

Original Article

A preliminary study on the peripheral retinal refractive status and the development of myopia in RP patients with myopia

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Abstract: Purpose: To study the relationship between peripheral retinal refraction and the development of myopia in retinitis pigmentosa patients with myopia. Methods: A total of 47 subjects (89 eyes) of RP patients with different degrees of myopia underwent peripheral refraction and visual field measurement. The visual field test results were grouped according to the AGIS scoring system, and classified into mild visual field defect group (24 eyes), moderate visual field defect group (41 eyes), and severe group (24 eyes). According to shadow moving, neutralization in the open view field condition, relative peripheral refractive errors (RPREs) were measured in the center and at the stare angles of 10°, 20° and 30° in the nasal and temporal fields, respectively. A complete set of data for each eye included one central diopter and six peripheral diopeters. The RPREs of the nasal and temporal fields at 10°, 20° and 30° were determined by subtracting each peripheral diopter from central diopter, $RPRE = M_a - M_o$, a is central diopter, o is peripheral diopter. Results: The relative refractive errors of temporal fields between mild and moderate group were significantly different at temporal field eccentricities of 20° and 30° (Independent-samples t-tests, $P = 0.01, 0.004$). The peripheral hyperopia state was positively correlated with the degree of visual field damage. In mild to moderate group, there was also a positive correlation between peripheral hyperopia state and visual field damage degree ($P = 0.012, <0.05$). Conclusion: For RP patients with myopia, there was a positive correlation between peripheral hyperopia state and retinal damage when the damage was mild. For the severe retinal damaged group, the central diopter did not correlate with the peripheral retinal damage.

Keywords: Retinitis pigmentosa (RP), myopia, peripheral refraction, visual field

Introduction

With the application of electronic products, refractive errors have become the most common eye diseases. However, the pathogenesis of myopia is unclear [1]. Genetic studies demonstrate that, the genomic loci of high myopia causative genes are proximal to those of RP. Clinically, genetic RP is usually combined with high myopia [2]. A large number of animal and clinical studies demonstrate that peripheral refractive state have a substantial impact on emmetropization, resulting in the onset and progression of myopia [3-10]. Compared to

visual signals from the central retina [4], the peripheral refractive state has a significant impact on emmetropization at the fovea [5]. Retinitis pigmentosa (RP) is a group of retinal diseases caused by gene mutations that result in retinal atrophy. It has been shown that RP patients tend to have high myopic errors and high astigmatic errors [11]. The retinal degeneration process of RP patients starts from the peripheral retina to the macula, which causes changes of peripheral vision and peripheral refraction state in the beginning, and expands to the central retina gradually, similar to the development of myopia. Whether the change of

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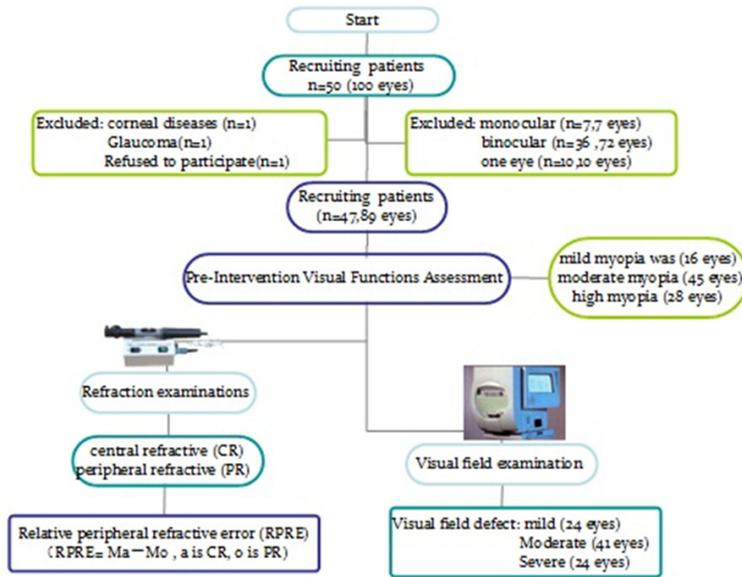


Figure 1. Outline of study procedures.

peripheral refraction state of sporadic RP patients leads to myopia is unclear and warrants detailed characterization. Our study retrospectively collected and analyzed data from sporadic RP patients associated with myopia, and investigated the relationship between the peripheral retinal refraction state and the development of myopia.

