey

2- Ophthalmologist, Cekirge State Hospital, Bursa

Received: 14.02.2020
Accepted: 17.02.2020
Glo-Kat 2020; 15:1-7
DOİ: 10.37844/glauc.cat.2020.15.1

Correspondence Adress:
Selim DOGANAY
Ophthalmology Department of Uludag University, Medicine School, Bursa, Turkey

Phone: +90 532 416 4553
E-mail: odoganay@windowslive.com

these cases, crystalline lens size is within normal range. In normal eyes, lens volume comprises 4% of overall ocular volume while this can be up to 30% in nanophthalmos eyes. Abnormalities such as irregular astigmatism, rudimentary foveal avascular zone, optic disc drusen, retinoschisis, central retinal vein occlusion, choroidal thickening in subfoveal area, abnormal distribution of thickness in retinal layers, choroidal folds, micro-papilla, retinal cysts, retinitis pigmentosa and foveal dysgenesis can be present in nanophthalmos eyes.[3-11] On contrary to nanophthalmos, only axial length is shorter and no additional anomaly is seen.

In these cases, typical characteristics include deep orbit, narrow palpebral fissure and high myopia ranging from +8 to +25 D.[12,13] Wu et al.[14] define nanophthalmic eye as narrow anterior chamber, axial length<21 mm and posterior wall thickness>1.7 mm. Yalvac et al.[15] defined nanophthalmic eye by adding axial length <20.5 with presence of high lens: eye volume to tabove-mentioned criteria.

In the literature, another issue is differential diagnosis between nanophthalmos and posterior microphthalmos. Posterior microphthalmos is a subtype of microphthalmia and characterized by shorter posterior segment alone. In these cases, anterior chamber depth and angle configuration are normal. Some authors consider nanophthalmos and posterior microphthalmos as synonymous disorders.[16] It is suggested that anterior chamber is more narrow while lens is thicker and cornea is more perpendicular in eyes with nanophthalmos when compared to those with posterior microphthalmos.[12] In particular, profound amblyopia can be seen due to uncorrected hypermetropia in younger ages.

Some glaucoma- and retina-related complications can develop in nanophthalmos. It was shown that increased ratio of lens volume to overall ocular volume (by 4-to-8 folds) and thick and firm sclera (accumulations of glycosaminoglycans in the sclera) play role in the pathogenesis of complications.[17,18-20] These cases generally presents with acute, chronic or intermittent angle-closure glaucoma between third and fifth decades of life.

Acute angle-closure develops due to pupillary block in 69.2% of cases.[12] Ciliolenticular (non-pupillary) block seems to be resulted from thick sclera, thick choroid and decreased venous drainage.

Chronic angle-closure glaucoma occurs as result of anterior synechiae developed during episodes on intermittent angle-closure. These eyes are lost due to optic atrophy since angle-closure are not diagnosed and treated.

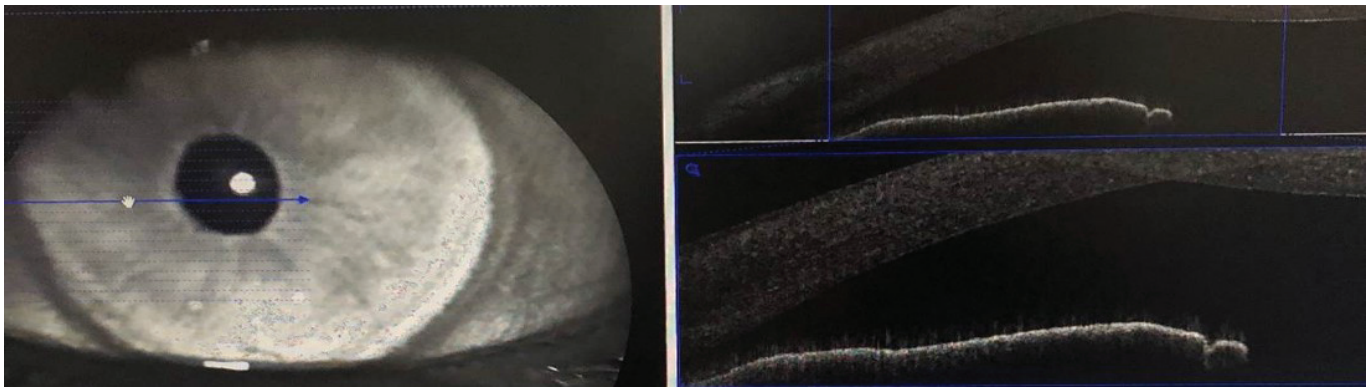
In a previous study, angle-closure glaucoma was obsrved in 69.23% of eyes with nanophthalmos but it was seen none of the eyes with posterior microphthalmos.[21] In that study, macular fold incidence was 0% in cases with nanophthalmos whereas 24% in posterior microphthalmos.[21]

