Clinical Characteristics of Comorbid Retinal Dystrophies and Primary Angle Closure Disease

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Research Article

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Abstract

Purpose: To assess the clinical characteristics of comorbid retinal dystrophies and primary angle closure disease.

Design: Retrospective study from January 1992 to June 2020.

Methods: This descriptive study included 92 eyes of 46 patients with comorbid retinal dystrophies and primary angle closure disease (PACD) that included eyes with primary angle closure suspect, primary angle closure and primary angle closure glaucoma. Demographic profile, clinical characteristics of PACD and its association with retinal dystrophies are described.

Results: The study included 46 patients (92 eyes). Males were majority, 63%. Mean (± standard deviation) age when retinal dystrophy was diagnosed was 29.6 ± 9.4 years and PACD was diagnosed at 32.23±7.92 years. Mean BCVA at presentation was 1.07±0.87 log MAR (95% confidence interval (CI):0.87,1.26). Mean Intraocular pressure at diagnosis of glaucoma was 27±16 mmHg (95% CI:23.5,31.5 mmHg). The most common retinal dystrophy associated with PACD was retinitis pigmentosa (RP) followed by RP with retinoschisis. The hospital-based prevalence of PACD among all patients with RP and retinoschisis was 0.19% and 0.15% respectively. Laser peripheral iridotomy (LPI) was performed in 74 eyes (80.5%). Glaucoma was managed medically in majority of the eyes (58 eyes, 63.04%) and minority required surgical management with trabeculectomy (11, 11.9%).

Conclusion: Retinitis pigmentosa is the most common retinal dystrophy associated with PACD. Comorbid PACD in eyes with retinal dystrophies was observed in 2nd to 3rd decade of life. This calls for screening for angle closure in eyes with retinal dystrophies from second decade onwards to identify the comorbid PACD and treat or refer them appropriately.

Introduction

Glaucoma in eyes with retinal pathology is not uncommon and is often secondary and associated with poor visual prognosis.[1–4] Coexisting primary glaucomas with retinal conditions are reported with a prevalence of 15.7% for Primary open angle glaucoma, 10.7% for Normal tension glaucoma and 12.3% for Primary angle closure disease. The subjects in these studies are older and the associated retinal conditions are diabetic retinopathy and age related macular degeneration.[3] The occurrence of Primary angle closure glaucoma (PACG) with coexisting retinal dystrophies like retinitis pigmentosa is reported in younger individuals with a prevalence ranging from 1.03–2.13%.[5–8] Retinal dystrophies belong to a group of inherited retinal conditions affecting mainly the photoreceptor cells, retinal pigment epithelium (RPE) with or without involvement of vitreous.[9] The pathophysiology behind occurrence of PACD in retinal dystrophies is multifactorial, including angle abnormalities, excess pigment accumulation in the trabecular meshwork, thick lens and vitreous abnormalities. There are isolated case reports on association of PACD with other retinal dystrophies like X-linked juvenile retinoschisis, best vitelliform macular dystrophy, autosomal recessive and autosomal dominant bestrophinopathies.[10–13]

The present study aims to describe the epidemiology, clinical profile and management of patients with coexisting retinal dystrophies and primary angle closure disease presenting to a tertiary eye care institute in India.

Methods

The present study consists of a retrospective analysis of patient data between January 1992 and June 2020 with diagnosis of retinal dystrophy and primary angle closure disease (PACD) in any age group. The study adhered to the tenets of declaration of Helsinki and was approved by the Institutional review board.