Materials and methods

Subjects

A total of 47 RP patients (89 eyes) with different degrees of myopia who visited the Eye Center of the First Affiliated Hospital of University of South China from March, 2014 to May, 2016 were recruited in the study. Patients with other known ocular diseases such as cataract, glaucoma, corneal diseases or blind and systemic disease or previous surgery history were excluded. Outline of study procedures shown in **Figure 1**. Among these patients, there were 36 patients (76.6%) with binocular RP and 7 patients (7.8%) with monocular RP. Patients ranged in age from 30 years old to 40 years old, with a mean age of 33.94 ± 2.16 years; 61.7% of the patients were men ($n = 29$) and 38.2% were women ($n = 18$). Moreover, there were 58.5% patients with uncorrected visual acuity (UCVA) less than 0.1 and 2.2% greater than or equal to 0.3. The percentage of high myopia (≥ -6.00 D) was 31.4%, moderate myopia (-3.00 D \sim -6.00

D) was 50.6% and mild myopia was 17.9% (≤ -3.00 D).

Refraction examinations

All patients were examined with YZ24 ribbon shape lighting skiascope (Suzhou sixty-six) and Humphrey720i perimeter (Germany Zeiss). Basic refraction examinations included subjective refraction and auto-refraction. The visual activity, refraction and best-corrected visual acuity (BCVA) were recorded. Peripheral refraction state was measured by streak retinoscopy, a common method to measure the refractive errors. It is based on shadow moving neutralization lens selection [12]. Measurements with the subjects turning their eyes and fixating on the object in the nasal and temporal fields at 10° , 20° , and 30° angles were recorded sequentially, under the condition of an open visual field. Each subject was instructed to stay steady to avoid any head movement, open the pupil with diameter greater than 4 mm, and stare at a cross Maltese object at 2.5 m distance (the size of the cross Maltese object was $25 \text{ cm} \times 20 \text{ cm}$, contrast was greater than 80%) at 10° intervals from nasal 30° to temporal 30° visual fields. According to the neutral condition of shadow moving, peripheral refractive errors were measured at the visual angle of 10° , 20° , and 30° , respectively.

Each measurement was calculated as the arithmetic mean of three replicates. For each visual angle, a complete set of data for each eye included one CR and six PR. The relative peripheral refractive error (RPRE) was determined by subtracting each peripheral refractive (PR) with central refractive (CR) measurement ($\text{RPRE} = M_a - M_o$, a is CR, o is PR) [13].

Visual field examination

Visual field examination

Visual field tests were conducted with a Humphrey720i perimeter using the central 30-2 threshold test with SITA standard threshold strategy. Subjects stayed in a darkroom for 5~10 min before examination to ensure the pupil diameter greater than 4 mm. Tests were

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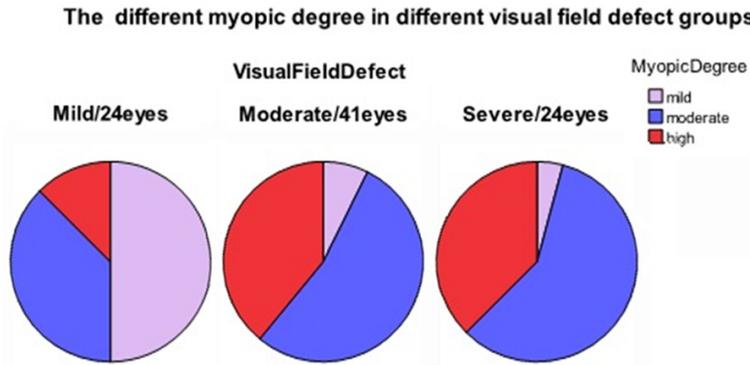


Figure 2. The ratio of different myopic degree in mild, moderate and severe visual field defect group visual field defect groups.