In nanophthalmic eyes, abnormal collagen deposition and increased scleral thickness can cause angle-closure glaucoma, exudative retinal detachment and uveal effusion by impairing vortex vein flow and transscleral protein flux.

Uveal effusion results from inflammatory eye disorders or hydrostatic alteration or hypotonia developed following posterior uveitis or glaucoma surgery. If etiology of uveal effusion could not be identified, the condition is termed a uveal effusion syndrome. Although it is known that uveal effusion syndrome is idiopathic, it is seen that the syndrome develops due to nanophthalmos in some cases. In uveal effusion syndrome, typical exacerbation and remission periods are present. The most common presenting complaint is superior visual field defect while some patients can present with metamorphopsia and blurred vision. Choroid detachment typically starts from periphery; exudative retinal detachment can accompany and macula can be affected. Deep retinal and subretinal exudates and edema at optic nerve head can be seen.

These exudates regress spontaneously within months and years in most cases.[22] Moderate number of cell is observed in vitreous body (vitritis). In general, leopard spot appearance develops due to hyper-pigmentation in retinal pigment epithelium in such cases.[23] It becomes a chronic condition over time, resulting in severe impairment in visual acuity. Although spontaneous regression of exudates is observed in most cases, it is rather slow, taking months or years. In previous studies, glycosaminoglycan-like material deposition across collagen fibrils is shown in

Picture 1. *Shallow anterior chamber in anterior segment image of patient with nanophthalmos*



Picture 2. *Shallow anterior chamber of a patient with nanophthalmos on anterior segment optic coherence tomography imaging.*

nanophthalmic cases with uveal effusion.[24-27] It was shown that albumin and other proteins in subretinal fluid are 2-3 folds higher in these cases when compared to normal individuals and that there is increased protein without pleocytosis in cerebrospinal fluid.[28] These findings suggest that transscleral protein efflux from choroid is impaired due to hyper-osmotic gradient. Another hypothesis regarding uveal effusion development is that dilatation in scleral veins and impairment in normal flux of choroidal fluid due to abnormal sclera in cases with nanophthalmos leads accumulation beneath choroid.[29] Gass et al. explain this picture by hypoplasia or lacking of vortex veins.[22,28]

In nanophthalmic cases, presence of chronic angle-closure, dilated episcleral veins and blood in Schlemm canal can be considered as resistance in venous drainage system in these patients. In a study by Uyema et al.[20] it was shown that there is disorganized collagen in sclera and proteoglycan deposition in extracellular tissue with thickened sclera in cases with nanophthalmos. Thus, authors suggested that, in the surgical treatment of uveal effusion, lamellar sclerotomy can be helpful in only cases with thickened sclera.[20]

