Ocular abnormalities in a large Western China patient cohort with Retinitis Pigmentosa

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Abstract

Background: To report the prevalence of ocular abnormalities and investigate visual acuity in a large Western China cohort of retinitis pigmentosa (RP) patients.

Methods: A retrospective study was performed, reviewing the medical records and ophthalmic examination reports of 2,127 eyes from 1,065 RP patients in one eye hospital. The authors investigated the prevalence of ocular abnormalities and the relationship between best corrected visual acuity (BCVA) and macular abnormalities.

Results: Nyctalopia (58.2%) and blurred vision (27.1%) were the leading consultation causes. BCVA measurements in the better eyes at first clinical presentation showed that 304 patients (28.5%) were categorised as blind and 220 patients (20.7%) as low vision. The most common ocular abnormalities were cataracts (43.1%) and macular abnormalities (59.7%), including epiretinal membranes (51.1%), cystoid macular oedema (18.4%), vitreomacular traction syndrome (2.4%), macular holes (2.3%) and choroidal neovascular membranes (0.05%). Glaucoma was found in 35 eyes (1.6%). The proportions of epiretinal membranes ($P = 0.001$) and macular holes ($P = 0.008$) increased significantly with age. The proportions of vitreomacular traction syndrome ($P = 0.003$) and epiretinal membranes ($P < 0.001$) in pseudophakia and aphakia eyes were significantly higher than in eyes that had not received operations (including cataracts and clear lens). Cystoid macular oedema was significantly associated with poorer visual acuity in RP patients with clear lens ($P = 0.002$).

Conclusion: Cataracts and macular abnormalities are common in RP patients. In the macular abnormalities, cystoid macular oedema may have a negative effect on BCVA in RP patients with clear lens.

Background

Retinitis pigmentosa (RP) is the most common type of inherited retinal dystrophy, causing progressive degeneration of the retinal pigment epithelium (RPE) and photoreceptors [1]. RP prevalence is approximately 1/4,000 and > 1.5 million patients are affected worldwide [2]. Nyctalopia and blurred vision are the most common RP symptoms, but other rare symptoms (e.g., photophobia, blurred vision) also prompt RP patients to see doctors [1–3]. However, little systematic information has been published on the clinical symptoms RP patients experience.

Ocular abnormalities (e.g., glaucoma, cataracts, maculopathy, etc.) may occur as RP progresses [4]. The typical histopathological change in RP is thinning of the photoreceptor's outer segments, which worsens with RP progression [4–5]. Although central vision acuity could remain normal for several years, anatomical macular abnormalities may occur in early-stage RP [6–7]. Epiretinal membranes (ERMs) and cystoid macular oedema (CME) are the most common macular abnormalities in RP patients, as detected by optical coherence tomography (OCT). Other macular abnormalities also accompanied by, such as macular holes (MH), vitreomacular traction syndrome (VMT) and choroid neovascularisation membrane (CNVM) [5–9]. To the authors' knowledge, visual acuity and prevalence of ocular abnormalities, have not yet been reported in a large cohort of Western Chinese RP patients.

This study, therefore, assesses the ocular abnormalities in a large cohort of Western Chinese RP patients. It also investigates correlations between visual acuity and macular abnormalities.

Methods

Study design and subjects recruitment

The authors retrospectively extracted medical records of patients diagnosed with RP between January 2014 and January 2019 at Southwest Hospital/ Southwest Eye Hospital, Third Military Medical University (Army Medical University), Chongqing, China. These records included information on each patient's age, gender, medical and surgical history, family

history, complaints, best corrected visual acuity (BCVA), intraocular pressure, lens status, slit-lamp anterior segment and dilated fundus examination from the first clinical presentation. RP diagnosis was based on: (1) presence of night blindness or blurred vision and peripheral vision field restriction; (2) characteristic fundus changes, such as pale optic disc, attenuated vessels and bone-spicule-like pigmentation deposits in the mid- or far-periphery; and (3) reduced or non-detectable full-field electroretinogram (ffERG) rod and cone amplitudes [1, 4, 5]. Systemic syndrome RP patients were included in the study. The exclusion criteria were: (1) trauma history; (2) vitreoretinal surgery and intravitreal therapy history; (3) pathological myopia; (4) other vascular retinopathy, such as hypertensive retinopathy, diabetic retinopathy, retinal periphlebitis, etc.; (5) age-related macular degeneration; (6) atypical RP, such as unilateral pigmentary retinopathy or sectorial pigmentary retinopathy; (7) secondary retinal pigmentosa; and (8) severe systemic diseases. The study was performed according to the Declaration of Helsinki and approved by the Ethics and Research Committee of Southwest Hospital, Army Medical University (KY2020096).

