Optical Coherence Tomographic Analysis of Retina in Retinitis Pigmentosa Patients

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Key Words

Retinitis pigmentosa · Optical coherence tomography · Retinal structure · Visual function

Abstract

Retinitis pigmentosa (RP) is a progressive inherited retinal disease characterized by nyctalopia, visual field constriction, and reduced full-field electroretinograms. The progressive loss of photoreceptors leads to vision loss at the end stage of RP. The prevalence of RP is approximately 1/4,000. Since it is one of the major causes of visual impairment worldwide, morphological and functional assessments are useful for estimating the retinal structure and function in RP. Optical coherence tomography (OCT) is a well-established method of examining retinal structure in situ, and the obtained images by OCT help to analyze morphological abnormalities. Changes revealed by OCT have provided insights into the pathology of RP as well as for predicting the prognosis of RP. In this review, we present the typical morphological changes in RP and their relationships with visual function in eyes with RP.

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Introduction

Retinitis pigmentosa (RP) is an inherited retinal disease characterized by progressive loss of the photoreceptors and eventual central visual loss [1, 2]. The clinical diagnosis of RP is based on the presence of nyctalopia, visual field constriction, bone spicule pigmentation, and a reduction in electroretinograms (ERGs). In RP patients, retinal degeneration begins with a loss of the rod photoreceptors which leads to nyctalopia. With the advancement of the disease, the cone photoreceptors become involved, leading to severe vision loss at the end stage of RP. Previous studies of RP verified that the earliest histopathological changes were the shortening of the photoreceptor outer segments [3–5]. These changes begin in the periphery and progress toward the central retina; therefore, morphological and functional assessments of the retinal changes can be useful in estimating the disease advancement and the remaining retinal function of RP patients.

In this review, we aimed to summarize the typical morphological changes by optical coherence tomography (OCT) and their relationships with visual function in the eyes with RP. A systematic search of PubMed and Web of Science was performed up to September 10, 2015. The following terms were used for the search: ‘retinitis pigmen-

Table 1. List of OCT layers agreed by the experts in retinal imaging

Layer No.	OCT description	Consensus nomenclature
1	Hyperreflective	Posterior cortical vitreous
2	Hyporeflective	Preretinal space
3	Hyperreflective	Nerve fiber layer
4	Hyporeflective	Ganglion cell layer
5	Hyperreflective	IPL
6	Hyporeflective	INL
7	Hyperreflective	OPL
8	Hyporeflective band	Inner half: Henle's nerve fiber layer; outer half: ONL
9	Hyperreflective	ELM
10	Hyporeflective	Myoid zone of the photoreceptors
11	Hyperreflective	EZ of the photoreceptors
12	Hyporeflective	Outer segments of the photoreceptors
13	Hyperreflective	Cone interdigitation with RPE
14	Hyperreflective band	RPE/Bruch's membrane complex
15	Thin layer of moderate reflectivity in inner choroid	Choriocapillaris
16	Thick layer of round or oval-shaped hyperreflective profiles with hyporeflective cores in mid-choroid	Sattler's layer
17	Thick layer of oval-shaped hyperreflective profiles with hyporeflective cores in outer choroid	Haller's layer
18	Zone at the outer choroid with a marked change in texture in which large circular or ovoid profiles abut a homogenous region of variable reflectivity	Choroidal-scleral juncture

tosa' or 'RP' in combination with 'optical coherence tomography' or 'OCT'. In addition, in order to include as many related studies as possible, references of the included studies were also examined.