GLAUCOMA TREATMENT IN CASES WITH NANOPHTHALMOS

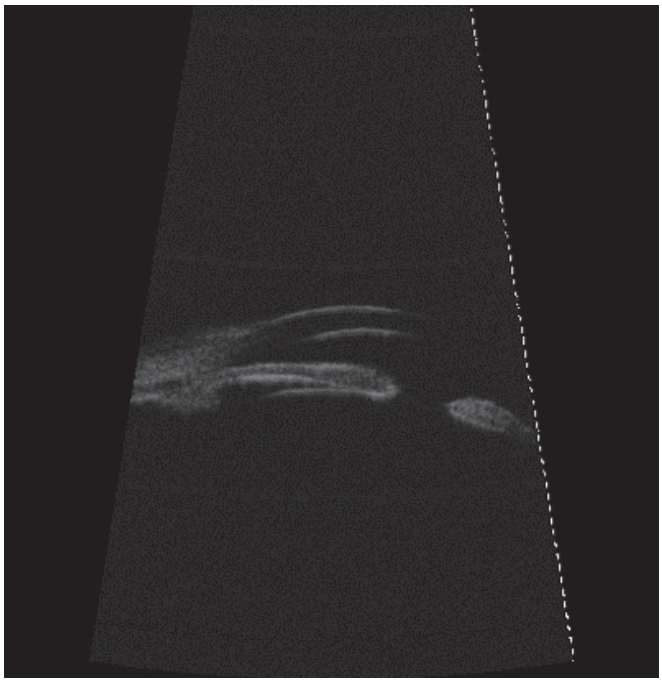
In cases with nanophthalmos, peripheral anterior synechia is generally present at varying degrees.

In these cases, acute-angle closure glaucoma attack develops through occlusion of anterior chamber angle by peripheral iris as a result ciliary body detachment, annular ciliochoroidal effusion and anterior rotation of ciliary processes. However, chronic angle-closure glaucoma may also develop due to anterior synechia caused by intermittent opening and closure episodes of anterior chamber angle. In cases with nanophthalmos, response to medical therapy is limited in both acute and chronic angle-closure glaucoma. In these cases, miotic agents can worsen the condition by causing relaxation in lens zonules. In early phased of glaucoma, laser peripheral iridotomy can limit peripheral adhesions by preventing pupillary block mechanism but it is unable to prevent peripheral synechia completely. Thus, argon laser peripheral iridoplasty is a good option to prevent formation of peripheral synechia following laser iridotomy.[30]

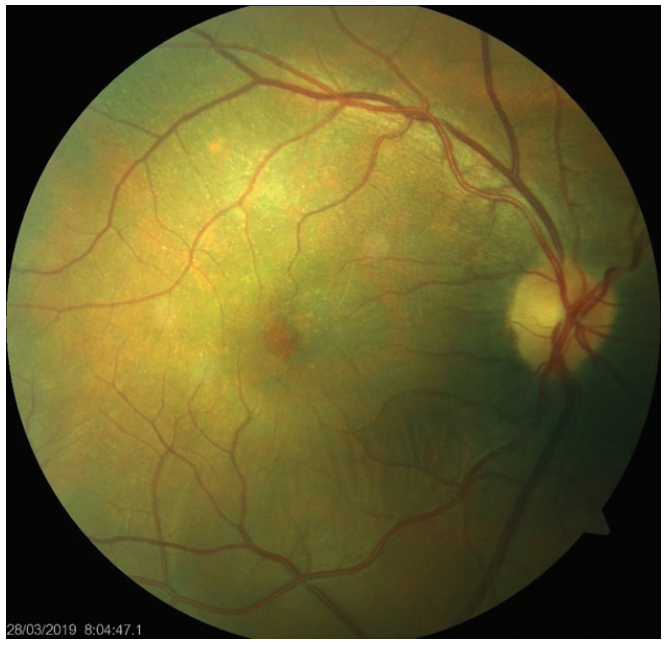
In cases with nanophthalmos, surgical glaucoma treatment modalities appear as last resort in case of peripheral anterior synechia development. However, in such cases with excessive intraocular pressure, sudden relieve of intraocular pressure by glaucoma surgery can lead severe complications such as massive uveal leffusion and suprachoroidal bleeding. Complications also include retinal detachment, intraocular bleeding, malignant glaucoma and severely decreased visual acuity.

