Title
Optical coherence tomography angiography findings in pigmented paravenous chorioretinal atrophy.

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Abstract

Purpose: To analyze the retino-choroidal vascular characteristics of patients affected by pigmented paravenous chorio-retinal atrophy (PPCRA) by means of optical coherence tomography angiography (OCTA).

Methods: The study was designed as an observational, cross-sectional case series. Multimodal imaging included fundus autofluorescence (FAF), structural optical coherence tomography (OCT) and OCT angiography (OCTA). The quantitative OCTA analyses included the calculation of the vessel density (VD) and choriocapillaris porosity.

Results: Overall, 12 patients (24 eyes) affected by PPCRA were recruited. Structural OCT of the areas involved by PPCRA as visualized on FAF showed a complete EZ and ELM absence, with thinning of ganglion cell complex (GCC), outer nuclear layer (ONL), and outer plexiform layer, but associated with the optical partial preservation of the retinal pigment epithelium (RPE). OCTA quantitative assessment of the retinal regions affected by PPRCA, as visualized by FAF, were characterized by normal VD at the level of superficial capillary plexus, but significantly altered VD of deep capillary plexus (DCP) and choriocapillaris, with higher choriocapillaris porosity.

The presence of macular atrophy was significantly correlated with worse DCP and choriocapillaris VD values. Furthermore, a statistically significant correlation between the FAF patterns and the retinal vascular status was found.

Conclusions: OCTA quantitative analyses in PPCRA demonstrate a specific impairment at the level of the DCP, which could in turn bring about a thinning of GCC and ONL. The alterations at the level of the choriocapillaris and the choroid in general, could then represent a secondary effect.

Summary Statement

In the present study, we assessed retino-choroidal vascular characteristics of patients affected by pigmented paravenous chorio-retinal atrophy (PPCRA), highlighting significant of deep capillary plexus, choriocapillaris and the choroid, ganglion cell complex, and outer nuclear layer.

Introduction

The definition of pigmented paravenous chorioretinal atrophy (PPCRA) refers to a heterogeneous form of chorioretinal atrophy primarily involving the paravenous area with variable clinical severity.[1-6] In particular, the fundus picture can be identified on the basis of pigment migration, pigment clumping and bone spicules.[4] Patients with PPCRA are usually asymptomatic and characterized by well-preserved visual acuity. Electroretinogram responses and visual field findings are variable but are often characterized by marked interocular asymmetry.[3-9] In most reported cases, progression is limited and when present relatively mild/moderate, with overall good preservation of visual function over time.[4-6]

PPCRA aetiology remains uncertain but likely variable, with the atrophic fundus changes being the results of a number of disparate conditions including inflammation, infection, and trauma.[4-6,9-17] Independent of the underlying cause, no study has thoroughly analysed the vascular alterations typical of PPCRA, especially by means of optical coherence tomography angiography (OCTA). Two previous case reports have mainly described the choriocapillary impairment.[18-19] The assessment of the level of the retino-choroidal vascular involvement may reflect the nature of the different PPRCA subforms and may also contribute to subsequent the evolution of the disease. The aim of the present study was to analyse the retino-choroidal vascular characteristics of patients affected by PPRCA by means of OCTA.

Methods

The study was centered on a prospective, observational, cross-sectional case series, recruiting patients diagnosed with PPRCA at the Ophthalmology Departments of San Raffaele Hospital in Milan, Hadassah-Hebrew University Medical Center in Jerusalem, and University Eye Hospital in Ljubljana, between January 2019 and January 2020. The protocol was approved by the institutional review board and the procedures followed the tenets of the Declaration of Helsinki (study ID: MIRD). Written informed consent was obtained from all subjects.

Patients

Patients with a clinical diagnosis of PPCRA were included, based on the detection of typical fundus findings of chorioretinal atrophy primarily along the retinal veins, with variable pigmentation, often with inter-ocular asymmetry.[5] Clinical data obtained from review of cases notes included presence of symptoms, previous ocular inflammation/infection, previous trauma, family history of inherited retinal disease.

A group of age- and sex-matched healthy control subjects was also included in the study.

