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<td>Author(s)</td>
<td>Makiyama, Yukiko; Oishi, Akio; Otani, Atsushi; Ogino, Ken; Nakagawa, Satoko; Kurimoto, Masafumi; Yoshimura, Nagahisa</td>
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Prevalence and spatial distribution of cystoid spaces in retinitis pigmentosa: investigation with spectral domain optical coherence tomography

Running title: Distribution of cystoid spaces in RP

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Keywords: retinitis pigmentosa, cystoid macular edema, optical coherence tomography
PURPOSE: To investigate the prevalence and spatial distribution of cystoid spaces (CS) in retinitis pigmentosa (RP) patients with spectral domain optical coherence tomography (SD-OCT).

METHODS: 529 eyes of 275 patients with RP were examined with spectral domain optical coherence tomography. Presence or absence of CS was judged for each eye. Retinal layer and outer retinal status where the CS existed were also investigated. Statistical analysis was done using one eye per one patient.

RESULTS: CS were present in 119/529 eyes (22.5%) of 74/275 patients (26.9%). There were no significant differences between the cases with and without CS except for central foveal thickness ($p < 0.001$). CS were noted in inner nuclear layer (INL) in almost all eyes (98.6%) and outer nuclear layer (ONL)/outer plexiform layer (OPL) was also involved in many eyes (27.8%). CS were sometimes seen in ganglion cell layer (6.9%). CS were predominantly (78.9%) distributed in the relatively preserved retina where external limiting membrane was retained. The presence of epiretinal membrane (ERM) or posterior vitreous adhesion was associated with the presence of CS ($p<0.001$) but showed no relationship with the spatial location of CS ($p=1.000$).

CONCLUSIONS: The prevalence of CS in RP patients was 26.9% and contrary to previous reports, most CS were present in INL. In addition, most CS were observed in relatively retained retina, which is compatible to prevailing notion. ERM or posterior vitreous adhesion was also associated with the development of CS. The distribution of
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1 CS in inner and preserved retina may provide insight for the pathogenesis of CS in RP.
INTRODUCTION

Retinitis pigmentosa (RP) is sometimes complicated by cystoid macular edema (CME), which may impair central vision in any stage of the disease. Several therapeutic strategies have target CME in RP patients including topical or oral administration of carbonic anhydrase inhibitor, steroid administration, intravitreal injection of anti-vascular endothelial growth factor agent, photocoagulation, or even vitrectomy. The beneficial effects of each of these therapies are not consistently observed in all patients. The establishment of therapeutic approaches is complicated by the limited knowledge regarding the pathophysiology of CME in RP patients. Some mechanisms including anti-retinal antibodies, vitreous traction, RPE dysfunction, and Müller cell edema were proposed. If there are several etiologies for the development of CME, different therapeutic strategies may be required to treat each etiology. However, the evidence for how these mechanisms are involved in the development of CME is limited.

To investigate the etiology of CME in RP patients, we focused on retinal layers where cystoid spaces (CS) are located. As cysts are not limited to macular tissues, we use the term cystoid spaces in the present study. Some of the retinal structures, e.g., the inner and outer plexiform layers contain abundant tortuous dendritic processes, connecting fibers, and invaginated synapses, which are considered to work as a barrier. The external limiting membrane consists of zonula adherens between apical processes of Müller cells and photoreceptors of the inner segment, and limits the
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diffusion of large molecules such as albumin. The semi-permeable nature is thought to contribute to the accumulation of intra-retinal fluid. Thus, we hypothesize that these structures may affect the distribution of CS in different etiologies.

The main location of CS in pseudophakic macular edema is the inner nuclear layer (INL), throughout the majority of retinal layers in patients with central retinal vein occlusion, and predominantly in the outer plexiform layer (OPL) in diabetic macular edema. In addition, Tsujikawa et al. investigated retinal vein occlusion and suggested that CME progresses to serous detachment when the barriers of external limiting membrane (ELM) break down. These studies indicate that the distribution of CS is dependent on the etiology and retinal status and the patient. While histological examination of the retina is both difficult and impractical in routine clinical investigations, optical coherence tomography (OCT) is widely used to study retinal pathologies and has also been used for the diagnosis and monitoring of RP. For example, OCT has been shown to be more sensitive, or at least as sensitive, as fluorescein angiography for the detection of CME in RP. Other studies showed that evaluating retinal structure with OCT is useful for the assessment of retinal function.