Singh et al.[31] performed filtration surgery in cases with nanophthalmos. Authors reported failure in 9 of 15 cases and vision loss in 86.6% of the cases. Yalvac et al.[15] performed trabeculectomy with mitomycin C augmentation plus inferior sclerotomy and reported success are at year 1, 2, 3, 4 and 5 as 85&, 78.4%, 74.6%, 70.6% and 47%, respectively. However, authors observed choroidal detachment rate up to 50% and 5% at early and late periods, respectively.[15]

Uveal effusion can also be seen in cases with nanophthalmos. Uyama et al.[20] defined 3 types of uveal effusion syndrome. In type 1, mean length of anterior-posterior axis was given 16 mm. In type 2, non-nanophthalmic eye was defined as abnormal sclera, axial length of 21 mm and low refractive error. Abnormal collagen fibril structure and proteoglycan deposition are present in type 1 and 2. In type 3, non-nanophthalmic eye and normal sclera are present. In this context, it is suggested that only type 1 and 2 can benefit from scleral surgery in the surgical treatment



Picture 3. *Shallow anterior chamber in a patient with nanophthalmos on sonographic biomicroscopy.*



Picture 4. *Exudative retinal detachment in a patient with nanophthalmos on anterior chamber image.*

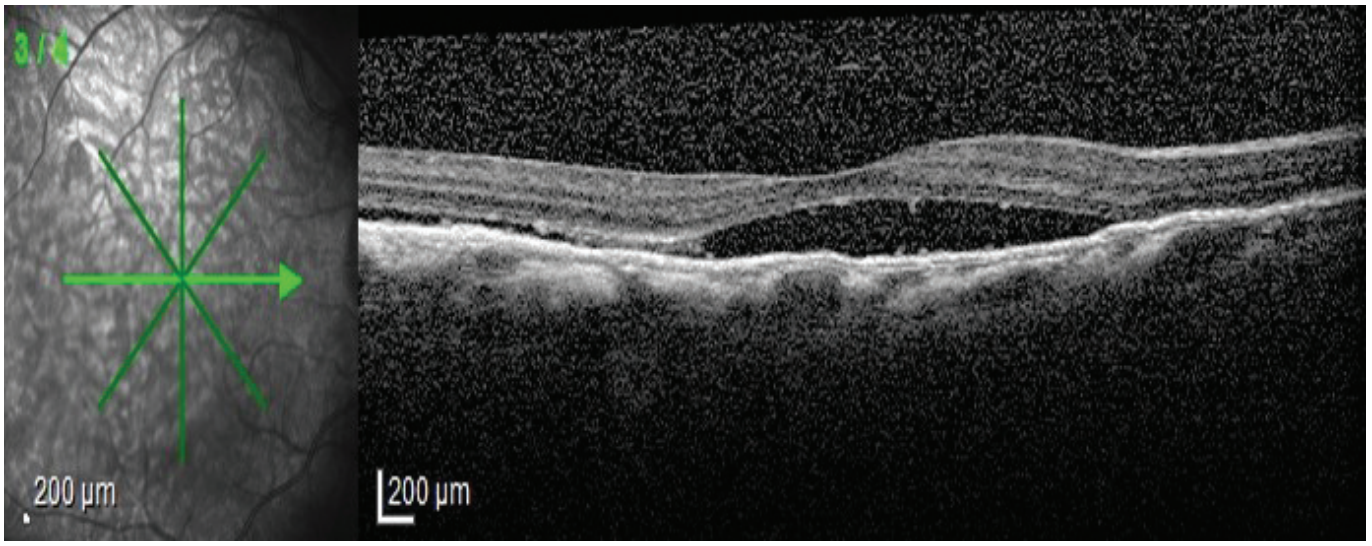
of uveal effusion.[20] Brockhurs suggested that vortex vein decompression by scleral resection can decrease and resolve uveal effusion by reducing protein and fluid leakage.[32] Another approach is sclerotomy in these cases. Jin et al.[33] reported that cases with uveal effusion can be treated by leaving non-sutured full-thickness, V-type sclerotomy. However, scleral attenuation via posterior approach can result in risk for intraocular bleeding, scleral rupture or retinal incarceration. However, based on recommedations by Yalvac et al.[15] scleral attenuation via anterior approach seems more reasonable since thick uveal tissue and strong vitreous may prevent such complications. Systemic corticosteroids and immunomodulatory agents are used in the medical treatment of uveal effusion. However, in recent publications, it has been reported that uveal effusion is associated with good response to oral, periocualr and topical steroids. Shields et al.[34] suggested that, in cases with normal axial length and sclera thickness, response is good to oral, topical and periocular treatment and their combinations. Non-surgical treatment options include laser photocoagulation, extended release indomethacin and topical prostaglandin analogues.[35] Thus, resolution can generally be achieved by medical approach in uveal effusion developed in non-nanophthalmic eyes.