Retinal dystrophies were diagnosed based on clinical examination and multimodal imaging features including fundus autofluorescence (FAF), optical coherence tomography (OCT), electroretinogram, electrooculogram and visual field analysis whenever available in the records.[14] Types of retinal dystrophies included were retinitis pigmentosa (RP), retinoschisis, stargardt's disease, bests vitelliform macular dystrophy (BVMD) and autosomal recessive bestrophinopathy (ARB). The diagnostic criteria used for RP were diffuse widespread retinal pigment epithelial degeneration, arterial narrowing, disc pallor, commensurate visual field loss, and whenever available reduced amplitudes on electroretinogram (ERG) with evidence of rod and cone involvement.[14] Retinoschisis was diagnosed with symmetric bilateral macular involvement with or without peripheral involvement, optical coherence tomography showing schisis of layers of the retina in the macula.[15, 16] Stargardts macular dystrophy was diagnosed when fundus showed diffuse retinal flecks, predominantly around the macula, with variable midperipheral distribution, with macular atrophy in later part of life. FAF showing distribution of flecks clearly, OCT showing macular atrophy and photoreceptor loss, full-field electroretinography showing predominantly cone involvement with or without involvement of rods.[17]

BVMD was diagnosed when bilateral fundus changes of egg-yolk appearance, layering of lipofuscin, scrambled egg appearance or central RPE and retinal atrophy were seen at macula clinically, macular OCT showing different patterns in various stages of bests disease and electrooculogram (EOG) showing reduced Arden ratio.[18] ARB was diagnosed when widespread funduscopic changes and vitelliform material deposition were seen with abnormal or subnormal full-field electroretinography and OCT having intraretinal cystic changes with subretinal fluid.[19, 20]

Primary angle closure disease (PACD) was classified as i) Primary angle closure suspects (PACS): An eye in which ≥ 180 degree appositional irido-trabecular contact (ITC), normal IOP and no optic disc damage, ii) Primary angle closure (PAC): An eye with ≥ 180 degree iridotrabecular contact with goniosynechiae or blotchy pigments or peripheral anterior synechiae or elevated IOP, iris whorling, sphincter atrophy, anterior subcapsular lens opacities, "glaucomfleken", without optic disc damage. iii) Primary angle closure glaucoma (PACG): features of PAC with glaucomatous optic disc damage. Eyes with secondary glaucomas or post-surgical eyes were excluded. Characteristics of PACD and its association with retinal dystrophies are described.

Descriptive statistics using mean ± standard deviation and median with inter-quartile range (IQR) were used to elucidate the demographic data. Chi square and paired t test (Stata software, Stata Corp. 2015. College Station, TX: Stata Corp LP) were used for univariate analysis.

Results

Demographic and clinical features

In total, the study included 46 patients and 92 eyes. 63% or nearly 2/3rd of them were males. (Figure 1) Mean BCVA at presentation was 1.07 ± 0.94 log MAR (95% Confidence interval (CI), 0.87 to 1.26). Mean age at the diagnosis of any retinal dystrophy was 29.6 ± 9.4 years, and mean age at the diagnosis of PACD was 32.23 ± 7.92 years. Retinal dystrophy presented at an earlier age than PACD. Mean Intraocular pressure at diagnosis of glaucoma was 27 ± 16 mmHg (95% CI, 23.50 to 31.54 mmHg) and majority of the eyes (53 eyes, 57.6%) were diagnosed with glaucoma during their periodic retinal follow up. All 92 eyes had occludable angles. At presentation 57.6% (53/92) of the eyes had primary angle closure glaucoma (PACG), 34.7% (32/92) of the eyes had primary angle closure (PAC) and 7.6% (7/92) of the eyes were primary angle closure suspect (PACS). 10 eyes had acute angle closure attack. All 92 eyes were phakic at the time of diagnosis of PACD. The mean cup disc ratio (CDR) at baseline was 0.60 ± 0.29 (95% CI, 0.54 to 0.67).