Optical Coherence Tomography

OCT was introduced to ophthalmology more than 20 years ago, and it has become the standard for assessing anatomical abnormalities in situ via high-resolution tomographic images. Spectral-domain OCT (SD-OCT) has enabled the high-resolution visualization of retinal morphology, showing clearly distinguishable hyperreflective layers: choroidal vessels, Bruch's membrane, retinal pigment epithelium (RPE), interdigitation zone (IZ), ellipsoid zone (EZ), external limiting membrane (ELM), outer plexiform layer (OPL), inner plexiform layer (IPL), and retinal nerve fiber layer (RNFL) [6–8]. As a noninvasive retinal imaging technology, SD-OCT has significantly increased our understanding of the structural changes in retinal disease [4, 9], and the well-established method has helped to evaluate the morphological changes related to retinal function in RP patients [10, 11]. In this review, we

summarized the recent advances in OCT imaging and the relationships with retinal function in RP eyes.

In human eyes, rods account for 95% of the photoreceptors, which are absent at the fovea but peak in the zone about 20° outside of the fovea. Cones comprise 5% of the photoreceptors, which are distributed throughout the fovea, and the density decreases in the perifoveal area [12, 13]. Since the earliest histopathological changes are the shortening of the photoreceptor segments, the integrity of the photoreceptor lines has been widely studied. The hyperreflective region (the second outer retinal hyperreflective band) between the inner and outer photoreceptor segments was known as IS/OS line. However, the connecting cilium between the inner and outer photoreceptor segments is a loose collection of microtubules, which does not correspond to the hyperreflective region [14]. The hyperreflective region was confirmed to be the ellipsoid portion of the inner segments, which was packed with mitochondria [15]. Another hyperreflective region (the third outer retinal hyperreflective band) known as the cone outer segment tips (COST) line was represented to be the interdigitation of the apical processes of the RPE with the cone outer segments [14]. So experts in retinal imaging have defined a consensus for OCT imaging ter-

Fig. 1. Nomenclature for normal anatomic landmarks seen on SD-OCT images proposed and adopted by the International Nomenclature for Optical Coherence Tomography Panel. Healthy retina imaged using Heidelberg Spectralis. The picture was taken from Staurengi et al. [14].

minology. The second and third outer retinal hyperreflective bands were termed the ‘ellipsoid zone’ and the ‘interdigitation zone’. The 18 zones progressing from the innermost to the outermost layers of the retina are listed in numerical order in table 1, and the detailed structural layers are shown in the pictures captured by OCT (fig. 1, 2) [14]. So the three highly reflective lines are the ELM, EZ, and IZ from the inner to the outer retina, which are commonly used to evaluate the integrity of the photoreceptor segments [16].

Photoreceptor Segments

In RP, the photoreceptor lines are shortened with the degeneration of photoreceptors. Rod photoreceptor death is followed by degeneration of the RPE cells and eventually leads to the loss of the cones [17]. With regard to the photoreceptor segments, the IZ band has been

found to be absent in the region of EZ band abnormalities, which suggests that the EZ band was longer than the IZ band [18]. A clinical study found that fundus autofluorescence (FAF) imaging indicated disrupted lipofuscin in the RPE as well as abnormalities in the photoreceptor layer [19]. FAF imaging demonstrated that the residual macular area was presented as a normal autofluorescent area surrounded by a hyperautofluorescent ring. In this study, the intact EZ band was found to correspond with the normal autofluorescent area, and the ELM was found in a larger area corresponding with the hyperautofluorescent FAF ring, manifesting that ELM was longer than the EZ band. With regard to shortening, the lengths of the residual ELM, EZ, and IZ bands were measured on SD-OCT images (fig. 3) [20]. The results showed that the length was longest in the ELM, followed by the EZ and IZ bands, suggesting that the three lines become disorganized first at the IZ, followed by the EZ, and finally at the ELM. The clinical findings were consis-

Fig. 2. Nomenclature for normal anatomic landmarks seen on SD-OCT images proposed and adopted by the International Nomenclature for Optical Coherence Tomography Panel. Healthy retina imaged using Zeiss Cirrus. The picture was taken from Staurengi et al. [14].