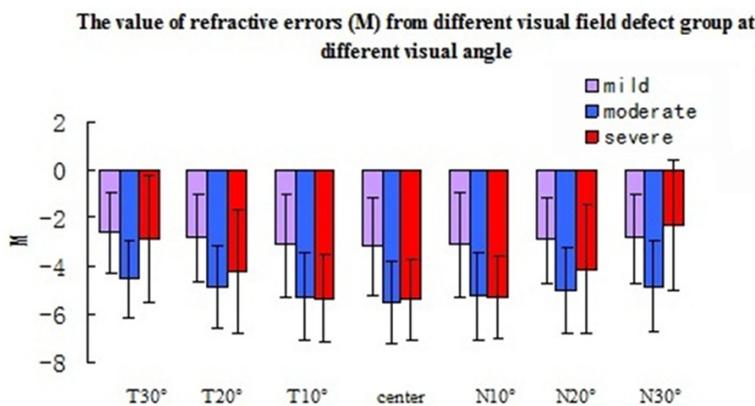


Figure 3. The value of refractive errors (M) from mild, moderate and severe visual field defect group at temporal field eccentricities of 10° (T10°), 20° (T20°) and 30° (T30°), at the 10° (N10°), 20° (N20°), and 30° (N30°) nasal field eccentricities.

adjusted with appropriate correction lens based on the patient's refractive status and age. There was a 30 minute break between examinations. All patients were examined three or more times. Excluding two test sites above and below the physiologic blind spot, there were a total of 74 test sites for analysis. The visual field test results were grouped according to the Advanced Glaucoma Treatment Study (AGIS) scoring system [14]. AGIS system was scored by the defect depth and quantity of normal threshold in the overall deviation figure from the nasal visual field, the upper half visual-field and the bottom half visual-field visual field tests. The scores ranged from 0 (no defect) to 20 (worst). The highest score was 20 that included two points from nasal and 9 points from each half visual-field. AGIS were classified into five stages: first stage: 0 points, normal visual field; second stage: 1-5 points, mild visual field defect; third stage: 6-11, moderate visu-

al field defect; 4th stage: 12-17, severe visual field defect; 5th stage: 18-20 points: absolute visual field defect. According to inclusion and exclusion criteria, 24 eyes (26.97%) were mild visual field defect, 41 eyes (46.06%) were moderate visual field defect, and 24 eyes (26.97%) were severe visual field defect.

Statistical analysis

Data were analyzed with the statistical software PASW Statistics 18.0. Independent samples t-tests were used to compare the central refraction, AGIS scores, and the RPRES values between mild visual field defect group and moderate group, and between moderate group and severe visual field defect group. The peripheral refractive state between the nasal fields and temporal fields from two groups were analyzed by Paired t-tests. The difference was statistically significant when *P* values were less than 0.05.

Results

As illustrated in **Figure 2**, in the mild visual field defect group, mild myopia accounted for about 50%, moderate myopia was 37.5%, and high myopia was 12.5%. In the moderate group, mild myopia was 7.3%, moderate myopia was 53.6%, and high myopia was 39%. In severe group, mild myopia accounted for 4.2%, moderate myopia and high myopia was 58.3% and 37.5%, respectively. In the mild visual field defect group, mild myopic was the major form. And moderate to severe visual field defect group mainly showed moderate myopia.

As shown in **Figures 3** and **4** the relative refractive errors of temporal fields between mild and moderate group were significantly different at temporal field eccentricities of 20° and 30° (Independent-samples t-tests, *P*-value = 0.01, 0.004). The peripheral hyperopia sta-

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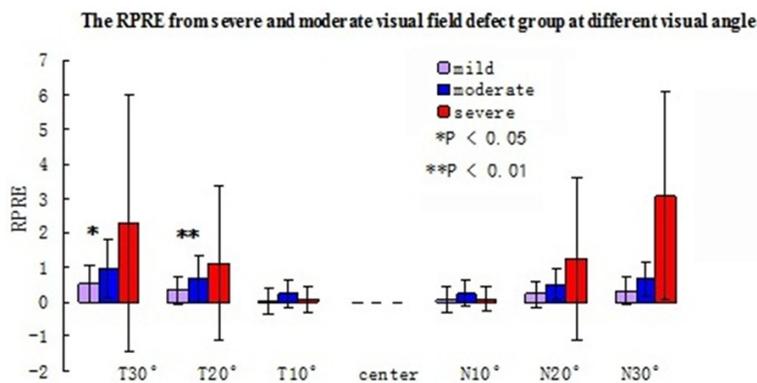


Figure 4. The RPRE from mild, moderate and severe visual field defect group at temporal field eccentricities of 10° (T10°), 20° (T20°) and 30° (T30°), at the 10° (N10°), 20° (N20°), and 30° (N30°) nasal field eccentricities.