Little evidence exists as to which layer is predominantly involved in the development of CS associated with RP, with the exception of a single report with a small case series. We assumed that detailed evaluation of retina using OCT in larger numbers of RP patients would provide some insight in the pathogenesis of CME in RP.

In addition to the retinal “layers”, we investigated retinal “areas” where CS exist.
There is a prevailing notion that CME less frequently occurs in the late stages of the degenerative pathology, but this is yet to be clearly shown to our knowledge. In the present study, we also investigated outer retinal integrity and the association with CS location to confirm whether CS preferentially occurs in early to moderate stage RP. As an indicator of outer retinal preservation, ELM, which were reported to be correlated with visual function in various diseases was used.

METHODS

All procedures conformed to the tenets of the Declaration of Helsinki and the study design was prospectively approved by the Institutional Review Board and ethical committee at Kyoto University Graduate School of Medicine. The review board waived the need for written informed consent because the study design consisted of retrospective chart review.

Participant information

Diagnosis of RP was made with clinical interview of family history, the presence of night blindness, characteristic fundus appearance, concentric or ring shaped scotoma in Goldmann perimetry, and the result of electroretinogram (ERG). Full-field ERGs were recorded according to ISCEV standard protocol recommended in 2004 or 2008 using LS-C (Mayo Co, Nagoya, Japan) and Neuropack MEB-2204 (Nihon Kohden, Tokyo, Japan). We retrospectively reviewed 529 eyes of 275 patients with RP (120 men and 155 women) who underwent spectral domain (SD)-OCT scan with Spectralis (Spectralis HRA+OCT®; Heidelberg Engineering, Heidelberg, Germany) from February 2008 to
September 2011. In the present study, we use the term RP as to indicate progressive rod cone dystrophy, which was classified in the previous review article.\textsuperscript{41} We routinely perform SD-OCT examination for patients who visited our degenerative retinal disease service at each visit. Thus, the investigated population represents almost all RP patients who visited our institution during the period. Those who showed a subnormal or non-recordable electroretinogram were included. The thinning of outer nuclear layer and the disruption of outer retinal structures including inner segment / outer segment junction depicted with SD-OCT were considered to represent retinal degeneration in the area and the findings were used to confirm the diagnosis.\textsuperscript{42} We carefully excluded Leber’s congenital amaurosis (LCA), cone rod dystrophy, X-linked retinoschisis, choroideremia, Stargardt disease, paraneoplastic retinopathy, or autoimmune retinopathy.

We further analyzed age, visual acuity, mean central foveal thickness (CFT; μm), and score of mean deviation (MD) in a Humphrey field analyzer using the Mann-Whitney U test. Visual acuities were measured with Landolt C and were converted to the logarithm of the minimum angle of resolution (logMAR) equivalents. The Spectralis HRA+OCT has a built-in digital caliper to measure thickness or length. We measured the thickness at the center of the fovea with horizontal and vertical B-scan images, and averaged scores were used as the CFT. Humphrey field analyzer tests were performed within 6 months of OCT examination with the program of Swedish Interactive Threshold Algorithm standard 10-2.

**Measurements of Cystoid Spaces (CS)**
Cross-hair scans, which consisted of horizontal and vertical 30-degree scans, centered on the fovea were obtained. Six-line over 20-degree radial scans and over 30×10-degree volume scans centered on the fovea were also obtained. Automated eye tracking and averaging was used for each measurement as follows: 100 averages for cross scans, more than 20 averages for radial scans, and more than 2 averages for volume scans. When a patient underwent serial OCT examinations, the most recent series of scans were analyzed.

Patients were categorized by presence or absence of CS. Patients with even a single CS were categorized as having CS. Throughout the present study, SD-OCT images were evaluated by two independent investigators (YM, AO). In cases of discrepancies, a third investigator (KO) was consulted. And we also judged the existence of epiretinal membrane (ERM) or posterior vitreous adhesion simultaneously.