Fig. 3. SD-OCT image of a vertical scan. In addition to the photoreceptor IS/OS junction line (EZ band), the ELM and COST lines (IZ band) are clearly seen on the SD-OCT image. Red arrows (color in online version only) indicate end points of the COST line (IZ band), blue arrows indicate end points of the IS/OS line (EZ band), and yellow arrows indicate end points of the ELM line. Note that the line length was the longest in the ELM, followed by the IS/OS (EZ band) and COST (IZ band). The picture was taken from Tamaki and Matsuo [20].

tent with the histopathological changes and confirmed that the earliest abnormalities in RP were the photoreceptor outer segments [3, 4].

In addition, the abnormality in the connecting cilia could lead to decreased protein transport from the inner to the outer photoreceptor [16]. So the earliest abnormality in the photoreceptor layers was the band displaying the shortest IZ band in OCT images. Besides, the restored orders of the photoreceptor layers have been studied in macular hole surgery, with the restoration occurring first at the ELM and followed by the EZ and IZ bands [21]. The results suggested that the ELM restoration preceded EZ and IZ repair. From a pathological perspective, the ELM consists of photoreceptor and Müller cells, so the ELM influenced by Müller cells restored earlier. As a result, there exists an order of photoreceptor impairment or restoration, and the changes can be shown in the OCT images.

In RP, thinning of the photoreceptor outer segments was followed by a decrease in outer nuclear layer (ONL)

thickness [5, 22]. Based on the SD-OCT line scans, the ONL thinning was found most in patients with more advanced disease and patients of older age [23].

With the degeneration of the photoreceptors, retinal structural changes determined by OCT have been found to correlate with the visual functions in RP. Clinical studies implied a correspondence between a loss of light sensitivity and a decrease in receptor layer thickness on OCT scans [8, 24]. The results showed that normal retinal thickness was observed with normal visual thresholds, and reduced retinal thickness was accompanied by elevated rod and cone thresholds. Recent studies showed that visual field decreased linearly with the thinning of photoreceptor outer segment thickness [6, 25], and the length of the EZ line corresponded with a sharp drop in visual field sensitivity [8, 12]. The visual field extent was lost in RP patients without detectable photoreceptor outer segments [25]. The studies implied that the absent border of the EZ provided a structural marker for the edge of the visual field. So the length of the photoreceptor segments provides a useful OCT parameter to assess the extent of the visual field.

The photoreceptor area that reflects the total preserved photoreceptor amount is expected to be a better parameter for assessing macular function. The preserved photoreceptor area was calculated through horizontal and vertical EZ lengths or derived from advanced en face images [26]. The results showed that the photoreceptor area was significantly related to the visual field area, but had a worse correlation with the visual field area than the EZ line [26]. Apart from the photoreceptor segments, good agreement between the thickness of the ONL and the extent of the local field has been obtained [24]. Therefore, a combined assessment of the photoreceptor and visual field is useful for estimating the visual functions in RP patients.

What is more, the condition of the EZ line is an objective OCT index for assessing visual acuity in RP patients [27]. A number of clinical studies have reported correlations between the EZ line and BCVA [10, 28, 29]. Based on the EZ length, the RP patients were separated into three groups, and the BCVA was found to be significantly better with a longer EZ line [29]. The results suggested that the presence of the EZ line indicated preserved photoreceptor function in RP. Similar conclusions have been confirmed in other diseases as well, such as macular hole [30, 31] and central serous chorioretinopathy [32].