Patient and controls underwent a complete ophthalmic examination, including best-corrected visual acuity (BCVA) on standard ETDRS charts, colour fundus photography, blue-light fundus autofluorescence (FAF), spectral-domain optical coherence tomography (SD-OCT) (Spectralis, HRA Heidelberg, Heidelberg, Germany), and OCTA (Swept Source DRI OCT Triton, Topcon Corporation, Japan).

Imaging

FAF classification included a focal pattern showing limited hypo-autofluorescent signals that were separate from each other, a paravenous pattern with continuous hypo-autofluorescent signal along the large retinal veins in a geographic manner surrounded by linear hyper-autofluorescence extending to the periphery, and a confluent pattern characterized by extensive areas of hypo-autofluorescent signal coalescing and extending beyond the vasculature.[5,6]

We used the ETDRS grid provided by Heidelberg software to calculate the mean thickness of the following retinal layers: retinal nerve fiber layer (RNFL), ganglion cell complex (GCC), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), ellipsoid zone (EZ), external limiting membrane (ELM), retinal pigment epithelium (RPE). Central macular thickness (CMT) and subfoveal choroidal thickness (CT) have been also included.

The segmentations of superficial capillary plexus (SCP), deep capillary plexus (DCP), choriocapillary (CC) and radial peripapillary capillaries (RPC) were carefully inspected and, if necessary, manually

corrected by two expert ophthalmologists (MBP, AA), only considering high-quality images (Topcon quality index > 80). All OCTA images were captured by the same two ophthalmologists at least twice, to assess both reproducibility and repeatability. Quantitative OCTA analyses included the calculation of vessel density (VD), separately considering macular "m" and optic nerve head "n" plexa (for example mSCP and nSCP). All reconstructions were loaded in ImageJ software11 to calculate VD. The pipeline method employed ran as follows: Import .tiff image -> Adjust -> Threshold -> Automatic threshold -> Mean thresholding -> Binarized image -> VD calculation. Furthermore, we separately calculated VD in the altered region detected by BAF.
In-house scripts were used to calculate VD of SCP, DCP and CC. The foveal avascular zone area was manually segmented and excluded from VD calculation.
We have also calculated mCC porosity, intended as a measure of the flow voids characterizing mCC.[20] nCC was not considered because of the presence of big retinal vessels interfering with the proper detection of flow voids and considering the extensive atrophy characterizing nCC in PPCA eyes. To calculate mCC porosity, we used the porosity pipeline, included in ImageJ, considering the binarized mCC images.
Primary outcome of the study was to analyze the retino-choroidal vascular characteristics of patients affected by PPRCA by means of OCTA.

Statistics

To compensate for the low number of eyes, as well as the inclusion of both PPCRA eyes in the statistical analyses, we used linear mixed models that included patient and eye as random factors. The group (Controls vs PPCA) was considered as a fixed factor. The following dependent variables were analyzed: LogMAR BCVA, CMT, CT, RNFL, GCC, IPL, INL, OPL, ONL, EZ, ELM-RPE, mSCP VD, mDCP VD, mCC VD, RPC VD, nSCP VD, nDCP VD, nCC VD, and mCC porosity. Mixed models were built using lme4 package version 1.1-23 under R software package (release 3.5.2). Statistical significance was assessed by means of Kenward-Roger approximation of F-test, as provided by the KRmodcomp function, part of pbkrtest package. Bonferroni approach was adopted to address the multiple comparisons issue; this choice resulted in an alpha value of 0.05/19=0.002, which was necessary to obtain an overall alpha value of 0.05.

Results

Overall, 12 patients affected by PPCRA (24 eyes) were recruited, along with 12 control subjects (24 eyes). The demographic and clinical characteristics of the patients are listed in Table 1.
Mean subfoveal CMT was 252 ± 61µm ($p<0.05$), whereas mean subfoveal CT was 241 ± 100µm ($p>0.05$).
Two out of 12 patients (16%) disclosed asymmetry in the fundus appearance, whereas another patient (8%) showed PPCRA in one eye and a genetically confirmed retinitis pigmentosa in the fellow eye.