Filtration surgery is performed with several modifications in cases with nanophthalmos. In these cases, it is important to use mitomycin augmentation, tight closure of scleral flaps, postoperative suturolysis and tight and uniform closure of conjunctiva. Despite all measures, choroid detachment can be encountered after filtration surgery. When long-term outcome is assessed in filtration surgery, failure in reducing IOP is observed in a significant proportion of cases. Thus, alternative surgical techniques have gained popularity in cases with nanophthalmos in recent years.

Transparent lens extraction via anterior or posterior approach can be considered for glaucoma prophylaxis due to glaucoma development in third and fifth decades of life in cases with nanophthalmos. Intraocular lens with high degree can be required since these cases generally have high hypermetropia. However, pigyback IOL implantation should be avoided in cases with nanophthalmos as it may lead inter-lens opacification and pigment discharge caused by friction to iris.

During phacoemulsification, to perform gonioscopic examination and to relieve anterior synechia, if present, can be protective and even therapeutic for glaucoma in these cases.

Risk for malignant glaucoma is high in cases with nanophthalmos. Malignant glaucoma development is explained by anterior displacement of lens, iris and iris hyaloid diaphragm and anterior rotation of ciliary body. In the treatment of malignant glaucoma, primary goal is to establish passage between anterior chamber and vitreous cavity by eliminating blockade at cilio-hyaloid area. For this purpose, Nd-Yag laser and vitreoretinal approaches can be considered in pseudophakic cases while vitreoretinal approaches with lensectomy in phakic cases. In cases with



Picture 5. *Exudative retinal detachment in a patient with nanophthalmos on optic coherence tomography imaging.*

nanophthalmos, it is suggested that anterior vitrectomy through posterior capsulotomy or peripheral iridectomy is effective by establishing connection between anterior chamber and vitreous space in the treatment of malignant glaucoma developed following cataract surgery. [36-37] In another study, it was suggested that posterior capsulotomy or anterior vitrectomy during cataract surgery may be effective in the prophylaxis for malignant glaucoma development.[38] Singh et al.[39] recommended irido-zonulo-hyaloid vitrectomy combind with pars plana vitrectomy to prevent malignant glaucoma development in patient with nanophthalmos who underwent phacoemulsification and IOL surgery. On the other hand, pars plana lensectomy provides advantages such as functional conventional flow via enlarged anterior chamber angle and prevention of early synechia development in cases with glaucoma. Zhang et.[40] reported no complication after pars plana vitrectomy plus lensectomy in 21 eyes of 21 cases and 71.4% of success rate.

In addition, it was suggested that, because of narrow anterior chaber, lens extraction via anterior approach can be safer than pars plana due to potential challenges such as iris prolapsus, corneal endothelial injury, difficult capsulorhexis, and corneal edema resulting in IOP elevation. In addition, since cases are generally young, pars plana lensectomy can be readily aspirated without need for ultrasound energy as similar to lens phacoemulsification, providing additional protection for endothelium Avoiding rapid alterations in IOP by more stabile fluid balance, both intraoperative and postoperative choroidal detachment is prevented. However, phacoemulsification via anterior approach following enhancing anterior chamber depth via anterior vitrectomy from pars plana can be an option in these cases.

In nanophthalmic cases with refractory glaucoma, lens extraction via phacoemulsification and concurrent endoscopic endocylophotocoagulation can be used as an alternative treatment option. In these cases,Seton surgery and diode cyclophotocoagulation can be applied when phacoemulsification and goniosynechiae surgery, vitrectomy surgery and trabeculectomy with mitomycin C augmentation failed to control intraocular pressure.[41]

In conclusion, serious complications can be encountered in all stages of treatment in cases with nanophthalmos. Thus, all therapeutic processes should be performed in centers with glaucoma and retina clinics and surgeons should have sufficient experience and skills to overcome potential complications.