In RP patients, multifocal ERG (mfERG) is a commonly used method for evaluating macular function, so the correlation between the EZ line and mfERG has been

studied in RP patients [27]. While the mfERG amplitude was preserved within the area of 0–6°, the photoreceptor segments were relatively intact [33]. The patients with longer EZ lines had significantly larger mfERG amplitudes than the patients with shorter or absent EZ lines [27]. However, the correlation between the EZ line and the mfERG amplitude was weak in this study. One reason was that some eyes with relatively intact EZ lines had reduced mfERG amplitudes. It was the abnormality of the IZ line that led to reduced mfERG amplitudes, while the EZ line was intact in OCT images [34]. A second possibility was that the functional abnormality preceded the structural changes in RP eyes. While the EZ line had subtle structural changes beyond OCT detection, electrophysiological function has been affected. Cytological changes examined by immunofluorescence showed that the immunoreactivity of certain cytoplasmic proteins was lost before the discovery of cytological changes in response to rod cell degeneration [35]. These alterations occur without the morphological changes shown in the OCT images. Thus, these results suggest that the retinal structures are significantly correlated with retinal function in RP patients.

Inner Retina

Compared with ONL thinning, changes of the inner retinal layers show different patterns. In spite of progressive ONL thinning, most studies showed that the inner retinal layers remained histologically intact, including the inner nuclear layer (INL) and the ganglion cell layer [23, 36]. In a clinical study, a decreased outer segment thickness without a significant decrease in the total retinal thickness suggested the presence of inner retinal thickening [37], and morphological studies reported less cellular loss in the INL than in the photoreceptor layers, which was consistent with the presentation of OCT images [38, 39].

The preservation of the inner retinal layers with the thinning of the outer retina has been described in a number of studies [36, 40], and a strong correlation between the preserved inner retina and outer retina thinning has been found in RP patients [23]. In this study, there was a loss of photoreceptor with normal ONL in younger patients. In patients with more advanced disease or at older ages, ONL was thin with normal or hyperthick inner retinal thickness, and inner retinal thickening was detectable and strongly associated with ONL loss at all ages. It was interesting that while the reduced extent of the outer ret-

ina was observed, the inner retina was relatively intact. There are some reasons accounting for thinning of the outer retina and thickening of the inner retina. Some researchers speculated that Henle fibers occupying a large portion of the total retinal thickness was less susceptible to RP changes [41]. Edematous RNFL responding to RNFL loss was another aspect making for the relative preservation of the inner retina [42]. In animal models of RP, dendritic retraction of the bipolar cells and increased reactivity of the amacrine and Müller cells have been reported with findings of progressive ONL thinning [23]. So it was supposed that inner retinal thickening was likely to reflect a neuronal-glial retinal remodeling responding to the outer retinal thinning.

However, the RP groups in late-stage or advanced RP [3, 38] both showed less ganglion cells in the pericentral region [40]. It has been suggested that compromised transneuronal axonal transport led to retinal ganglion cell loss in the process of RP development. In a histopathological study, the examination found that the greatest photoreceptor loss was in the inferonasal region [43, 44]. Therefore, it could be concluded that the inferonasal quadrant was the region where the compromised axonal transport caused damage to the ganglion cells. As the conclusions of different studies vary, a large number of studies are needed to confirm the retinal ganglion cell changes.

The importance of ganglion cells in assessing visual acuity has already been proven in glaucoma and anterior ischemic optic neuropathy [45, 46]. Therefore, the use of ganglion cells in evaluating visual function in RP patients should be studied. In clinical studies, the correlation between the ganglion cells and mfERGs has been studied. The results reported that the ganglion cells and the IPL complex were relatively preserved in patients with detectable mfERGs, while the complex was thinner in patients with undetectable mfERGs [40]. Therefore, it was supposed that the ganglion cells were related with macular function in eyes with RP. The measurement of ganglion cells might provide important information for determining the changes of the inner retinal layers in RP.

Hyperreflective Foci

Hyperreflective foci (HFs) have been reported in age-related macular degeneration [47] and diabetic retinopathy [48], and these were considered to be composed of macrophages, migrating RPE cells, and extravasated lipoproteins. HFs have also been observed in RP patients [49], and the mechanisms for the presence of HFs in RP were

different from those in other retinal diseases. The distribution of HFs was shown in the INL, ONL, and subretinal space. HFs in the ONL were found to be accompanied with a disrupted RPE line. RP patients with a relatively healthy RPE layer showed no HFs in the ONL, and advanced RP patients showed more HFs in the group with a disrupted RPE line. In spite of RPE cells, RP patients with a disrupted EZ line had more HFs than the group with a continuous EZ line [49]. Therefore, the presence of the HFs was considered to be correlated with the condition of the RPE layer and the EZ line.