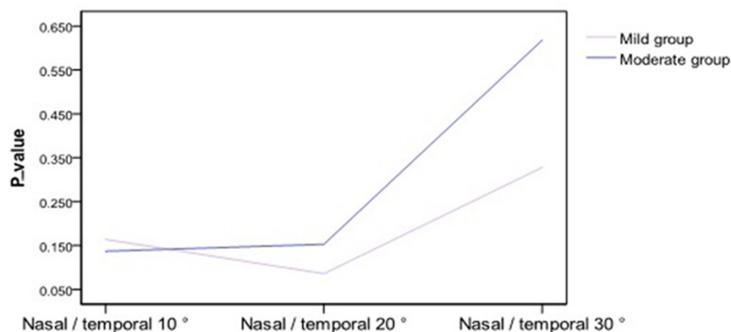


Figure 5. Paired t-tests results about RPRE from nasal and temporal retinal fields between each two visual field defect groups.

te was positively correlated with the degree of visual field damage. In mild to moderate group, there was also a positive correlation between peripheral hyperopia state and visual field damage degree (P -value = 0.012, <0.05). The peripheral state was hyperopic at the 10° temporal field eccentricities, but there was no significant correlation between the peripheral retinal degeneration and the peripheral hyperopia state near the macula (Independent-samples t-tests, P -value = 0.125, >0.05). In addition, RP patients showed a peripheral hyperopia state at the 10°, 20°, and 30° nasal field eccentricities, but no significant differences were observed in the degree of pigmentary degeneration (Independent-samples t-tests, P -value = 0.190, 0.217, 0.101, >0.05).

Figures 3 and **4** indicated that RP patients in the moderate to severe group showed relative peripheral hyperopic errors. However, about half of RP patients preserved only a narrowing

central visual acuity in the severe group, and the peripheral refraction could not be measured by retinoscopy at nasal field eccentricities of 20° and 30°, and we were not able to evaluate the RPRE effectively. Meanwhile, there was no significantly correlation of RPRE between nasal field eccentricities of 20° and 30° (P -value = 0.930, 0.787, >0.05). In AGIS scores, there was no statistical significance in the central refractive state in moderate and severe group, suggesting that for severe pigmentary degeneration patients, the central refractive state is not associated with the peripheral retinal degeneration.

As shown in **Figure 5**, there was no significant different of the RPRE in the nasal (P -value = 0.328, 0.086, 0.164, >0.05) and temporal (P -value = 0.618, 0.153, 0.037, >0.05) fields at 10°, 20°, and 30°. At the temporal field, there was a correlation between the degree of pigmentary degeneration and the development of myopia. The results of the peripheral refraction degree also showed asymmetry between nasal and temporal retina, which is consistent with the conclusions from Millodot.

Discussion

Retinitis pigmentosa and myopia are common eye diseases. Myopia could result in peripheral retinal degenerations that may lead to retinal holes or retinal detachment, causing constricted visual fields and eventually visual loss [15]. Similarly, retinal degeneration in the majority of RP patients starts from the peripheral retina, leading to tunnel vision and blindness gradually. RP patients are often myopic and have cylindrical refractive errors. However, the exact pathogenesis and progresses are different. Paula (8) and Bokd' [16] showed that most sporadic RP patients with high incidence of myopia were mild to moderate myopia. Moreover, high myopia can be caused by genetic factors [17].