REFERENCES

1. Carricondo PC, Andrade T, Prasov L, et al. Nanophthalmos: A review of the clinical spectrum and genetics. J Ophthalmol. 2018 May 9;2018:2735465. doi: 10.1155/2018/2735465. eCollection 2018.
2. Elder MJ. Aetiology of severe visual impairment and blindness in microphthalmos. Br J Ophthalmol. 1994;78:332-4.
3. Srinivasan S, Batterbury M, Marsh IB, et al. Corneal topographic features in a family with nanophthalmos. Cornea.2006 ;25:750-6.
4. Walsh MK, Goldberg MF. Abnormal foveal avascular zone in nanophthalmos. Am J Ophthalmol. 2007;143:1067-8.
5. Crespí J, Buil JA, Bassaganyas F, Vela-Segarra JI, et al. A novel mutation confirms MFRP as the gene causing the syndrome of nanophthalmos-renititis pigmentosa-foveoschisis-optic disk drusen. Am J Ophthalmol. 2008;146:323-8.
6. Zacharias LC, Susanna R Jr, Sundin O. Efficacy of topical dorzolamide therapy for cystoid macular edema in a patient with MFRP-related nanophthalmos-retinitis pigmentosa-foveoschisis-optic disk drusen syndrome. Retin Cases Brief Rep. 2015;9:61-3.
7. MacKay CJ, Shek MS, Carr RE, et al. Retinal degeneration with nanophthalmos, cystic macular degeneration, and angle closure glaucoma. A new recessive syndrome. Arch Ophthalmol. 1987;105:366-71.
8. Albar AA, Nowilaty SR, Ghazi NG. Nanophthalmos and hemiretinal vein occlusion: A case report. Saudi J Ophthalmol. 2015;29:89-91.
9. Demircan A, Altan C, Osmanbasoglu OA, et al. Subfoveal choroidal thickness measurements with enhanced depth imaging optical coherence tomography in patients with nanophthalmos. Br J Ophthalmol. 2014;98:345-9.
10. Xiao H, Guo X, Zhong Y, et al. Retinal and choroidal changes of nanophthalmic eyes with and without secondary glaucoma. Retina.2015 ;35:2121-9.
11. Helvacioglu F, Kapran Z, Sencan S, et al. Optical coherence tomography of bilateral nanophthalmos with macular folds and high hyperopia. Case Rep Ophthalmol Med. 2014;2014:173853.
12. Relhan N, Jalali S, Pehre N, et al. High-hyperopia database, part I: clinical characterisation including morphometric (biometric) differentiation of posterior microphthalmos from nanophthalmos. Eye (Lond).2016 ;30:120-6.
13. Khan AO. Posterior microphthalmos versus nanophthalmos. Ophthalmic Genet. 2008;29:189.
14. Wu W, Dawson DG, Sugar A, et al. Cataract surgery in patients with nanophthalmos: results and complications. Cataract Refract Surg. 2004;30:584-90.
15. Yalvac IS, Satana B, Ozkan G, et al. Management of glaucoma in patients with nanophthalmos. Eye (Lond). 2008;22:838-43.
16. Nowilaty SR, Khan AO, Aldahmesh MA, et al. Biometric and molecular characterization of clinically diagnosed posterior microphthalmos. Am J Ophthalmol. 2013;155:361-72
17. O'Grady RB. Nanophthalmos. Am J Ophthalmol. 1971;71:1251-3.
18. Trelstad RL, Silbermann NN, Brockhurst RJ. Nanophthalmic sclera. Ultrastructural, histochemical, and biochemical observations. Arch Ophthalmol. 1982;100:1935–8.
19. Yue BY, Duvall J, Goldberg MF, et al. Nanophthalmic sclera. Morphologic and tissue culture studies. Ophthalmology. 1986;93:534–41.
20. Uyama M, Takahashi K, Kozaki J, et al. Uveal effusion syndrome: clinical features, surgical treatment, histologic examination of the sclera, and pathophysiology. Ophthalmology. 2000;107:441–9.
21. Patel N, Khan AO, Alsahli S, et al. Genetic investigation of 93 families with microphthalmia or posterior microphthalmos. Clin Genet. 2018;93:1210–22.
22. Gass JD, Jallow S. Idiopathic serous detachment of the choroid, ciliary body, and retina (uveal effusion syndrome). Ophthalmology. 1982;89:1018-32.
23. Johnson MW, Gass JD. Surgical management of the idiopathic uveal effusion syndrome. Ophthalmology. 1990;97:778-85.
24. Brockhurst RJ. Nanophthalmos with uveal effusion. A new clinical entity. Arch Ophthalmol. 1975;93:1989-99.
25. Trelstad RL, Silbermann NN, Brockhurst RJ. Nanophthalmic sclera. Ultrastructural, histochemical and biochemical observations. Arch Ophthalmol. 1982;100:1935-8.
26. Ward RC, Gragoudas ES, Pon DM, et al. Abnormal scleral findings in uveal effusion syndrome. Am J Ophthalmol. 1988;106:139-46.
27. Yue BY, Duvall J, Goldberg MF, et al. Nanophthalmic sclera. Morphologic and tissue culture studies. Ophthalmology. 1986;93:534-41.
28. Gass JD. Uveal effusion syndrome: a new hypothesis concerning pathogenesis and technique of surgical treatment. 1983. Retina. 2003;23(6 Suppl):159-163.
29. Jackson TL, Hussain A, Salisbury J, et al. Transscleral albumin diffusion and suprachoroidal albumin concentration in uveal effusion syndrome. Retina. 2012;32:177-82.
30. Ritch R, Chang BM, Liebmann JM. Angle closure in younger patients. Ophthalmology 2003; 110: 1880–9.
31. Singh OS, Simmons RJ, Brockhurst RJ, et al. Nanophthalmos: a perspective on identification and therapy. Ophthalmology 1982; 89: 1006–12.
32. Brockhurst RJ. Vortex vein decompression for nanophthalmic uveal effusion. Arch Ophthalmol 1980; 98: 1987–90.