According to the distribution, HFs had different characteristics in size and density. HFs in the ONL were relatively small and hyperreflective, while HFs in the INL were larger and hyporefective. It was found that HFs in the INL were located around the absent border of the EZ with normal RPE-Bruch's membrane complex. Therefore, the HFs in the INL seemed to be related with the state of the photoreceptor cells. Besides, it has been reported that reactivation of Müller cells, migration of activated microglia, and synaptic remodeling of horizontal and amacrine cells also contributed to the presence of HFs [50–52].

HFs in the ONL resulted from the death of the photoreceptor and RPE cells, so it was supposed that HFs were related to visual acuity. A clinical study showed that eyes without HFs had better BCVA than eyes with HFs in the ONL [49]. So the presence of HFs in the ONL was another OCT parameter to reflect retinal function in RP patients, and the BCVA of the eyes with HFs showed no difference from that of the eyes without HFs in the INL. Therefore, the new findings of HFs in the different retinal layers provide supplemental information in determining the pathology of RP.

Retinal Nerve Fiber Layer

Along with the progression of ganglion cell death, RNFL thinning was thought to be attributable to retinal atrophy in eyes with RP. However, the RNFL thickness was found to be retained or thickened in the majority of RP patients, and the measurement results are shown in table 2 [44, 53–58]. In addition to the mean RNFL changes [44, 55], the quadrants of the RNFL thickening or thinning were different. The RNFL thickening was most common in the temporal and superior quadrants [36], whereas the RNFL thinning was mostly found in the nasal and inferior quadrants. However, Hwang et al. [59] determined that RNFL thickening was found mainly in the

Table 2. The detailed values of RNFL thickness in RP patients

First author	Country	OCT	RNFL thickness, μm				
			mean	superior	temporal	nasal	inferior
Yildirim [57]	Turkey	SD-OCT	97.57 ± 3.21	119.18 ± 4.47	84.68 ± 2.31	75.09 ± 3.34	113.88 ± 4.25
Xue [56]	China	RTVue-OCT	115.82 ± 20.10	146.67 ± 28.78	89.14 ± 17.80	77.19 ± 27.04	150.27 ± 29.26
Garcia-Martin [58]	Spain	SD-OCT	82.90 ± 10.40	86.10 ± 12.20	103.10 ± 11.10	67.70 ± 11.90	136.70 ± 12.10
Hwang [59]	Korea	Cirrus HD-OCT	112.76 ± 16.96	138.76 ± 22.96	88.71 ± 16.84	83.68 ± 15.92	139.82 ± 22.33
Hood [36]	USA	FD-OCT	128.20 ± 16.70				
Oishi [53]	Japan	Stratus OCT	104.10 ± 21.70				

horizontal direction and less commonly in the vertical direction. Although the areas of RNFL thinning and thickening were different in several studies, the majority of RP patients showed both RNFL thickening and thinning. It has been speculated that the proliferation of fibrous astrocytes and edematous residual RNFL contributed to thickened RNFL [4, 60].

As the proliferation of fibrous astrocytes is most common on the surface of the optic nerve head [3], the thickest RNFL is closest to the optic disc, leading to a wax yellow color. Other investigators supposed that a purely mechanical factor compelled the thickening RNFL to fill the quadrants where the receptors degenerated [36], so RNFL thickening might be most found in the sector of receptor degeneration. However, whether the RNFL was thinning or thickening, both showed a trend to thinning in the late stage of the disease [61]. In addition to the development of the disease, RNFL thickness measurements demonstrated that decreased RNFL thickness was found more in older RP patients [61], so age was another factor influencing RNFL thickness. Thus, RNFL thickening in RP patients of younger age was more prominent than in older patients [62, 63]. These findings suggest that the abnormal thinning of the RNFL will be found more without the presence of RNFL thickening by following up over a long time. Therefore, retinal ganglion cell layer thickness would provide a better index in assessing RNFL thickness in RP patients [36].

