PIGMENTED PARAVENOUS CHORIORETINAL ATROPHY- DETAILED CLINICAL STUDY OF A LARGE COHORT

Abbreviated title: PPCRA-Detailed clinical study

Shona OA FWACS, FRCS[1], Farrah Islam FCPS FRCS[1,3], Anthony G. Robson PhD[1,2], Andrew R. Webster MD(Res) FRCOphth[1,2], Anthony T. Moore FRCOphth FMedSci [1,2,4], Michel Michaelides MD(Res) FRCOphth[1,2]

1. Moorfields Eye Hospital, London, UK.

2. University College London, Institute of Ophthalmology, University College London, UK.

3. Retina Department, Al-Shifa Trust Eye Hospital, Rawalpindi, Pakistan.

4. Ophthalmology Department, School of Medicine, University of California San Francisco, USA.

Corresponding author:

Prof. Michel Michaelides MD(Res) FRCOphth [1,2]

1. Medical Retina Service, Moorfields Eye Hospital, EC1V 2PD, London,

2. University College London, Institute of Ophthalmology, University College London, UK.

Email: michel.michaelides@moorfields.nhs.uk

michel.michaelides@ucl.ac.uk

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SUMMARY STATEMENT

PPCRA is a rare retinal disorder of uncertain pathogenesis. In this large case series, we highlighted the characteristic clinical features. The absence of family history, the lack of progression in the majority of patients, and the asymmetry of the retinal findings supports the contention that PPCRA is likely an acquired rather than inherited retinal disorder.

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ABSTRACT:

Purpose: To review and describe in detail the demographics, functional and anatomical characteristics, and clinical course of Pigmented Paravenous Chorioretinal Atrophy (PPCRA) in a large cohort of adults and children.

Methods: This is a retrospective case series of consecutive patients diagnosed with PPCRA at a single UK referral centre from 1974 to 2016**.** Clinical records, retinal imaging (color fundus photography, fundus autofluorescence (FAF), and optical coherence tomography (OCT)), and electrophysiological assessments were reviewed.

Results: Twenty-three patients were identified (13males and 10females). The mean age at presentation was 35 years (range 10-67years). Mean follow-up was 6.7 years (range 0-30 years). There was no family history of similar retinal disease. Thirteen (57%) patients were asymptomatic. Symptoms included photopsia(n=1, 4%), blurred vision (n=4, 17%), peripheralvisual field loss(n=3,13%), and nyctalopia (n=2, 8%).Onepatient had previous intermediate uveitis. Twenty-one (91%) patients had ≥ 6/12 in the better seeing eye at final follow-up; visual acuity loss over time was recorded in 2 patients. Colour vision was normal in all 14 patients assessed. Paravenous hypo-autofluorescence with surrounding increased FAFwas characteristically observed. OCT over the retinal changes demonstrated choroidal, RPE and outer retinal layer thinning. Peripapillary atrophic changes on fundus photography was evident in 20 (87%) patients. Interocular asymmetry of fundus and electroretinography (ERG) findingswas common. The ERGs showed a similar degree of generalised rod and cone photoreceptor dysfunction in the majority of cases.

Conclusions: Overall most patient with PPCRA maintained stable vision. The lack of other affected family members, slow or absent progression, and interocular asymmetry of the retinal features is suggestive of an acquired rather than inherited retinal disorder. generally non-progressive disorder. We identify that patients commonly have marked inter-ocular asymmetry both on structural and functional assessment.

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INTRODUCTION

Pigmented paravenous chorioretinal atrophy (PPCRA) is a rare form of chorioretinal atrophy in which there is bilateral paravenous retinal pigment epithelial atrophy and pigment clumping.[1] It was first termed retino-choroiditis radiata in 1937.[2] Since then a limited number of small case series have been published.[1,3-7] It has been reported to be more common in males, most published cases are sporadic, and it is usually diagnosed on routine examination in asymptomatic patients.[8,9] Vision is generally normal or mildly reduced at presentation, with minimal to no progression described over time.[5] Diagnosis is based on the characteristic appearance on fundus examination, although detailed retinal imaging and retinal electrophysiology are helpful in confirming the diagnosis. [8] Electroretinography (ERG) shows a spectrum of abnormalities and in contrast to most inherited retinal dystrophies often shows marked interocular asymmetry.