Retinal and vitreous changes

The most common retinal dystrophy associated with PACD was retinitis pigmentosa (RP) (40/46 patients) followed by RP with retinoschisis (2/46 patients). Others in less occurrence were Best's and bestrophinopathies. (Figure 2) The hospital-based prevalence of PACD among all patients with RP and retinoschisis presenting to the clinic from the period of January 1992 to June 2020 was 0.19% (40/20750) and 0.15% (1/651) respectively in our study. Out of 80 eyes (40 patients) with RP, typical retinitis pigmentosa pigmentation (mid periphery and beyond bony spicule pigmentation) was seen in 74 eyes (Figure 3), 4 eyes had inverses retinitis pigmentosa (bony spicule pigmentation involving macula more than mid periphery) and 2 eyes had RP sine-pigmento (lack of bony spicule pigmentation). All eyes with RP had pallor of optic disc except 2 eyes with sine-pigmento variety of RP 34.7% of the eyes with RP at presentation had macular involvement like foveal atrophy, pigmentary changes, macular schisis and epiretinal membrane. 8.7% of the eyes with RP had some form of vitreous abnormalities (vitreous opacities/floaters, vitreoschisis and degenerative changes).

Management

Of the 92 eyes (46 subjects), 80 eyes (40 subjects) had primary angle closure disease and RP, among them, 49 eyes had PACG, 24 eyes had PAC and 7 eyes were PACS. Mean IOP at presentation was 27 ± 16 mmHg (95% CI, 23.50 to 31.54 mmHg).

YAG laser peripheral iridotomy (LPI) was performed in 74 eyes (80.5%). Among these 74 eyes, 63 eyes underwent LPI at our tertiary care and rest 11 eyes had undergone LPI before referral to us. Out of 74 eyes that underwent LPI, 47 eyes (63.51%, 47/74) underwent LPI during their first visit to the hospital and 27 eyes (36.48%, 27/74) underwent LPI during subsequent follow up visits. In 18 eyes (19.5%) LPI was not performed, the reason being poor vision (perception of light or no perception of light) with late presentation. At the time of diagnosis of PACD at our institute, 53 eyes (57.6%) were not on any antiglaucoma medications (AGM), 39 eyes (42.4%) were on AGM of which 17 eyes (18.5%) were on single AGM, 10 eyes (10.9%) on two AGM, 10 eyes (10.9%) on three AGM and 2 eyes (2.17%) on four AGM. Among 39 eyes on AGM, 11 eyes underwent LPI before visiting us, 18 eyes for whom LPI was not performed were on AGM for IOP control and the rest 10 eyes were diagnosed as open angles elsewhere and found to have occludable angles at our tertiary center and underwent LPI.

Following LPI, glaucoma was managed medically in majority of the eyes (58 eyes, 63.04%) and a minority required surgical management ie 15 eyes (16.3%). 11 eyes (11.9%) needed trabeculectomy. Post trabeculectomy one patient had shallow anterior chamber depth with aqueous misdirection and malignant glaucoma which was treated with pars plana vitrectomy with iridozonulo-hyaloidotomy and malignant glaucoma resolved. Three eyes underwent transscleral cyclophotocoagulation and one eye underwent pars plana vitrectomy with iridozonulo-hyaloidotomy along with trabeculectomy in view of contralateral eye complicated with malignant glaucoma. (Figure 4).

Discussion

We describe the clinical profile of patients with coexisting retinal dystrophies and primary angle closure disease presenting to a tertiary eye care hospital in India. PACD association with retinal dystrophies is rare, prevalence of PACG in retinitis pigmentosa is reported to range from 1.03–2.13%.[5–8] Association of PACG with other rare retinal dystrophies like X-linked juvenile retinoschisis, best vitelliform macular dystrophy, autosomal recessive and autosomal dominant bestrophinopathies are also reported.[10–13] In the present study, the prevalence of PACD with RP was 0.19%, lesser than previous reports and PACD with retinoschisis was 0.15%.