Data collection and processing

The age of onset (that is, of symptoms) was defined as the patient's age subtracted from the year with positive disease history. BCVA was measured with a Tumbling E chart and converted into the logarithm of the minimum angle of resolution (logMAR) value for analysis [10]. BCVA was classified according to the World Health Organization's (WHO) category of vision as follows [2]: BCVA worse than 3/60 in the better eye was considered blindness; BCVA of 3/60–6/18 in the better eye was considered low vision; and BCVA of 6/18 or more was considered normal. The researchers did not classify visual acuity according to vision field. According to the International Society of Clinical Electrophysiology of Vision (ISCEV) standards, ffERG testing was performed [11]. The macular microstructure in RP patients was examined with either Spectral Domain OCT (Cirrus HD-OCT, Carl Zeiss Meditec, Dublin California, USA) or Heidelberg Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany). Two experienced ophthalmologists independently evaluated the images. If the results differed, a third ophthalmologist re-evaluated them. Macular abnormalities were documented as follows: ERM, CME, MH (including lamellar and full-thickness MH), VMT and CNVM [1, 12].

A specialist diagnosed glaucoma based on the presence of glaucomatous optic neuropathy, intraocular pressure over 21 mmHg, with or without the presence of iridotrabecular contact [13]. Lens condition was classified as clear, cataract, pseudophakic and aphakic. Some patients voluntarily underwent molecular diagnosis, and inherence patterns were categorised according to genetic test reports: autosomic dominant (AD), autosomic recessive (AR), X-linked (X-L) and sporadic cases (i.e., patients showing negative genetic reports or no evidence of other affected family members). RP patients' ages were divided into four groups (≤ 15 years, 16–44, 45–64 and ≥ 65) for statistical analysis, according to the International Classification of Disease.

Statistical analyses

SPSS 22.0 was used to conduct analyses. Continuous variables, such as counselling age, age of onset and BCVA (logMAR), were expressed as means ± standard deviation (SD) and were compared with independent sample t-tests. Categorical variables (gender, complaints, inherence pattern, age group, lens condition and macular abnormalities) were presented as counts and percentages and compared with Chi-squared or Fisher's exact tests. Multiple linear regression investigated the relationship between BCVA (logMAR) and macular abnormalities. Coefficients of the estimated regression (β), the corresponding statistical significance (*P*), the exponential parameter and its confidence interval were presented for each factor. A *P*-value of < 0.05 was considered statistically significant.

Results

2127 eyes belong to 1,065 patients (493 [46.3%] female and 572 [53.7%] male, respectively.) were sampled. Table 1 describes the patients' demographic characteristics. The number of eyes was odd because three eyeballs in three female patients were enucleated because of glaucoma. The mean ± SD counselling age (i.e., age at patients' first doctor visit) was 41.9 ± 15.7 years (range: three months to 83 years; females: 43.4 ± 16.0; males: 40.6 ± 15.3; $P = 0.000$). The mean ± SD age of onset for RP patients was 21.9 ± 19.2 years (females: 24.1 ± 19.7; males: 20.0 ± 18.6; $P = 0.000$). In both age of onset and mean counselling age, female patients were older than males. 352 of 1,065 patients (33.1%) chose molecular diagnosis, and the most common inheritance pattern was AR (57.7%), followed by Sporadic (27.6%), AD (8.8%) and X-L (6.0%) (Table 1).

Table 1
Demographic characteristics of the 1,065 RP patients in this study

	Female	Male	Total
No. patients	493(46.3%)	572(53.7%)	1065(100%)
No. Eyes	983*(45.2%)	1144(53.8%)	2127(100%)
Counseling Age(yrs)	43.4 ± 16.0	40.6 ± 15.3	41.9 ± 15.7
Mean age of onset(yrs)	24.1 ± 19.7	20.0 ± 19.6	21.9 ± 19.2
Inheritance pattern			
Autosomic dominant (No.)	14(8.6%)	17(9.0%)	31(8.8%)
Autosomic recessive (No.)	99(60.7%)	104(55.0%)	203(57.7%)
X-linked (No.)	3(1.9%)	18(9.5%)	21(6.0%)
Sporadic (No.)	47(28.8%)	50(26.5%)	97(27.6%)
Total (No.)	163(100%)	189(100%)	352(100%)
*: Three eyeballs in three female patients were enucleated because of glaucoma.			

Nyctalopia (58.2%) and blurred vision (27.1%) were the sampled patients' main complaints (see Fig. 1). 11.2% had experienced poor vision since childhood (≤ 15 years old). Other reasons for RP patients visiting the hospital included routine physical examination (1.1%), metamorphopsia (0.7%), photophoby (0.5%), black floating spots (0.5%) and other unusual symptoms (0.7%, including pain, photopsia, narrow vision field and double vision).