There are several hypotheses regarding the cause, with uncertainty about whether this has a genetic or inflammatory/infectious aetiology. There is only rarely a family history but there has been one report of a heterozygous *CRB1* mutation of uncertain significance identified in a family with apparently dominantly inherited PPCRA with variable expressivity [10]. Perivascular atrophy has also been described in autosomal dominant retinitis pigmentosa (RP) associated with mutations in the *TOPORS* gene but the retinal appearance is atypical for PPCRA.[11] In contrast, in one report the monozygotic twin of an affected adult was unaffected, suggesting that at least some cases are non-genetic.[12]

Given the limited descriptions of small case series in the literature to date, there is a need to improve our knowledge of this rare disease. Our study reviews the functional and anatomical characteristics of PPCRA in the largest cohort to date seen at a single center, with the aim of providing a detailed description of demographics, presentation, associations, phenotype and natural history of PPCRA.

METHODS

The study adhered to the tenets of the Declaration of Helsinki and was approved by the Moorfields Eye Hospital ethics committee. We retrospectively reviewed records of patients diagnosed with PPCRA at Moorfields Eye Hospital between 1974 and 2016. The diagnosis

of PPCRA was based on the presence of a characteristic fundus appearance of chorioretinal atrophy with variable pigmentation along the retinal veins in one or both eyes.

The clinical data reviewed included age of onset, ethnicity, gender, presence of symptoms, duration of follow up, previous ocular inflammation, family history of inherited eye disease, visual acuity, color vision, color fundus photography (CFP), fundus autofluorescence (FAF) imaging, optical coherence tomography (OCT) and electrophysiological assessment.

The age of onset was defined as the age at which the retinal changes were first noted. Duration of the disease was defined as the difference between the age of onset and the most recent examination. Best-corrected vision was measured using the Snellen visual acuity chart. Color vision was assessed using Ishihara pseudo-isochromatic plates.

Fundus photographs were obtained with either a TRC-50LA Retinal fundus camera (Topcon Tokyo Japan) or Optos wide-field camera (Optos Panoramic 200; Optos PLC., Dunfermline, Scotland, United Kingdom). Fundus autofluorescence(FAF) images were obtained with either Spectralis HRA OCT; (Heidelberg Engineering, Heidelberg, Germany) or Optos wide-field camera. Retinal lamination and central retinal thickness was evaluated using the Spectralis HRA OCT (Heidelberg Engineering, Heidelberg, Germany). Eighteen of 23 patients underwent ERG testing. Full-field and pattern electroretinogram (ERG; PERG) were performed in most with gold foil recording electrodes. Additional multifocal electroretinogram (mfERG) and electro-oculogram (EOG) were performed in some. The electrophysiology incorporated the ISCEV (International Society for Clinical Electrophysiology of Vision) standard protocols[13-17] except in 1 young patient that underwent ERG testing with skin electrodes without mydriasis using a previously reported protocol. [17]

RESULTS

Twenty- three patients; 10 females and 13 males with the diagnosis of PPCRA were identified. The ethnic background was diverse with 15 White (66%), 4 Asian (18%), 1 Turkish (4%), 1 Colombian (4%), 1 Nigerian (4%) and 1 Chinese (4%) patient. Mean age of onset was 36.6 years (range 10-67 years). The mean follow up period was 5.3 years (range, 0-30 years) – with two patients only attending a single visit. General clinical, structural and functional characteristics of the entire cohort are described below (summarised in Tables 1, 2 and 3, with representative imaging and electrophysiology in Figures 1,2 and supplementary figures 3 to 6), with subsequent selection of specific patients of particular interest for further discussion.