Our study has the largest cohort (46 patients) including retinal dystrophies with co-existing PACD. As per our study, PACD with retinal dystrophies was noted more commonly in males (63%) than females (36.9%). PACG was noted in 33 eyes of males and 20 eyes of females in our study. Babeed *et al* had reported three males with PACG and RP in their series of five patients.[1, 4, 5] Pradhan *et al* had reported female more common than males in their five patients case series.[8] The reason for the male preponderance might be because the retinal dystrophies are more common in males, and also possibility of the female patients with retinal dystrophies not accessing care. In our study the mean age at diagnosis of any retinal dystrophy was 29.6 ± 9.4 years, and mean age at diagnosis of PACD was 32.23 ± 7.92 years. This indicates presentation of retinal dystrophy at an earlier age than PACG. This association is logical as most of the retinal dystrophies present usually at first or second decade of life.[9]

Gao *et al* have studied the etiologies and the clinical characteristics of angle-closure glaucoma (ACG) patients in younger group (≤40 years) including primary and several secondary angle closure glaucomas.[21] Mean age of the patients in their study was 25.6± 13.0 years. PACG (32.6%), uveitis (20.3%), and anterior segment dysgenesis (ASD) (15.1%) were the most common etiologies for occurrence of ACG in their study. Few other common etiologies found in association for ACG included iridocorneal endothelial syndrome, neovascular glaucoma, nanophthalmos, retinitis pigmentosa, spherophakia, bestrophinopathy, persistent fetal vasculature, iridociliary cysts, congenital retinoschisis, Marfan's syndrome, retinopathy of prematurity, familial exudative vitreoretinopathy, congenital retinal folds, Coat's disease, and neurofibromatosis. In their study 3% of the patients with ACG had RP and 2% of the patients with ACG had bestrophinopathy. The mean age at diagnosis of PACG in their patients was 34.4 ± 5.1 years (range, 13–40 years) similar to our study. The mean age of patients with RP and bestrophinopathy was 29.7 ±7.0 (range 18–39 years) and 26.2 ±6.4 (18–34) years respectively similar to our study.

Another study by Chang *et al had also* described the occurrence of angle closure in young patients (≤40 years).[22] Mean age of the patients at hospital presentation was 34.4 ± 9.4 years (range, 3-68 years). Most common etiologies found were plateau iris syndrome, iridociliary cysts, retinopathy of prematurity and uveitis. The mean age of RP patients with PACG was 42.2 years (range 3-94 years) in various other studies.[5, 8] All our patients had primary angle closure and had retinal dystrophies for which they were under follow up, hence it is possible that the primary angle closure was diagnosed at an earlier age. All our patients had occludable angles with phakic lens status. Studies before have postulated the occurrence of PACG in RP patients is secondary to the laxity of the zonules and anterior lens subluxation leading to angle closure, which is a possibility, however no obvious lens subluxation with phacodonesis was noted in any of our cases.[8, 9] LPI followed by medical treatment based on the need was the primary modality to treat the angle closure in our study. 10 eyes in our study were misdiagnosed as open angles elsewhere and found to have occludable angles at our tertiary center. This highlights the need of proper gonioscopy and classification of PACD for appropriate treatment. Hence, gonioscopy is advised yearly to pick up coexisting angle closure in cases of retinal dystrophies with shallow anterior chamber or whenever the IOP is elevated. It is important to identify coexisting angle closure/glaucoma which is a potentially blinding disease. As in our study, although these subjects had retinal pathology and were advised follow up, many missed regular follow up and presented late. At the time of diagnosis of glaucoma, 18 eyes (19.5%) had poor vision (perception of light or no perception of light) due to advanced glaucoma. Hence it is important to educate the retinal specialists to counsel the patients for regular follow up and also evaluate for angle closure from second decade onwards.

RP was the most common dystrophy associated with PACG similar to previous studies. Other less common dystrophies were retinoschisis, best's dystrophy and bestrophinopathies. Angle abnormalities, pigment accumulation in angles, lens thickness variabilities and vitreous disturbances have been postulated to be the pathophysiology behind occurrence of PACG in retinal dystrophies.[3, 5, 8, 12] Synechial angle closure with pigmentation was seen in 9 eyes with RP in our study, typical retinitis pigmentosa pigmentation (mid periphery and beyond bony spicule pigmentation) was seen in 74 eyes

and 8 eyes with RP had some form of vitreous abnormalities (vitreous opacities/floaters, vitreoschisis and degenerative changes).