Fundus Autofluorescence

PPCA eyes were classified on the basis of the FAF pattern as focal in 3/24 eyes (12%), paravenous in 16/24 eyes (67%), and confluent in 5/24 eyes (21%). Macular atrophy was present in 6/24 eyes (25%), whereas 9/24 eyes showed peripapillary sparing (38%).

Optical Coherence Tomography

Structural OCT of the areas involved by PPCRA as visualized on FAF showed a complete EZ and ELM absence, with thinning of ONL and OPL, but associated with the optical partial preservation of the RPE.
OCT examination disclosed different results on the basis of macular involvement. In particular, eyes with macular atrophy revealed a generalized thinning of all the retinal layers (Table 2), whereas eyes with no macular atrophy had a statistically significant thinning of RNFL, GCC, and ONL (Figure 1). Subfoveal CT did not differ in eyes with and without atrophy, and with respect to control eyes ($p>0.05$), but CT was thinner in the areas involved by PPCRA.

Optical Coherence Tomography Angiography

Overall, OCTA quantitative analysis of the macula and optic disc showed similar values irrespective of the presence of macular atrophy. In particular, VD values turned out to be statistically significantly lower at the level of mDCP, mCC, nDCP, nCC, and mCC porosity (Table 3). Nevertheless, a more severe vascular impairment was found in eyes affected by macular atrophy.
On the other hand, the retinal regions affected by PPRCA, as visualized by FAF, were characterized by normal VD at the level of SCP and RPC, but significantly altered VD of DCP and CC, with higher CC porosity (Figure 2).
The correlation analysis is reported in Table 4. The presence of macular atrophy was significantly correlated with worse mDCP and mCC VD values (Tau Kendall coeff. -0.452; $p<0.05$ and Tau Kendall coeff. -0.464; $p<0.05$, respectively). Furthermore, the presence of peripapillary sparing was significantly correlated with higher nDCP and nCC VD values (Tau Kendall coeff. 0.562; $p<0.05$ and Tau Kendall coeff. 0.643; $p<0.05$, respectively). Furthermore, we found a significant correlation between the FAF patterns and the retinal vascular status. Outer retinal and choroidal impairments are shown in Figure 3.
Overall, repeatability and reproducibility of all the measurements performed was 0.92 (range 0.86-0.95) and 0.93 (range 0.87-0.96), respectively.

Discussion

PPCRA is a heterogeneous condition essentially characterized by the paravenous location of chorioretinal atrophic changes, which can vary in severity and extension. Several reports have described the variable clinical spectrum of the condition, ranging from focal paravenous involvement to extensive chorio-retinal impairment associated with central and/or peripheral visual loss.[4-7] Etiopathogenesis of PPCRA is unknown, even though the influence of genetic, inflammatory, infectious, and traumatic factors have been suggested.[4-6,9-17]
Some studies have hypothesized that choroidal involvement may represent a key factor in the pathogenesis of PPCRA, based on the detection of choroidal thinning on structural OCT.[4-6,21] In line with that finding, OCTA analyses have demonstrated the CC impairment, as shown in two case reports.[18,19] Nevertheless, no study has specifically focused on the global appraisal of the chorio-retinal vascular impairment occurring in PPCRA.
Our data indicate that PPCRA is characterized by remarkable vascular alterations, especially involving the DCP, both the macular region (with or without atrophy) and the affected paravenous areas, as demonstrated by the reduced DCP VD. The choroidal involvement is more gradual and variable, the mean CT resulting similar to control subjects at subfoveal level, but reduced in correspondence with the affected paravenous areas as visualized on FAF; whereas CC VD and CC porosity were altered both in the macula and in the affected paravenous areas.
The generalized partial preservation of the RPE band, along with the thinning of GCC and ONL in PPCRA cases showing no macular atrophy, corroborate the OCTA finding that the most involved vascular plexus is represented by the DCP.
Bearing in mind the well-established clinical heterogeneity of PPCRA, we hypothesize that the phenotypic appearance is influenced by many factors. Nevertheless, the paravenous location of the DCP vascular impairment could represent the chief alteration typical of PPCRA. In particular, the DCP originates from vessel projections of the SCP in correspondence with the retinal veins, whose development is influenced by local cues, including vascular endothelium growth factor, semaphorins and Notch signaling.[22-26]
Our results on OCTA demonstrate a specific impairment at the level of the DCP, which could in turn bring about a thinning of GCC and ONL. The alterations at the level of the CC and the choroid in general, could then represent a secondary effect.
Thus, PPCRA may be essentially regarded as a vascular disease with paravenous location, whose expressivity is modulated by concomitant conditions/modifying factors. Further studies regarding the complex interplay of cues regulating the vascular development and remodelling could provide more evidence regarding the pathogenesis of PPCRA. However, OCTA may be considered as a useful