BCVA in the better eye at first clinical presentation showed that 304 (28.5%) patients were blindness, and 220 (20.7%) had low vision (see Fig. 2a, Supplemental Table 1). Although the percentage of normal vision at first presentation in females (53.1%) was slightly higher than in males (48.8%), no significant gender difference was observed in visual acuity distribution ($P = 0.283$). According to Fig. 2b and Supplemental Table 2, patients over the age of 44 showed a lower proportion (45–64y: 45%; ≥65y: 31.5%) of normal vision than patients under 44 (≤ 15y: 59.0%; 16–44y: 57.6%) at first presentation, and the proportion of blindness at first presentation in patients over 44 (45–64y: 34.6%; ≥65y: 43.8%) was higher than in patients under 44 (≤ 15y: 8.5%; 16–44y: 14.8%). There was also a significant increase in the percentage of blindness with age ($P = 0.000$).

Cataracts were observed in 917 eyes (43.1%, 917/2,127 eyes) from 469 patients (44.0%, 469/1,065 patients). Pseudophakic and aphakic eyes were classed as presenting cataracts. Therefore, of the eyes in which cataracts were observed, pseudophakia was seen in 157 eyes (7.4%) from 95 patients (4.5%), and aphakia was seen in 22 eyes (1.0%) from 14 patients (0.7%). Glaucoma was found in 35 eyes (1.6%; 35/2,127) from 21 patients (2.0%; 21/1,065). 1,388 eyes (65.3%; 1,388/2,127) from 704 patients (66.1%; 704/1,065) received macular OCT, and macular abnormalities were seen in 829 eyes (59.7%, 829/1,388) from 481 patients (68.3%; 481/704).

Typical OCT and corresponding fundus photography of macular abnormalities in RP patients were provided in Fig. 3 (a-j), and the prevalence of macular abnormalities in this study were distributed as follows:

- ERM: 709 eyes (51.1%; 709/1,388), 418 patients (59.4%, 418/704).
- CME: 255 eyes (18.4%, 255/1,388), 150 patients (21.3%, 150/704).
- VMT: 33 eyes (2.4%, 33/1,388), 25 patients (3.6%, 25/704).
- MH: 32 (2.3%, 32/1,388 eyes), 26 patients (3.7%, 26/704).
- CNVM in one eye (0.05%, 1/,2127), one female patient (0.09%, 1/1,065).

Supplemental Tables 3–5 demonstrate macular abnormality frequencies (stratifying patients according to gender, age and lens status) and present corresponding statistical analysis. The results show no significant differences among the classifications of macular abnormalities and gender (Fig. 4a, CME: $P = 0.193$; VMT: $P = 0.176$; MH: $P = 0.383$), except for ERM (males: 55.7%; females: 46.3%; $P = 0.006$).

MH and VMT were not found in patients ≤ 15 years old. ERM ($P = 0.001$) and MH ($P = 0.008$) were significantly more prevalent in elder RP patients, and that prevalence increased with age (Fig. 4b, Supplemental Table 4). No differences were observed in CME ($P = 0.283$) and VMT ($P = 0.619$) distributions among age groups. Because parts of patients had undergone cataract surgery (pseudophakic and aphakic eyes), the authors compared macular abnormality distribution between lens status. ERM ($P < 0.001$) and VMT ($P = 0.003$) were significantly more frequent in pseudophakic and aphakic eyes than in unoperated eyes (clear lens and cataracts) (Fig. 4c, Supplemental Table 5). The researchers also analysed the relationship between macular abnormalities and BCVA (logMAR) for RP patients with clear lens, and poor BCVA seemed significantly associated with CME ($P = 0.002$) (Table 2).

Table 2
Linear regression between macular abnormalities and BCVA (logMAR) in RP patients with clear lens

Variable (eyes, no.)	*β*	*t*	*P* value	Lower 95%CI	Upper 95%CI
ERM (709)	0.020	0.406	0.685	-0.076	0.115
CME (255)	-0.201	-3.058	0.002*	-0.329	-0.072
MH (32)	0.194	0.842	0.400	-0.258	0.646
VMT (33)	0.167	0.756	0.450	-0.266	0.599

ERM epiretinal membrane, CME cystoid macular oedema, MH macular hole, VMT vitreomacular traction syndrome
(*)=Significant values

Discussion

To our knowledge, this is the first study to report on the prevalence of ocular abnormalities in a large cohort of Western Chinese RP patients and to also investigate the relationship between BCVA with macular abnormalities demonstrated by OCT. Results revealed that the most common ocular abnormalities were cataracts (43.1%) and macular abnormalities (59.7%). For macular abnormalities, CME was significantly associated with poorer visual acuity in RP patients with clear lens.