Eyes with CS were further divided by the vertical and horizontal location of the CS. Vertically, we divided according to the layer where CS existed: ganglion cell layer (GCL), inner nuclear layer (INL) or outer nuclear layer (ONL)/OPL. When CS were found in ONL or OPL, the border between ONL and OPL became unclear, thus we categorized them together as ONL/OPL (Figure 1). Horizontally, we checked the location of CS in relation to the area with preserved outer retinal structure. The presence of ELM was considered to indicate relative preservation of outer retina. When even a single CS was noted in the area where ELM was not preserved, patients were classified as having CS outside the area of preserved outer retina (Figure 2).
Statistical analyses of data

Although we reviewed clinical records of 529 eyes of 275 patients, statistical analysis was done using one eye per one patient, because the status of right and left eyes of a patient is considerably similar. In cases with bilateral involvement, we used the left eyes unless media opacity or poor fixation impaired the image quality. For those patients where the examination of left eye showed inadequate quality, right eyes were used for the analysis. Statistical analyses were conducted using IBM SPSS Statistics Desktop (version 19.0, IBM Japan, Tokyo, Japan). Descriptive analyses are reported as means ± standard deviation unless otherwise specified. Clinical characteristics were compared between groups using Mann-Whitney U-test or Fisher’s exact test or Yates Chi-square test, as appropriate. \( P \) values less than 0.05 were considered statistically significant.

RESULTS

Prevalence of CS

CS were detected in 119 out of 529 eyes (22.5%) in 74 out of 275 patients (26.9%). Forty-five patients (60.8%) of the 74 patients had CS in both eyes. Among the studied subjects, 48 patients underwent genetic screening using microarray or direct sequencing. Mutations in EYS gene was detected in 12 patients, mutations in RHO gene were detected in 3 patients, mutations in RDS gene were detected in 2 patients, and mutation of CRX, FSCN2, ROM1, CRB1, and PDE6B were detected in one patient, respectively. Characteristics of participants are shown in Table 1. There were no significant differences between those with and without CS except for CFT (\( P < 0.001 \)). In fact, visual
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Retinal location of CS

We investigated the location of CS in 72 eyes of 72 patients. CS were located in GCL, INL, or ONL/OPL in all cases. Of the eyes with CS, 48 eyes (66.7%) had CS in the INL (Figure 1, A) and 18 eyes (25.0%) had CS in the INL and OPL/ONL (Figure 1, B).

Five eyes had CS also in the ganglion cell layer (GCL); Three eyes (4.2%) had CS in the GCL and INL, and two eye (2.8%) had them in the GCL, INL, and OPL/ONL (Figure 1, C).

Notably, CS were observed in the INL in 98.6% of investigated eyes. Only one eye (1.4%) had an isolated intra-retinal space in the ONL, however, the image in the case looked like a cleft and not a typical CS (Figure 1, D).

Considering the rare and atypical presentation, we excluded this case from the following analysis. We classified the rest of 71 eyes into two groups: Group 1 who had CS in the INL or in the INL and GCL (51 eyes), Group 2 who had CS in the INL and ONL/OPL or in the INL, ONL/OPL, and GCL (20 eyes). When we compared these two groups, there was no significant difference in age, foveal thickness, and MD. CFT was marginally thicker in Group 2. (Table 2)
We then evaluated the retinal area where CS existed. In 56 eyes of 71 eyes with CS (78.9%), CS were only found in the area where ELM was preserved, namely the area with relatively retained outer retinal structure (Figure 2, A and B). In fact, several cases showed asymmetric appearance in temporal and nasal retina, and only ipsilateral sides with preserved ELM had CS (Figure 2, B). In the remainder, CS could be seen adjacent to the remaining ELM (4 eyes, 5.6%; Figure 2, C), or in severely damaged retina with a thin RPE (6 eyes, 8.5%; Figure 2, D). Evident vitreal traction was noted in 5 of 71 eyes, in which ELM was not retained. (7.0%; Figure 2, E).

The presence of ERM or posterior vitreous adhesion showed no relationship with the spatial location of CS (p=1.000).