There was no family history of inherited eye disease in 22/23 (96%). One patient (Pt 13), who had been diagnosed as having retinitis pigmentosa(RP) by the referring physician, had a mother reported to have tunnel vision. Her 2 sons (age 2 and 4 years) were examined and found to have a normal fundus appearance. One patient (Pt 17) had a previous history of a positive Quantiferon gold test and intermediate uveitis but declined anti TB treatment. In patient 4, PPCRA was noted 3 years following generalized flu-like symptoms, encephalitis, and optic neuritis, which developed 3 weeks post mumps measles and rubella (MMR) immunisation at age 4 years. He was noted to have retinal edema at the time of presentation with optic neuritis.

Thirteen (57%) patients were asymptomatic. In patients who were symptomatic the presenting symptoms included photopsia (n=1, 4%), blurred vision (n=4, 17%), peripheral visual field loss (n=3, 13%), and nyctalopia (n=2, 9%). The majority of patients had no refractive error noted (n=17, 74%), with myopia in 5 of 6 patients with refractive error. At baseline,78% (n=18/23) of patients had visual acuity of ≥ 6/12 in each eye; and at final follow up ≥ 6/12 in 71% (n=15/21) patients in the right eye and 86% (n=18/21) in the left eye (Table 1). Color vision was normal in the 14 patients who had this assessed. Color fundus photographs (CFP) were available for 22 patients and FAF imaging for 20 patients at baseline. Retinal changes were asymmetrical in 16 (76%) of the 21 patients who had PPCRA in both eyes.

Selected Representative Patients

Case 1 - A ten-year-old boy was referred by his optician who noted retinal pigmentation on routine assessment. He was visually asymptomatic with a visual acuity of 6/5 in each eye. Retinal examination, retinal imaging, and perimetry revealed highly asymmetrical retinal findings in keeping with PPCRA, with normal macula and discs (Figure 1). Full-field ERGs were asymmetrical, consistent with generalised rod and cone photoreceptor dysfunction on the right and a mild loss of rod photoreceptor function on the left. There was no PERG evidence of macular dysfunction in either eye. Visual acuity, retinal appearance, imaging, and perimetry were all stable with no evidence of progression in either eye four years later.

Case 4 - At 4 years of age, 3 weeks post MMR immunization, he developed a flu-like illness, skin rash and reduced vision. Information from his referring physician indicated bilateral retinal oedema and abnormal visual evoked potentials and ERG, with a suspected coexisting optic neuritis. Magnetic resonant imaging of the brain was normal. Retinal oedema settled following treatment with intravenous steroids but he was noted to have developed a pigmented paravenous retinopathy 3 years later. He reported no deterioration of vision. At

presentation to us at 16 years of age, his visual acuity was 6/12 right, 6/6 left. Anterior segment was normal. Retinal examination showed pigmentary changes/clumps along the retinal veins and peripapillary area, to a greater extent in the right eye than left (Figure 1). OCT scans were normal and FAF imaging showed areas of reduced signal corresponding to the areas of retinal pigmentation (Figure 1). There was ERG evidence of generalised retinal dysfunction affecting rod more than cone systems bilaterally, at the level of the photoreceptors and additionally at a level that is post-phototransduction or inner retinal. Pattern ERGs were consistent with macular involvement bilaterally. At 12 months vision and retinal imaging were stable. Estermann binocular visual field testing identified only 2 missed test areas in the tested field of 120 degrees. Furthermore, no significant scotoma within or encroaching the central 20 degrees were seen as shown in Figure 5 (bottom row).