Macular abnormality was the most common ocular abnormality in RP patients, and it accounted for 59.7% of all checked cases and was distributed in our study as follows: ERM (51.1%), CME (18.4%), VMT (2.4%), MH (2.3%), and CNVM (0.05%). ERM have been reported to be the second most frequent macular abnormality in RP patients, with a prevalence rate of 0.6–35.4% (Table 3). However, the prevalence of ERM in our study was much higher (51.1%) than that recorded in previous studies [4, 14, 15], which may be due to the application of SD-OCT with higher resolution, different genetic backgrounds, and diagnostic methods. We noted the presence of ERM when even a subtle, hyper-reflective lesion adhered to the inner retinal surface, regardless of other abnormalities being present. Testa *et al* performed a retrospective study investigating the prevalence of macular abnormalities in Usher syndrome patients [12] and found its prevalence to be at 45.1%, and they designated the most frequent abnormalities as CME (20.4% eyes), followed by ERM (15.6%), VMT (5%), and MHs (2%). The mechanisms of ERM formation remains unclear. However, it may include (1) idiopathic preretinal glial cell proliferation, (2) inflammation revealed by elevated aqueous flare, and (3) chronic macular-vitreous traction [15–17]. Our results demonstrated that CME was the second most common macular abnormality, and this coincided with results from an Italian population for which Testa *et al* investigated macular abnormalities in 581 RP subjects [1] and found that the most frequent abnormalities was CME (20.4% eyes), followed by ERM (15.6%), VMT (5%), and MH (2%). CME varies between 5.5% and 49% in RP patients [4, 14]. The exact mechanism of CME in RP remains unclear; however, it may include (1) the breakdown of the blood-retinal barrier secondary to the degeneration of RPE and/or Müller cells, (2) anti-retinal antibodies, and (3) traction from ERM and VMT. There is no consensus on the relationship between CME and visual acuity in RP patients [15–16]. Sandberg *et al.* believed that retinal thinning and thickening appeared to be associated with lower visual acuity in RP patients [18]. Yoshida *et al.* demonstrated that a normal preoperative ellipsoid zone (EZ), also called the inner/outer segment junction (IS/OS), was significantly related to better BCVA after cataracts in RP patients [19]. Because cataracts and PSCs were prevalent in RP subjects and were negatively correlated with BCVA, we analyzed the relationship between macular abnormalities and BCVA (logMAR) only in eyes with clear lens. CME appeared to be significantly associated with poor BCVA in our study. The exact relationship between maculopathy and visual acuity requires greater attention in future studies. CNVM are rare, and until recently, no data has shown the prevalence of CNVMs in RP patients. For several years, this information could only be attained through case reports [9, 20, 21]. In our study, a CNVM was observed in only one eye from one female patient (prevalence: approximately 0.09%). It has been proposed that photoreceptor cell degeneration and choriocapillaris damage may lead to the formation of CNVM [20].

Table 3
Comparison of the prevalence of ocular abnormalities in RP patients with previous studies

First author	Country	Subjects/ Eyes(No.)	Macular abnormalities (Eyes / %)					Cataract (Eyes/%)	Glaucoma (Eyes/%)
			Total	CME	ERM	VMT	MH		
Hajali[6]	USA	124/248		115/46.4					
Testa[1]	Italy	581/1161	524/45.1	237/20.4	181/15.6	58/5.0	23/2.0		
Fujiwara[17]	Japan	117/206	73/35.4		73/35.4				
Liew[5]	UK	169/338		172/50.9	77/22.8				
Testa[12]	Italy	134/268	126/47.0	42/15.7	51/19.0	38/14.2	8/3.0		
Lee[22]	Korea	365/365						175/47.9	
Onakpoya OH[2]	Nigeria	96/192	70/36.5%					38/20	22/11.5
Our study	China	1065/2127	829/59.7	255/18.4	709/51.1	33/2.4	32/2.3	917/43.1	35/1.6

CME cystoid macular oedema, ERM epiretinal membrane, VMT vitreomacular traction syndrome, MH macular hole

Cataracts were the second most common ocular abnormality in our RP patients, and lens opacity developed at a relatively younger age than in the general population. The prevalence (43.1%) in our study was similar to the result of 47.9% reported by Lee *et al*. among Korean patients (Table 3) [22]. Posterior subcapsular cataracts (PSCs) are the most typical morphological abnormalities and occur in 63–83.9% of RP patients [19, 23, 24]. However, lens status was determined through medical records, and cataract type was unidentifiable in the study. Glaucoma is another ocular abnormality prevalent among RP subjects. There is some evidence to suggest similar genetic backgrounds for glaucoma and RP [13, 25]. Ko YC *et al*. reported a 3.64-fold greater odd of developing PACG in patients with RP than in the general population [26]. In our study, the prevalence of glaucoma was 2%, lower than the 11.5% reported by Onakpoya *et al* [2]. and the 7.5% reported in Eballe *et al*.[27], but similar to the prevalence in the general population (2–3%) [13]. The reason for the lower rate may be due to our larger sampled cohort and our study being retrospective study.

More than half of the RP patients in our study presented visual acuity deterioration at first clinical presentation, and the proportion of blindness and low vision defined by BCVA were 28.5% and 20.7%, respectively. We defined low vision or blindness according to central visual acuity and did not consider visual field defects and blindness. The low vision rates in the RP subjects were actually much higher than these results show.