In glaucoma, it has been confirmed that the ganglion cell IPL deviation map for detecting RNFL defects was equal to the papillary RNFL deviation map [64], and the localized papillary RNFL defects in different spaces corresponded to the ganglion cell IPL defects on the SD-OCT deviation map in glaucoma [65]. However, no consistent verdict has been reached with regard to the ganglion cell changes in RP patients, and whether RNFL defects are consistent with the ganglion cell IPL defects is

unknown. While there was a relationship between visual field and RNFL thickness in glaucoma [66], the association between the visual field extent and RNFL defect has been studied in RP [61]. However, RNFL thickness related to the visual field was only found in the inferior quadrant. Based on the visual field severity, the RP patients were subdivided into two groups, and the difference in the peripapillary RNFL thickness was not significant between the groups [54, 59]. Another analysis showed that there was no correlation between the peripapillary RNFL thickness and BCVA [20]. Sometimes, RP patients with poor visual acuity maintained a relatively normal peripapillary RNFL thickness [20], so peripapillary RNFL thickness might not be an optional OCT index for assessing the visual function in RP. Therefore, it would be prudent to make optimal use of the RNFL thickness to predict retinal ganglion cell changes in RP.

In addition to the changes in the RNFL, abnormalities in the optic nerve head have been studied in eyes with RP [20]. Compared with the control groups, the eyes with RP had greater rim areas and smaller cup-to-disc ratios [59], and it was the proliferation of the fibrous astrocytes and RNFL remodeling that accounted for the changes.

Macular Volume and Macular Thickness

In advanced RP patients, it is hard to identify the border between the retinal layers. Therefore, it is ideal to make optimal use of macular volume and retinal macular thickness to assess the condition of the retina. Macular volume is the sum of the retina in the central 6-mm area analyzed automatically using OCT [27]. Compared with the normal controls, the macular volume of the RP patients was significantly smaller, especially in the outer segments [20]. Whether a greater macular volume means better visual function has been assessed, and a significant-

ly positive correlation was found between the macular volume and the mfERG amplitude in RP patients [27]; the eyes with larger macular volumes had better mfERG amplitudes. Furthermore, no patients with normal mfERG amplitudes had severely reduced macular volumes, indicating that normal macular volume supported better macular function.

An increase or decrease in the retinal thickness has been reported in a study [10], which considered that cell loss led to retinal thinning and retinal edema led to retinal thickening. Therefore, the lower visual acuity seemed to be related to both retinal thinning and retinal thickening. However, in other studies, the BCVA was determined to be significantly better with greater retinal thickness of the inner ring areas [20] and with greater foveal retinal thickness [67]. Eyes with more severe visual field defects had thinner macula thicknesses than eyes with preserved visual field [59]. So moderate retinal atrophy with thicker retinal thickness was often associated with better BCVA. However, some eyes with poor visual acuity maintained the inner ring area thickness [20], and some eyes with worse visual acuity were accompanied with thicker central subfield thicknesses [68]. The presence of macular cysts accounted for the phenomena of thicker retina with worse visual acuity.

Otherwise, the correlation between retinal thickness and mfERG amplitude has been studied in RP patients [40]. According to the results of mfERG, the RP patients were divided into two groups: no detectable mfERG amplitude or detectable mfERG amplitude [40]. The results of the OCT showed that the group with detectable mfERG amplitude had significantly thicker retinas than the group with no detectable mfERG amplitude. Therefore, in the late stage of RP, the OCT parameters of macular volume and retinal macular thickness are useful indexes for assessing functional vision.