Case 11 - This 70-year-old man was diagnosed with retinitis pigmentosa by his local ophthalmologist 41 years prior to presentation 10 years ago. He had longstanding symptoms of loss of peripheral vision. He was unable to take his driving test because he failed to read the number plate at the required distance. He described problems with night vision. He retained good central vision until 3 years prior to presentation. There was no family history of visual problems. His four children and grandchildren were asymptomatic. His visual acuity was 6/60 in the right eye and HM in the left eye. There was bone spicule pigmentation around the blood vessels in both eyes and atrophic changes around the discs (Figure 2). There were areas of atrophy in the right macula. Three years later new small intraretinal cysts at the fovea in the right eye were noted which resolved without treatment (Figure 2).

Case 15 - 21-year-old woman presented with symptoms of photopsia and floaters which subsided over a short period. She reported no symptoms of night blindness. At the age of 11 years she was diagnosed elsewhere with a retinal dystrophy but has maintained stable vision. There was no family history of inherited eye disease. Perivascular pigment clumping radiating from the optic discs was evident in both eyes, left more than right eye (Figure 1). The disc appearance and vessel calibre was normal. She had bilateral generalised rod photoreceptor dysfunction on electrophysiological assessment. Visual field testing revealed full fields at baseline and 2 years later.

Case 17 - A 31-year-old woman who had experienced symptoms of flashing lights in her right eye for 6 years prior to presentation. She had been treated previously with oral steroids for intermediate uveitis/periphlebitis in the right eye. She had a positive Quantiferon gold and declined treatment for TB. Examination of the right eye revealed rare cells in the anterior chamber with pigmented keratic precipitates. The anterior vitreous also showed a trace of

cells. Fundus examination showed retinal pigmentary changes along the veins in the right eye only, with a vitreous condensation inferiorly (Figure 2). She had constricted right visual field and normal visual field in the left. There was ERG evidence of generalised rod and cone photoreceptor dysfunction in the right eye only. Pattern ERG and multifocal ERG were consistent with macular dysfunction on the right, worst over paracentral areas. Her symptoms and clinical findings have remained stable at 7 years follow-up.

Fundus appearance

We identified 2 characteristic fundus appearances: 1) Paravenous choroidal atrophic changes with pigment migration/clumping/bone spicule formation, ranging from mild to severe (Figures 1 and supplementary figure 3; patients 19, 4, and 14); and 2) Paravenous choroidal atrophic changes without pigmentary disturbance (supplementary Figure 3; patient 17). Twenty (87%) patients had normal optic disc appearance. Patient 4 who had a previous history of optic neuritis had bilateral temporal disc pallor (Figure 1). Patient 5, with bilateral extensive chorioretinal pigmentary paravenous changes and macular involvement had bilateral disc pallor (Table 1, supplementary Figure 5) and patient 23 had bilateral optic disc drusen. Peripapillary involvement with atrophy or pigmentation was commonly observed (n=20, 87%).

Fundus autofluorescence pattern

We identified 4 principal patterns of fundus autoflourescience(FAF):

1) **Type 1a:** Continuous absent/reduced FAF signal along the large retinal veins in a geographic manner surrounded by linear increased FAF of varying thickness extending to the periphery (more apparent on FAF than clinically or fundus photographs) (Figure 1, patient 4).

2) **Type 1b:** In contrast to Type 1a – a primarily continuous *increased* FAF signal along the large retinal veins in a geographic manner of varying thickness extending to the periphery (Figure 1, patient 15).

3) **Type 2:** *Focal* decreased or absent signal (discontinuous) along the retinal veins with normal intervening signal (Figure 1, patients 13 and 19).

4) **Type 3*:*** Extensive areas of decreased/absent paravenous FAF signal coalescing and extending beyond the vasculature with chorioretinal involvement into the periphery +/- macular involvement (Supplementary Figure 3, patients 9 and 14).

In our cohort, type 1 was the most common pattern observed (n=11/20, 55%). Type 2 and type 3 were each observed in 5/20 (25%) and 4/20 (20%)patients respectively.