This study had the advantage of a large sample size and assessed various ocular abnormality distributions and visual acuity simultaneously. However, it included several limitations. First, the study was retrospective, and other ocular abnormalities and details, such as corneal nebula, cataract and glaucoma types, and so on, remained unexplored. Secondly, some patients had no molecular diagnosis, and we could not sufficiently investigate ocular abnormalities in different genetic subtypes. Further studies including prospective investigations and more patients with genetic diagnoses, are needed to explore the relationship between the course of RP and BCVA or to clarify the relationship between the genetic phenotypes of RP and BCVA.

Conclusion

The results revealed that ocular abnormalities associated with RP are various and have high prevalence, especially cataracts and macular abnormalities. Additionally, severe visual impairment was prevalent at the first clinical presentation of RP subjects in Western China. For macular abnormalities, CME may have a negative effect on BCVA in RP patients with clear lens.

Abbreviations

RP: Retinitis pigmentosa; RPE: Retinal pigment epithelium; ERMs: Epiretinal membranes; CME: cystoid macular oedema; MHs: Macular holes; VMT: Vitreomacular traction syndrome; CNVMs: Choroid neovascularisation membranes; OCT: Optical coherence tomography; BCVA: Best corrected visual acuity; ffERG: full-field electroretinogram; ISCEV: International Society of Clinical Electrophysiology of Vision; AD: autosomic dominant; AR: autosomic recessive; PACG: primary angle-closure glaucoma; POAG: primary open-angle glaucoma.

Declarations

Availability of data and materials

Data are available on reasonable request. Data could be available from the corresponding author by reasonable inquire.

Ethics approval and consent to participate

This study was performed according to the Declaration of Helsinki and approved by the Ethics and Research Committee of Southwest Hospital, Army Medical University (KY2020096). Written consent from the patients was not necessary for this non-interventional retrospective chart-review study.

Consent for publication

Not applicable.

Competing Interests

The author declares no competing interests.

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Authors contributions

LT: data collection, interpretation and manuscript preparation, critical revision of the article; YL, ZL, XY, JR and CS: data collection; XM and SL: contributed equally to the study. Investigation design, manuscript preparation and critical revision of manuscript. All authors have read and approved the manuscript and are equally accountable for all aspect of this work.