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Table 1. Peripheral retinal refractive status in RP patients with myopia

Authors	Year	Subjects	Refractive error	Alteration
Present study	2016	RP patients with myopia	Peripheral refractive error	Peripheral hyperopia state
Radhakrishnan	2013	Teenager with myopia	Peripheral refraction	Relative peripheral hyperopia is associated with myopia
Mutti	2011	Children with myopia	Peripheral refractive error	Relative peripheral hyperopia
Harman	2010	REVIEW	Peripheral refraction	Relative peripheral hyperopia produces central axial myopia
Taberner	2009	Myopia	Peripheral refractive error	Relative peripheral hyperopia
Morichini	2007	RP patients	Refractive error	79% of subjects were myopia
Forte	1996	RP patients	Refractive error	65% of subjects were myopia
Sieving	1978	RP patients	Refractive error	75% of subjects were myopia

Studies have indicated that high myopia might be polygenic inheritance [16]. The genomic loci of high myopia causative genes are proximal to those of RP. As a consequence, genetic RP is usually combined with high myopia. However, according to the clinical manifestation, high myopia is different from sporadic retinitis pigmentosa. Sporadic RP patients lose night vision first, followed by the loss of peripheral vision, which causes tunnel vision. Eventually the vision of the macula, a central region of the retina, is lost. It is well known that rod photoreceptor cells are active in dim-light environment and allow for night vision. Cone photoreceptor cells are responsible for sensing different light wavelengths and allow for daytime and color vision [18]. As mentioned above, the progressive atrophy of the rod photoreceptor cells leads to a secondary death of the cone cells. On the contrary, most high myopia starts with poor light vision due to the degeneration of peripheral retina, followed by poor night vision. Furthermore, ocular fundus changes are different. The main retinal lesions of sporadic RP patients are that bone spicule-shaped pigment deposits in the retina along with RPE atrophy. As a result, the visual impairment or the ocular fundus changes in RP and high myopia are distinct from each other. In order to exclude the hereditary factor of RP patients, our study collected and analyzed data from sporadic RP patients to investigate the relation between myopic errors and non-hereditary RP patients.

Over the past decade, as shown in **Table 1**, there are large amount of experiments confirming that relative hyperopia in the periphery could influence the development of myopia. Through animal studies, Wiesel [19] and Smith [3] claimed that hyperopia in the periphery caused an elongation of the eye globe, while myopia in the periphery could prevent this

progress. In contrast, Earl [8] discovered that unrestricted central vision was not sufficient to ensure normal refractive development, and the fovea was not essential for emmetropizing responses and ametropias production. However, the peripheral retina is essential for this process. Mutti's [10] study suggested that the optical state in the periphery retina was closely associated with the development of axial myopia. The main pathological changes of myopia are comus and leopard fundus. In addition to the pathologic changes of posterior pole fundus, the peripheral retina is often the pathologic site as well. In myopia, the peripheral retinal lesions are mainly diffusive choroidal thinning, solitary choroidal lesion and cystoid degeneration of retina. According to the statistic analysis of the axial length and the peripheral retinal lesions from 513 consecutive patients, Pierro [20] confirmed that the percentages of eyes with lesions in each axial length varied. It has been reported that eyes of greater axial length have a higher incidence of peripheral retinal lesions. In other words, there is a positive correlation between myopic errors and peripheral retinal degenerations. However, all findings mentioned above need more long-term trials or a larger number of samples. Yet, the typical pathological changes of sporadic RP patients are retina degeneration. The retina degeneration starts from the peripheral retina to the macula in general. At the same time, bone spicule-shaped pigment deposits accumulate at the peripheral retina. This manifests as the loss of peripheral vision at the beginning, followed by tunnel vision and then total blindness [21]. Thus, visual field defects in the peripheral retina from RP patients cause hyperopia state in the periphery. We collected a large amount of data from RP patients with visual field defects, to investigate the relation between refraction hyperopic state and the development

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of myopia. Clinically, RP patients can be diagnosed with the clinical presentations of night blindness, pigmentary degeneration, constricted visual fields, abnormal ERG or specific molecular genetic defect. Generally, the changes of constricted visual fields could be regarded as indicators of the disease severity. Therefore, this experiment regarded visual fields examination as an assessment to evaluate the RP condition. And based on the degree of visual field damage, we explored the relationship between the peripheral retinal hyperopia state and the development of myopia.