Optical coherence tomography

Macular optical coherence tomography(OCT) images were available in 18/23 patients, with 4/18 (22%) being normal. The macular changes varied from mild to severe disruption of the outer retina and RPE, and/or choroidal thinning (supplementary eFigures 3, 4 and 6). The most common finding was attenuation of all outer retinal and choroidal layers. Patient 11 (supplementary eFigure 3) with extensive PPCRA changes had macular intra-retinal cysts which resolved without treatment over 3 years.

OCT imaging of PPCRA-associated lesions was available in 2 patients (Supplementary efigure 4, patient 23; and supplemenatary eFigure 6, patient 2). Variable lamination was observed including: 1) thinning of the outer retinal layers corresponding to areas of increased FAF signal; 2) normal, disruption, or loss of RPE in the areas of decreased or absent FAF; 3) focal or generalised choroidal thinning associated with aforementioned outer retinal disturbance patterns.

Electrophysiology

Electrophysiological assessment was undertaken in 18 of 23 patients and the findings are summarised in Table 3, Figure 2 and Supplementary e Figures 7. Full-field ERGs were abnormal in 18 cases (Table 3 and Figure 2), consistent with generalised retinal dysfunction; these included 5 with bilaterally abnormal but markedly asymmetrical ERGs (cases 1, 3, 7, 8 and 12), 2 with unilateral retinal dysfunction (asymmetrical) (cases 16 and 22), and a further 2 with borderline ERG parameters in the better eye (cases 2 and 19). The inter-ocular asymmetries in the main ERG parameters are highlighted in Supplementary figure 7(b). Comparison of dark-adapted (DA) and light-adapted (LA) ERGs showed a similar degree of generalised rod and cone system dysfunction in most cases, but 5 eyes of 3 individuals showed ERG evidence of slightly greater rod than cone system involvement. There was evidence of both photoreceptor dysfunction (DA10 ERG a-wave reduction) and additional dysfunction occurring post-phototransduction or at the level of the inner retinal (b-wave reduction relative to the a-wave) in 6 eyes of 4 individuals, and in 1 (case 21) there was evidence of generalised On-bipolar cell dysfunction of both rod and cone systems, with preservation of photoreceptor function bilaterally. Most cases showed delay in the 30Hz flicker (LA 30Hz) ERG, asymmetrical (3ms or more difference) in 5 cases (Figure 2 and supplementary Figure 7a), and generally most delayed in those with the worst amplitude reduction. In the two patients with unilateral PPCRA, ERGs were normal in the other eye of

case 17 and borderline in the other eye of case 16. The EOG light peak to dark trough ratio was abnormal in 8 of 12 eyes tested and was borderline in one other eye; in no case was the reduction disproportionate to DA 10 ERG a-wave reduction.

Nine of 17 patients had pattern ERG P50 reduction consistent with bilateral macular dysfunction and a further two had unilateral P50 reduction (amplitude subnormal or significantly asymmetrical). In 3 cases (5 eyes) additional mfERGs indicated reduced responses that were most severe over paracentral areas. The severity of PERG reduction was not directly related to full-field ERG parameters; pattern ERGs were normal in 12 eyes with moderately severe to severe generalised retinal dysfunction, and were significantly subnormal in 6 eyes of 3 subjects with normal or near-normal ERGs. There was bilateral P50 reduction in one patient with unilateral PPCRA (case 16).

Serial ERG testing in cases 1, 8, 17 and 21 over periods of 2, 10, 14 and 15 years respectively, revealed a high degree of stability in both eyes (supplementary Figure 7b). Over the same periods pattern ERG P50 was stable bilaterally in case 1, showed mild worsening in both eyes of case 8, mild worsening in the right eye of case 17 and in case 21, the left eye P50 showed significant improvement after 10 years following treatment with Tacrolimus.