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Figures

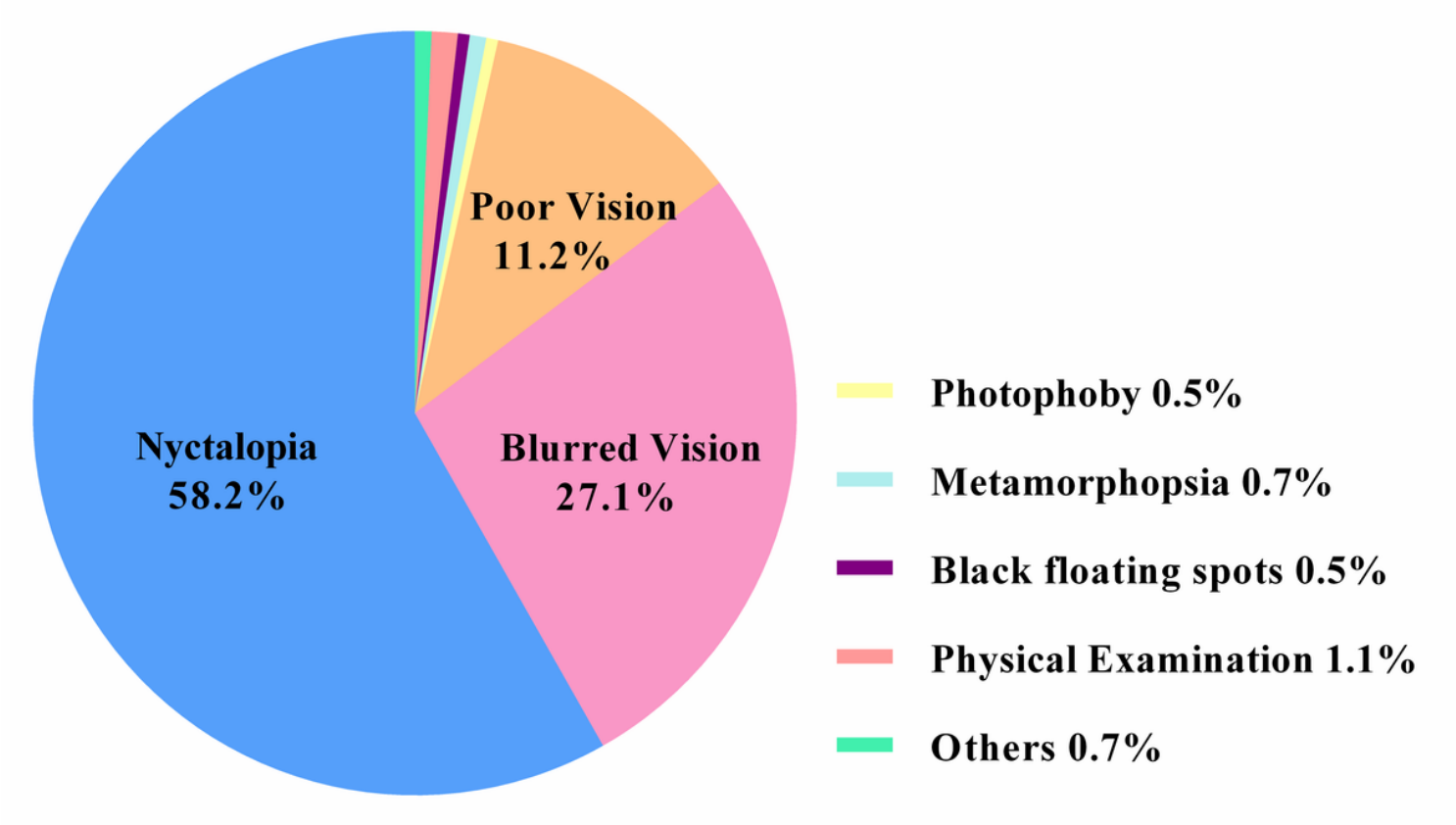

Figure 1

Distribution of chief complaints in the study cohort of patients with RP. The pie diagrams showed the sampled patients' complaint were distributed as follows: nyctalopia (58.2%), blurred vision (27.1%), poor vision since childhood (≤15 years old, 11.2%), physical examination (1.1%), metamorphopsia (0.7%), photophoby (0.5%), black floating spots (0.5%) and other unusual symptoms (0.7%, including pain, photopsia, narrow vision field and double vision).

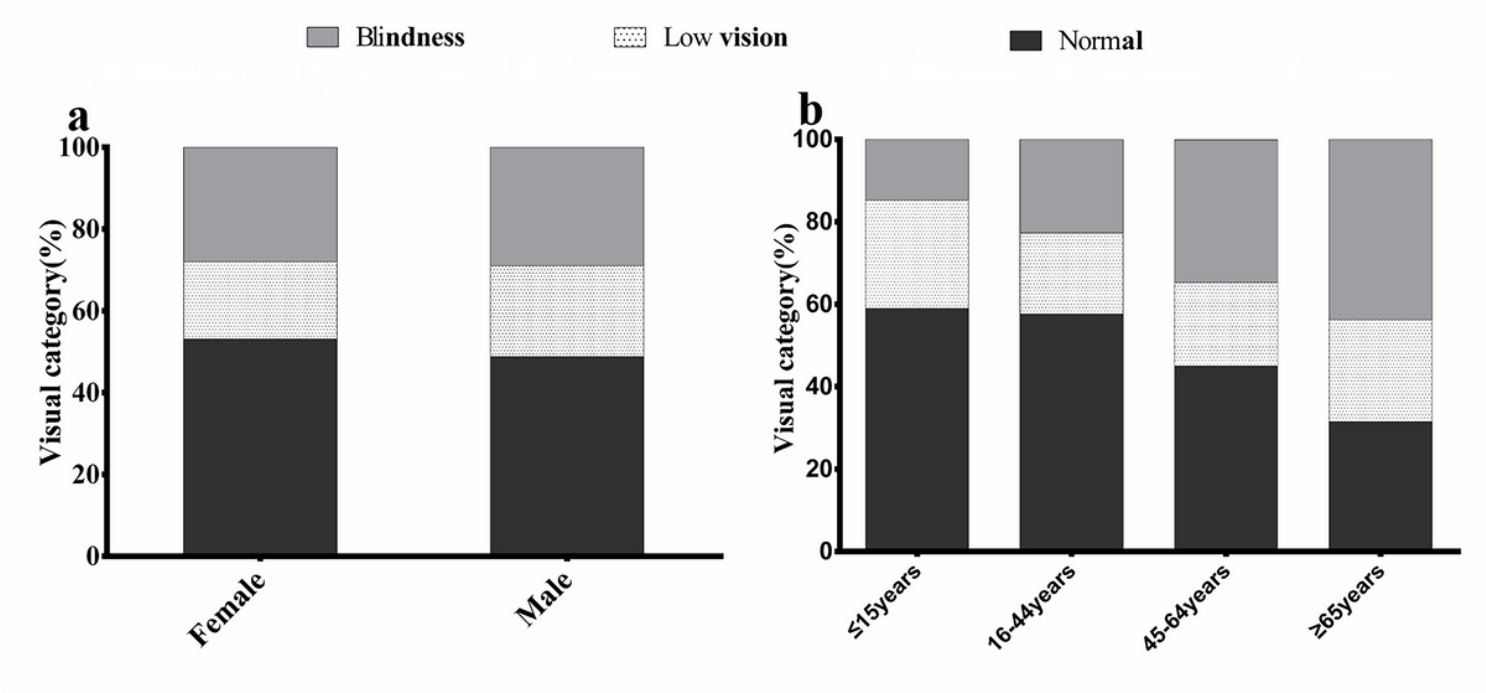

Figure 2

The best vision acuity (BCVA) in the study cohort of RP patients, stratified by gender and age. Bar graph demonstrated the distribution of BCVA in the sampled RP patients at first clinical presentation. a: more than half of the RP patients presented visual acuity deterioration at first clinical presentation and no significant difference was observed between gender. b: patients over the age of 44 showed a lower proportion of normal vision than patients under 44 at first presentation, and the proportion of blindness at first presentation in patients over 44 (45–64y: 34.6%; ≥65y: 43.8%) was higher than in patients under 44 (≤15y: 8.5%; 16–44y: 14.8%). The percentage of blindness significantly increased with age in the sampled RP patients (P=0.000).