In this investigation, peripheral refractive errors were measured by retinoscopy. In recent years, retinoscopy method is often applied to examine the peripheral refractive errors of rhesus monkeys. Hung [12] measured peripheral refractive errors of anesthetized infant rhesus monkeys by retinoscopy. And the peripheral refractive errors (RPE) were measured at the 15°, 30°, and 45° field eccentricities in the nasal, temporal and the central field. They also found that, in the longitudinal infants group, the relative peripheral refractive errors (RPRE) of the relative peripheral myopia underwent emmetropization in nature and increased as vision-dependent growth. Based on that, Huang [22] used retinoscopy to investigate the effects of form deprivation on refractive development in infant rhesus monkeys. It is reported that, like humans with myopia, monkeys with form-deprivation myopia exhibit relative peripheral hyperopia, indicating that abnormal visual experience can alter the shape of the posterior globe and the pattern of relative peripheral refractive errors in infant primates. These results showed that retinoscopy could be used to examine the spherical-equivalent refractive errors in the periphery, the regular astigmatism, the refractive status, and ocular axial dimensions. Although this process uses subjective shadow moving as the readout, and examination is discontinuous, slow and time-consuming, measurements in the study were obtained at a 1 m working distance, and the visual angle was set for 10°, 20°, and 30°. It is reasonable to use the retinoscopy method to measure the peripheral refractive errors. Various methods have been used to define the peripheral refractive errors of human eyes, including subjective refraction, retinoscopy, autorefraction, wavefront technology, double-pass technique, and

so forth. Previous studies have validated these methods. Among these, retinoscopy is the most accessible method for current study.

Our results showed that among different visual field damage extent, RP population with mild to moderate myopia was the majority, and the myopic degree increased with the increase of visual field damage degree (the degree of pigmentary degeneration). In addition, statistical analysis showed that RP patients exhibited relative peripheral hyperopia at temporal field eccentricities of 20 and 30 degrees. Furthermore, there were significant differences in peripheral hyperopia degree between low and moderate group, and the peripheral hyperopia state was positively associated with the visual field damage degree. In the moderate group, peripheral hyperopia state was similar to the visual field damage degree. The peripheral state exhibited hyperopic at the 10° temporal field eccentricities. However, there was no significant correlation between the peripheral retinal degeneration and the peripheral hyperopia state near the macula. In addition, retinitis pigmentosa patients showed a peripheral hyperopia state at the 10°, 20°, and 30° nasal field eccentricities, and no significant differences were observed in the degree of pigmentary degeneration. The above results were similar to the Smith [23] and Atchison [24] that there was a positive correlation between the peripheral hyperopia degree and myopic degree. At the temporal field, there was a correlation between the degree of pigmentary degeneration and the myopia degree [25]. However, that was not exactly symmetrical at the nasal field. It is consistent with the conclusions from Millodot that the results of the peripheral refraction degree were asymmetric between nasal and temporal retina [26].

In summary, in this study, we showed that the myopic degree in the RP patients was positively correlated with the peripheral hyperopia state. Genetic studies has been shown that RP patients tend to have high myopic errors and high astigmatic errors. The retinal degeneration process of RP patients starts from the peripheral retina to the macula, which causes changes of peripheral vision and peripheral refraction state in the beginning, and expands to the central retina gradually, similar to the development of myopia. In the present study,

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Our findings suggest that there were significant differences in peripheral hyperopia degree between low and moderate group, and the peripheral hyperopia state was positively associated with the visual field damage degree, which may help us to understand the pathophysiology between RP patients and the development of myopia, and could provide a research platform for clinical treatment of myopia. It has some drawbacks in this research. Because the peripheral refractive errors of severe pigmentary degeneration were measured by retinoscopy, a certain number of RP patients only remained tunnel vision so that we were unable to examine the peripheral refractive state. To some extent, once the peripheral retinal lesions affect vision, the central refractive state is not associated with the peripheral retinal degeneration. Considering the limited number of patients in this study, common and stable clinical examination were applied to the current research. Our results need to be validated on a larger number of subjects.

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Disclosure of conflict of interest

None.

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