**DISCUSSION**

In the present study, we showed that more than 20% of eyes with RP have retinal cysts (termed cystoids spaces (CS) in the current study). CS are predominantly distributed in the INL and in the area where the ELM is retained. The results suggest that the major source of fluid collection in CS associated with RP occurs in the inner retina. In addition, we confirm that CS associated with RP generally develop in areas of the retina that are relatively well preserved.

CS were detected in 22.5% of patients and 60.8% of whom had CS in both eyes. We found no difference in the prevalence of CS among each inheritance pattern and that was consistent with a previous report.\(^4^5\) Previously reported prevalence of CME or CS in RP patients ranges from 7.4–47%.\(^2^7, 3^1, 3^5, 4^5-4^9\) These differences in prevalence may
partly stem from the method used to detect CS which include fluorescein angiography (FA) or OCT. Previous reports showed the use of OCT rather than FA increases the detection rate of CS.\textsuperscript{27-29} Furthermore, image resolution is better with the current model of SD-OCT,\textsuperscript{50} which should further enhance detection sensitivity. The degree of CS included in prior studies may also account for these discrepancies. Some authors report the prevalence of CME based on macular involvement, and might have excluded minor parafoveal CS. Consistently, our previous work using time-domain OCT reports that the prevalence of CME was 7.5\%, which would increase to 14.9\% if minor CS were included.\textsuperscript{31} The result strongly suggests that OCT image resolution and the inclusion criteria influences the reported prevalence of CME and highlights the need to carefully consider inclusion criteria.

In the present study, almost all patients (98.6\%) had CS in INL. When CS were located in the GCL or ONL/OPL, they were almost always accompanied by CS in the INL. Although statistically non-significant, those with CS in the INL tended to have better visual acuity, suggesting the progression from CS in INL to INL+OPL/ONL. The frequent distribution of CS in the inner retina was in conflict with a previous report. Catier \textit{et al.} reported that 88\% of RP eyes with CME had CS in outer retinal layers.\textsuperscript{37} The discrepancy may also stem from resolution of the images. In the report, the authors used OCT 2000, which was a time-domain OCT model and resolution of the image was limited in comparison to more recent models. In addition, the study only examined 8 patients, therefore, the small sample size of the study might be biased toward evident CME, which
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would not necessarily reflect the overall characteristics of CS associated with RP. The preferential inner retinal distribution of CS may shed some light on the pathology of CS in RP. Among some proposed mechanisms, the present result supports the hypothesis of Müller cell dysfunction and swelling in the primary pathogenesis of CME development. The INL, where CS were predominantly distributed, is where Müller cell bodies exist. In addition, as discussed below, around 80% of cases only had CS located above the remaining ELM, which comprised zonula adherens of Müller cells and photoreceptors. Although the evidence is indirect, the localization of CS in the INL and in the area with preserved ELM supports the hypothesis that Müller cell dysfunction may contribute to CME development in retinal degeneration.

The present result supports the prevailing notion that CME seems less likely to appear in the late stages of the degenerative pathology. For example, Lupo et al. reported that RP patients with CME are younger than those with macular thinning and vitreomacular traction. Most CS in the present study were found in areas with preserved ELM. In addition, asymmetric distribution even within an eye as shown in figure 2 suggests that CS preferentially develop in preserved areas of the retina. The pathologic process including inflammation in degenerating retina might induce fluid accumulation or the fibrotic changes in degenerated retina might prevent the formation of CS.

The presence of ERM or posterior vitreous adhesion was associated with the presence of CS (Table 1, $p<0.001$) but showed no relationship with the location of CS.
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(Table2, $p=1.000$). In instances where CS were observed in damaged areas of the retina, OCT images often showed evident vitreal traction or the CS were found to be very small. We also suggest that vitreous traction and retinal tissue loss are the major contributing factors in cases of CS in advanced RP.

There are several limitations to the present study. Firstly, we could not perform FA in most patients because the examination is invasive and previous reports showed that OCT is superior to FA in detecting CME. The findings from FA, if available, could provide information about the involvement of inflammation or blood-retinal barrier breakdown in CS development. Secondly, morphologic observation does not provide direct evidence and other conclusions can be drawn from the observation. For example, CS in the INL may be a result of vascular leakage. Although vascular leakage does not appear to be a major contributor, the present results do not exclude other possible mechanisms. Thirdly, genetic screening was performed in part of the subjects, which identified few causative mutations. Lastly, we could not examine the circulating anti-retinal antibodies, which were suggested to be a major cause of CS in previous report of Heckenlively and associates.