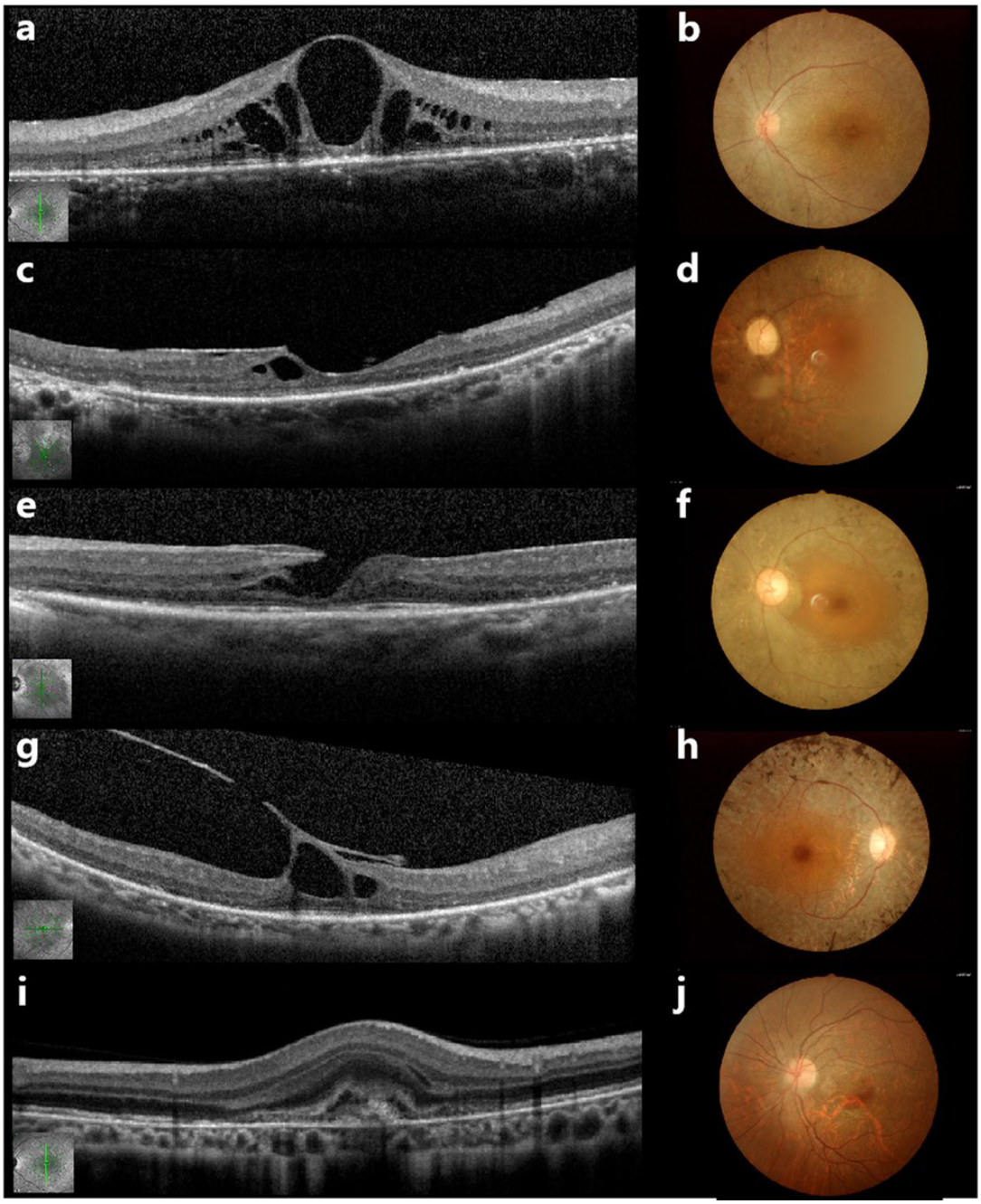

Figure 3

Representative optical coherence tomography (OCT) and corresponding fundus photography of RP patients with macular abnormalities. a: An OCT image with cystic-appearing spaces in the left eye. b: Fundus photograph of the left eye in picture a, showing bone spicule pigmentation in the mid-periphery and vessels attenuation. c: OCT scan showed a homogenous layer of moderately reflective material, present on the inner retinal layer. d: Fundus photography of the left eye in picture d, showed marked bone spicule pigmentation in the mid-periphery, waxy pallor of the optic disc and attenuated vessels. e: OCT scan with lamellar macular hole. f: Fundus photography of the picture e, revealed bone spicule pigmentation in the mid-periphery and vessels attenuation. g: OCT scan showed vitreomacular traction. h: Fundus photography of the right eye in picture g, showed marked bone spicule pigmentation in the mid-periphery, waxy pallor of the optic disc and attenuated vessels. i: OCT image showed disruption of the Bruch membrane/retinal pigment epithelium complex, accompanied by a hyper-reflective lesion connected with the subretinal pigment epithelium. j: Fundus photography of the left eye in picture i, showed hemorrhage located in the inferior-temporal macular area.