biomarker to ascertain the severity of the vascular impairment and may have a role in determining prognosis.
We are aware that the present study has several limitations, especially taking into consideration the cross-sectional design of the investigation and the diagnostic techniques employed. Indeed, there is no prospective follow-up in an attempt to detail the timeframes of the vascular impairment. In addition, the investigation is burdened by the technical issues related to the OCTA imaging, which can be affected by several artifacts. Lastly, the number of patients may be too scant to ensure a conclusive assessment of the complexity of the vascular involvement in PPCRA.
In conclusion, our study demonstrated that PPCRA is characterized by vascular impairment on OCTA, especially involving the DCP, with a more mutable choroidal involvement.
Further studies are warranted to analyse the vascular alterations occurring in PPCRA over a longitudinal follow-up.

Figure legend
Figure 1: Multimodal imaging of focal pigmented paravenous chorioretinal atrophy. Fundus autofluorescence shows slight hyper-autofluorescent alterations localized in the paravenous regions (A). Structural optical coherence tomography is characterized by normal macular morphology and reflectivity profile (B). Optical coherence tomography angiography reveals a normal superficial capillary plexus (C), a remarkably rarefied deep capillary plexus (D), and a choriocapillaris with flow voids (E).
Figure 2: Multimodal imaging of a case of paravenous pigmented paravenous chorioretinal atrophy. Color fundus image shows an extensive depigmentation, mainly localized in the inferior peripapillary region (A). Fundus autofluorescence confirmed the typical hypo-hyperautofluorescent signals characterizing the disease (B). Structural optical coherence tomography is normal in the macular region,revealing the absence of the ellipsoid zone and the external limiting membrane, with partial preservation of the retinal pigment epithelium in correspondence of the altered region on fundus autofluorescence (C). Optical coherence tomography angiography is characterized by normal macular superficial capillary plexus, remarkably rarefied macular deep capillary plexus, and macular choriocapillaris with several flow voids (D). Furthermore, optical coherence tomography angiography unveils flow alterations in the radial peripapillary capillaries, with normal nerve superficial capillary plexus and altered nerve choriocapillaris (E). The selective evaluation of the regions affected by the disease shows normal superficial capillaries, almost absent deep capillaries and remarkably altered choriocapillaris (F and G, with retinal regions in blue and orange squares).
Figure 3: Outer retinal and choroidal status in paravenous pigmented paravenous chorioretinal atrophy. We show three different cases characterized by partially preserved RPE and thin choroid in the retinal regions characterized by PPRCA-related alterations. For each case (A, D, G, respectively), we show a horizontal foveal scan (B, E, H, respectively) and structural OCT scan better highlight the morphological features of retinal regions affected by PPCRA (C, F, I, respectively).

Table legend
Table 1. Demographic and clinical characteristics of patients affected by pigmented paravenous chorioretinal atrophy (PPCRA) and control subjects.
Legend: The following abbreviation was used: best corrected visual acuity (BCVA), females (F), males (M).
Table 2. Results of eyes affected by pigmented paravenous chorioretinal atrophy (PPCRA) on optical coherence tomography.
Legend: The following abbreviations are used: best corrected visual acuity (BCVA), fundus autofluorescence (FAF), central macular thickness (CMT), retinal nerve fiber layer (RNFL), ganglion cells complex (GCC), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), ellipsoid zone (EZ), external limiting membrane (ELM), retinal pigment epithelium (RPE), choroidal thickness (CT).

Table 3. Results of eyes affected by pigmented paravenous chorioretinal atrophy (PPCRA) on optical coherence tomography angiography.
Table 4. Correlation analyses of eyes affected by pigmented paravenous chorioretinal atrophy (PPCRA).

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