In conclusion, the prevalence of CS in RP was 22.5% when using SD-OCT. They were usually observed in the INL and in areas where ELM are preserved. ERM or posterior vitreous adhesion was also associated with the presence of CS. The distribution of CS indirectly supported the involvement of Müller cells in the pathogenesis. Further studies are needed to reveal the mechanism of CS in RP.
Acknowledgements

None
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FIGURE LEGENDS

Figure 1: Spectral-domain optical coherence tomography (SD-OCT) images of patients with cystoid spaces associated with retinitis pigmentosa.
We classified the eyes into two groups according to localization of cystoid spaces (CS).
(A) An image of the left eye of a 35-year-old female. CS are located only in the inner nuclear layer (INL). These cases were classified as INL group. (B) An image of the left eye of a 47-year-old male. CS are located in the INL and outer plexiform layer / outer nuclear layer (OPL/ONL). These cases were classified as INL+OPL/ONL group. (C) An image of the left eye of a 58-year-old male. CS are located in the ganglion cell layer (GCL) and INL. The patient had CS also in OPL/ONL in another scan. These cases were also classified as INL+OPL/ONL group regardless of the presence of CS in GCL. (D) An image of the left eye of a 43-year-old female. This was an exceptional case, which showed CS or cleft-like space in OPL/ONL. The case was excluded from the comparison of location. Scale bar = 200 µm

Figure 2: Representative spectral-domain optical coherence tomography (SD-OCT) images of retinitis pigmentosa (RP) patients with cystoid spaces (CS).
SD-OCT revealed a correlation between the location of CS and the remaining external limiting membrane (ELM). A horizontal arrow indicates the area with remaining ELM. (A) An image of the left eye of a 35-year-old female. This is the most frequently observed pattern, which suggests that CS are predominantly located on the remaining ELM. (B) An image of the left eye of a 70-year-old female. Several cases showed similar asymmetric patterns. CS are observed only on the ipsilateral side where the ELM is preserved. (C) An image of the left eye of a 61-year-old male. Some cases (4.5%) showed CS adjacent to the remaining ELM. (D) An image of the left eye of a 18-year-old male. Some cases (9%) presented small CS where the outer retina is severely damaged. (E) An image of the left eye of a 71-year-old female. Epiretinal membrane was frequently observed in eyes with RP. Some cases were accompanied by vitreal traction as shown in the figure. Scale bar = 200 µm
Figure 3: Comparison of central foveal thickness (CFT) and visual acuity (VA) or mean deviation (MD).

The central foveal thickness was greater in the eyes with cystoid spaces (CS) but there was no significant difference in visual acuity or MD between the eyes with and without CS. ◇ represents eyes without CS and ■ represents eyes with CS. Solid straight lines are the best fitting linear function for eyes without CS (logMAR VA: y=1.21-0.0045x, MD: y=-35.8+0.0956x) and small-dashed straight lines are the best fitting linear function for eyes with CS (logMAR VA: y=0.63-0.0013x, MD: y=-24.1+0.0253x)
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### TABLES

**Table 1. Comparison of Patients with Retinitis Pigmentosa with and without Cystoid Space**

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Effect of ERM or posterior vitreous adhesion

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Mode of Inheritance

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CFT: central foveal thickness; CS: cystoid spaces; MD: mean deviation; AD: autosomal dominant; AR: autosomal recessive

*1 Mann-whitney U test; *2 Fisher’s exact test; *3 Chi square test
Distribution of cystoid spaces in RP

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Effect of ERM or posterior vitreous adhesion

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INL: inner nuclear layer; ONL: outer nuclear layer; OPL: outer plexiform layer;
CFT: central foveal thickness; MD: mean deviation; AD: autosomal dominant;
AR: autosomal recessive

*1Mann-whitney U test; *2 Fisher’s exact test; *3 Chi square test
Figure 3