Glaucoma was managed medically in majority of the eyes and a minority of the eyes (11.9%) required surgical management for glaucoma with trabeculectomy. Post trabeculectomy one patient had shallow anterior chamber depth with aqueous misdirection and malignant glaucoma.

Strengths of our study are, largest sample size so far assessing the clinical characteristics of comorbid retinal dystrophies and primary angle closure disease. Limitations are retrospective study. Lack of visual field data in all patients to quantify the amount of peripheral visual loss and progression which happens in both glaucoma as well as retinal dystrophy.

Conclusion: Our study is the largest study so far with comorbid retinal dystrophies and PACD to the best of our knowledge. Among all dystrophies, retinitis pigmentosa is the most common dystrophy associated with PACD. PACD in retinal dystrophies mostly affects 2nd to 3rd decade adults. Males were most commonly affected than females. Presentation of retinal dystrophy is earlier than PACD. Our study highlights the need to educate the retinal specialists to counsel the patients for regular follow up and also evaluate for angle closure from second decade onwards. PACG is the most common presentation with retinal dystrophies among PACD spectrums. LPI and trabeculectomy are useful in management of intraocular pressure for PACD in retinal dystrophies cases. Future prospective studies are required to identify the rate of visual loss and progression.

Declarations

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a. Funding/Support: Hyderabad Eye Research Foundation and Mr. Nataraja Foundation of the center for retinitis pigmentosa and allied disorders(C-REPID), Hyderabad, India

b. Financial Disclosures: "No financial disclosures."

C. Conflict of Interest Statement: None

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Figures

Figure 1

Age and gender distribution of patients with primary angle closure disease in retinal dystrophies

Figure 2

Distribution of retinal dystrophy in cases of primary angle closure disease

Figure 3

A case of retinitis pigmentosa with primary angle closure disease; A 40-year-old male who presented with both eyes (BE) central and peripheral diminution of vision (Right eye 20/30 and left eye 20/40) and high intraocular pressure (26 mm of Hg) in the left eye (LE) with both eyes (BE) having occludable angles on gonioscopy. BE fundus showing bony spicule pigmentary changes and retinal pigment epithelial degenerative changes (a, b). BE macular optical coherence tomography showing loss of photoreceptors parafoveally (c, d). Right eye (RE) optic disc showing 0.3 cup-disc-ratio and LE optic disc showing near total cupping and glaucomatous damage (e, f). BE full field electroretinogram showing extinguished scotopic and reduced photopic responses (g). The patient underwent BE YAG laser iridotomy followed by medical management.

Figure 4

A case of bestrophinopathy with primary angle closure disease; A 28-year-old male who presented with both eyes (BE) central diminution of vision (Right eye 20/50 and left eye 20/125) and uncontrolled intraocular pressure (Right eye 34 and left eye 46 mm of Hg) with history of BE YAG laser iridotomy. BE wide field fundus imaging and fundus autofluorescence showing multifocal subretinal yellow deposits with hyperautofluorescence suggestive of autosomal recessive bestrophinopathy characteristics. BE Optic disc showing glaucomatous disc damage. (a-f) Both eyes underwent trabeculectomy left eye (LE) followed by right eye (RE). Post trabeculectomy left eye had shallow anterior chamber depth with aqueous misdirection and malignant glaucoma. In view of this complication right eye underwent combined trabeculectomy and pars plana core vitrectomy with iridozonulo-hyaloidotomy (Note phakic eye with clear lens and inferior and temporal iridectomy opening through which the communication is established to the anterior vitreous-white arrow). RE post operative day one slit lamp photography images

showing a good bleb, with mild to moderate vascularization and a well-formed central anterior chamber (g). BE macular optical coherence tomography showing intraretinal cystic changes with subretinal fluid (h, i).