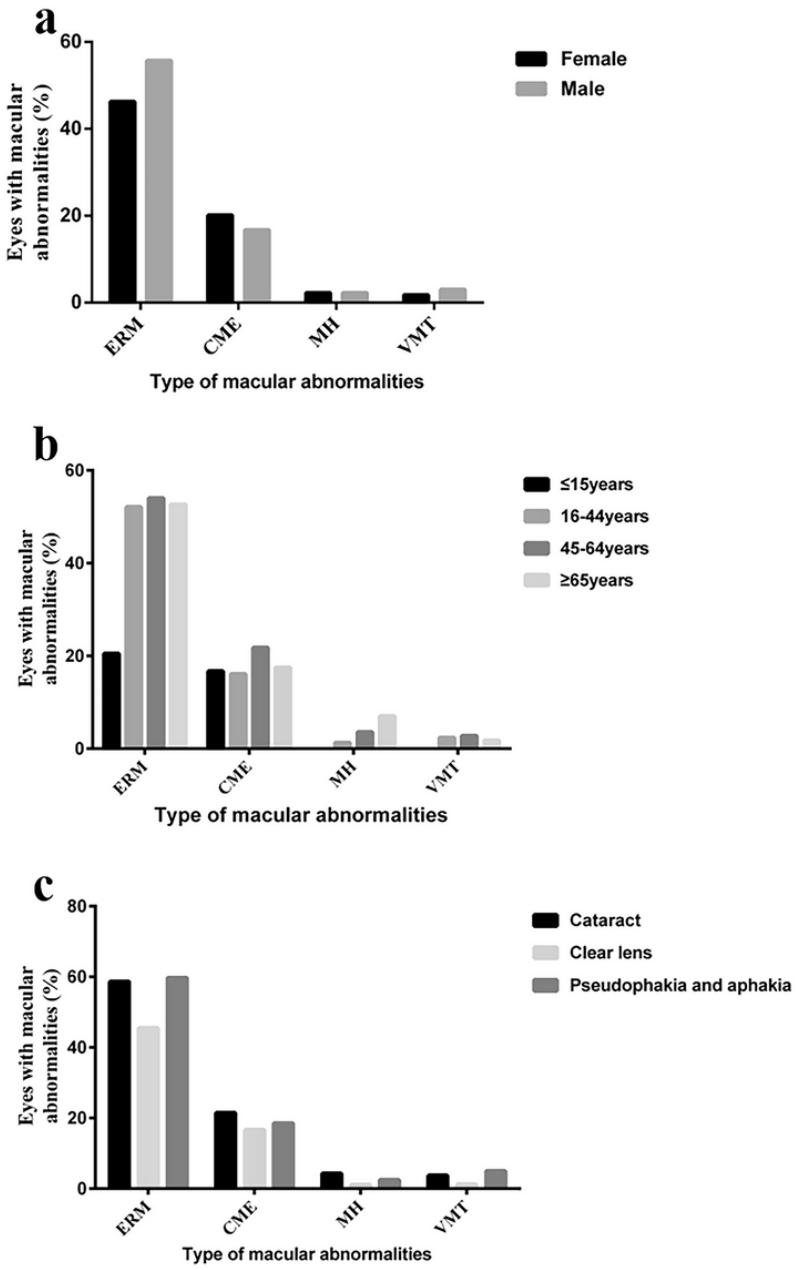

Figure 4

Classification of macular abnormalities in the study cohort of RP patients, stratified by (a) Gender; (b) Age; (c) Lens status. a: bar graph showed no significant differences among the classifications of macular abnormalities and gender (CME: P=0.193; VMT: P=0.176; MH: P=0.383), except for ERM (males: 55.7%; females: 46.3%; P=0.006). b: this bar graph revealed prevalence of ERM (P=0.001) and MH (P=0.008) were significantly increased with age, while no differences were observed in CME (P=0.283) and VMT (P=0.619) distributions among age groups. c: ERM (P<0.001) and VMT (P=0.003) were significantly more frequent in pseudophakic and aphakic eyes than in unoperated eyes (clear lens and cataracts). Abbreviations: ERM: epiretinal membrane; CME: cystoid macular edema; MH: macular hole; VMT: vitreomacular traction syndrome.

Supplementary Files

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