33. Jin JC, Anderson DR. Laser and unsutured sclerotomy in nanophthalmos. Am J Ophthalmol 1990; 109: 575–80.

34. Shields CL, Roelofs K, DiNicola M, et al. Uveal effusion syndrome in 104 eyes: Response to corticosteroids - The 2017 Axel C. Hansenlecture. Indian J Ophthalmol. 2017;65:1093-04.

35. Kumar A, Kedar S, Singh RP. The indocyanine gren findings in idiopathic uveal effusion syndrome. Indian J Ophthalmol. 2002;50:217-9.

36. Faisal AA, Kamaruddin MI, Toda R, et al. Successful recovery from misdirection syndrome in nanophthalmic eyes by performing an anterior vitrectomy through the anterior chamber. Int Ophthalmol. 2019;39):347-57.

37. Wang J, Du E, Tang J. The treatment of malignant glaucoma in nanophthalmos: a case report. BMC Ophthalmol. 2018;18:54.

38. Thompson AC, Challa P. Prophylactic anterior vitrectomy during cataract surgery in eyes at increased risk for aqueous misdirection. Am J Ophthalmol Case Rep. 2018;12:24-27.

39. Singh H, Wang JC, Desjardins DC, et al. Refractive outcomes in nanophthalmic eyes after phacoemulsification and implantation of a high-refractive-power foldable intraocular lens. J Cataract Refract Surg 2015;41:2394-2402.

40. Zhang Z, Zhang S, Jiang X, et al. Combined 23-G Pars Plana Vitrectomy and lensectomy in the management of glaucoma associated with nanophthalmos. Ophthalmic Res. 2018;59:37-44.

41. Golan S, Kurtz S. Diode laser cyclophotocoagulation for nanophthalmic Chronic angle closure glaucoma. J Glaucoma. 2015;24:127-9.