Choroidal Vessel Layer

In addition to the degeneration of the photoreceptor and RPE cells, RP was characterized by variable choriocapillaris atrophy [69, 70]. The changes in choroidal morphology and the choroidal vessel layer were observed in eyes with RP [70, 71]. The shape of the choroid was irregular, and the borders of the choroid and sclera were not smooth in RP patients [71]. In normal controls, the choroid was thickest beneath the fovea and thinnest nasally, while in RP patients, the choroid was thickest in the temporal area and thinnest nasally [71]. According to the

size of the choroidal vessel, the choroidal vessel layer was separated into large choroidal vessels, medium-sized choroidal vessels, and the choriocapillaris. In RP patients, it was difficult to resolve the choriocapillaris and the medium-sized choroidal vessels separately; therefore medium-sized choroidal vessels combined with the choriocapillaris were used to assess small choroidal vessels changes [71]. The large choroidal vessel layer occupied the main ratio of the choroidal thickness, and the results showed a preferential thinning of the large choroidal vessel layer in RP [71]. However, the thickness of the small choroidal vessel was found to be maintained, and the reasons for preferential thinning of the large choroidal vessels have been analyzed in experimental studies. It was believed that RPE cell loss subsequently led to choroidal vessel atrophy [72, 73], and the observations suggested that loss of RPE was responsible for choriocapillaris atrophy and degeneration of endothelial cells in rabbits. Studies in mouse models have confirmed that the reduction of the vascular endothelial growth factor (VEGF) derived from the RPE cells was one of the factors responsible for choriocapillaris degeneration [74]. However, a limitation in the animal studies was the analyses of total choroidal vessels changes, and the abnormalities in large choroidal vessels, medium-sized choroidal vessels, and the choriocapillaris should be studied further. Since the large choroidal vessels were the farthest from the RPE line, a preferential thinning of the large choroidal vessel layer suggested a relationship between the choroidal vessels and the RPE layer. Endothelin-1 (ET-1) was a vessel vasoconstrictor which played an important role in both normal and pathological choroidal vessels [75]. When the eyes were in stress conditions, the levels of ET-1 increased, and the vasoconstrictor effect of the ET-1 caused the choroidal vascular thinning.

The positive correlation between central retinal thickness and subfoveal choroidal thickness has been reported [71], so it was speculated that choroidal vessel thickness might be another useful parameter for assessing the disease severity. However, most clinical studies implied that subfoveal choroidal thickness had no association with the duration of the RP or BCVA [71, 76]. However, choriocapillaris atrophy was confirmed to be accompanied by RPE cell loss and macular photoreceptor loss [76], and RP patients with thinner choroids showed poorer visual acuity and a longer duration of symptoms in another prospective study [77]. As there were no consistent results in choroidal studies, further research studies are needed to determine the correlation between choroidal thickness and visual acuity.

Table 3. The prevalence of macular abnormalities in RP patients

First author	Country	OCT	Macular abnormalities, %			
			macular edema	ERM	VMT	Macular hole
Testa [78]	Italy	SD-OCT	20.4 (237/1,161)	15.6 (181/1,161)	5.0 (58/1,161)	2.0 (23/1,161)
Hagiwara [81]	Japan	FD-OCT	5.5 (34/622)	0.6 (4/622)	0.8 (5/622)	0.5 (3/622)
Giusti [82]	Italy	SD-OCT	12.5 (22/176)	27.3 (48/176)		4.5 (8/176)
Makiyama [80]	Japan	SD-OCT	22.5 (119/529)			
Hirakawa [79]	Japan	Cirrus OCT	13.0 (12/89)			
Gorovoy [83]	USA	Stratus OCT	24.5 (22/90)			

Macular Abnormalities

Compared with the general population, macular abnormalities were more prevalent in RP patients [78, 79] and were observed in 45.1% of RP eyes [80]. In clinical studies, cystoid spaces were present from 5.5 to 24.5% [79, 80], and the prevalence of epiretinal membrane (ERM) was reported in 15.6% [78]. Although the prevalence of macular abnormalities was different in several studies [78–83], as shown in table 3, the results displayed that the most frequent abnormality was macular edema, followed by ERM, vitreomacular traction syndrome (VMT), and macular hole [78]. Since the macular abnormalities caused vision loss in any stage of RP [80], it was important to assess the macular structure in time.

OCT has been shown to be parallel to or even more sensitive than fluorescence angiography in detecting cystoid macular edema in RP [79]. Therefore, OCT screening is highly recommended for evaluating macular morphologies.

In eyes with RP, macular edema showed similar presentation and central location to diabetic macular edema. However, the presentation in fluorescence angiography and spatial distribution were different. Macular edema in RP eyes showed little dye accumulation in fluorescence angiography, but the mechanism was not clear [79]. In RP patients, spatial distribution of the cystoid spaces was found mainly in the INL, but sometimes in the ONL/OPL and the ganglion cell layer [80]. When compared with RP, diabetic macular edema was predominantly located in the OPL, and macular edema in patients with central retinal vein occlusion was in the INL [84]. There are many reasons for the preferential spatial distribution in RP. In normal retina, intraretinal fluid distribution is restricted by the IPL and OPL, and

serum leakage from intraretinal vessels is mediated by Müller and RPE cells [85]. So it was supposed that the degeneration of RPE and Müller cells accounted for the preferential distribution of cystoid spaces in the inner retina in RP patients. Intraretinal layers, a barrier consisting of synapses and dendritic and connecting fibers, stopped fluid movement, but with the atrophy of retinal layers, the barrier damage contributed to the formation of cystoid spaces in the inner retina [86]. The ELM is another barrier that limits the diffusion of large molecules [87]; however, with the loss of Müller cells and photoreceptor segments, the ELM barrier is destructed. So in RP patients, retinal atrophy and the destruction of retinal layers led to macular edema, while the disrupted blood retinal barrier mainly accounted for macular edema in vascular diseases.

Eyes with diabetic retinopathy showed a good correlation between the thickness of the neurosensory retina and BCVA [7], but the results demonstrated no relationship between the two parameters in RP patients [79]. In a clinical study, the results indicated that an intravitreal aflibercept injection was an effective treatment for addressing macular edema in RP patients [88]. However, the level of VEGF was unknown in RP. Therefore, more studies are needed to confirm anti-VEGF treatment in curing macular edema related to RP.

In addition, the presence of ERM and VMT has been associated with cystoid spaces [80], and most cases of macular edema in the clinical study were found to be accompanied with ELM and VMT [80]. Cataract surgery and genotype were the other factors related to the presence of cystoid macular edema, and it has been reported that cystoid macular edema was more frequent in autosomally dominant groups compared with autosomally recessive, isolated, and Usher II genetic subtypes [89].

ERM defined as a membrane adherent to the inner retina has been presented as the second most frequent macular abnormality in RP patients [78], with an incidence of 19.8% after macular edema [78]. Many factors have been related to ERM, such as ethnic origin, environmental risk factors, and age [90], but the proliferation of fibrous astrocytes and RNFL remodeling have also claimed responsibility for the occurrence of ERM in RP patients. Therefore, observations of the macular structures by OCT help in finding macular abnormalities as well as in providing an insight into the pathogenesis of RP.

Conclusion

Recent studies have confirmed the ability of OCT to quantify photoreceptor segments and the thicknesses of retinal layers in RP patients. Correlations between the retinal structure and visual acuity have been obtained in eyes with RP. Therefore, OCT has been confirmed to be an ideal method for evaluating the morphological and functional changes in RP.

Disclosure Statement

The authors have no conflicts of interest to declare.

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