DISCUSSION

Pigmented paravenous chorioretinal atrophy (PPCRA) is a rare disorder with limited published descriptions to date. We present detailed clinical and imaging data in a large cohort of 23 affected patients seen at a single center, highlighting the interocular structural and functional asymmetry and non-progressive nature. There were no cases of families with more than one affected member consistent with an acquired rather than genetic aetiology.

Most patients were visually asymptomatic and the diagnosis was based on the characteristic fundus appearance, often detected on routine eye examination. [5,7,8]Two-thirds of the patients in our series were asymptomatic. Those with symptoms presented with complaints such as flashing lights, nyctalopia and loss of peripheral vision and showed more severe retinal changes. The average age at diagnosis was 36 years, the youngest being 10 years of age in our series, with no gender predilection.

The underlying basis of PPCRA is controversial, and includes genetic and post-inflammatory aetiologies[1,10]. McKay et al reported a heterozygous *CRB1* variant of uncertain significance identified in a family with apparently dominantly inherited PPCRA with variable expressivity. This variant was identified using Sanger sequencing of a positional candidate gene. It is feasible that this is not the causative variant and further investigation of the family using next generation sequencing may highlight another causative gene[18]. Obata et al described PPCRA in 2 Japanese siblings with different manifestation, where the brother was more affected than the sister[1]. Others have proposed degenerative[6], developmental[19] , vascular, or congenital aetiologies.[20]. Prior infection / inflammation has been proposed previously as causative including Tuberculous, congenital Syphilis, Bechet's, Measles, and Rubella.[8 21,22] Murray reported a 17-year-old Caucasian female who developed PPCRA after an episode of retinal swelling but no intraocular inflammation with resultant poor visual outcome after 20 years of follow up.[7] One child in our series similarly developed PPCRA following retinal oedema and optic neuritis that occurred after MMR vaccination. Slowly progressive PPCRA-like changes in two middle aged women with active bilateral panuveitis of several years duration of unknown aetiology have also been described.[21 23] The role of inflammation remains unclear, but interestingly patient 17 in our series developed PPCRA in the same eye that had previous active intraocular inflammation secondary to TB. However, it was not possible to ascertain if the PPCRA changes were present before the ocular inflammation because both were discovered simultaneously. Another patient(21) with intermediated uveitis treated with prednisolone and Mycophenolate mofetil for 10 years showed improvement clinically and on PERG after additional 9 months course of tacrolimus.HLA A29 and antiretinal antibodies were negative. There are no previous reports of an association with immunisation. Patient 4 who developed flu-like symptoms, retinal oedema and reduced vision 3 weeks after MMR immunisation, was subsequently noted to have bilateral PPCRA. This raises the possibility of a post-inflammatory mechanism, given the association between inflammatory disease, including optic neuritis, and various vaccinations.[24-26]

Several authors have attempted to classify PPCRA based on natural history, presumed aetiology (primary or secondary such as post inflammatory)[21,23,27], and/or severity (mild, moderate, severe). In our cohort the fundus appearance was variable – ranging from mild retinal changes including pigment clumps, chorioretinal paravenular disturbance, and sparing of the peripapillary region; to increasingly prominent retinal disturbance and peripapillary involvement ('severe' PPCRA). Of note, we only observed progression in one patient over a 10-year period. The macula is seldom clinically involved thereby accounting for the often good visual acuity – although there was evidence of macular disturbance on

spectral domain(SD-OCT) in 14/18 (88%) patients in our cohort. Despite these OCT changes most (86%) retained a VA ≥ 6/12 at final follow up.

Normal optic discs and retinal vessel calibre is commonly observed in PPCRA as noted in our series in 90% of our patients, in direct contrast with RP. Macular changes including cystoid macular oedema (CMO) and/or epiretinal membrane (ERM) are common in RP, occurring in approximately 20% of patients with RP.[28] Mild CMO was noted in only one patient in our cohort who had extensive chorioretinal changes – with CMO resolution without treatment after 3 years. There is no previous documentation of CMO in PPCRA in the literature, the pathogenesis of which might be similar to CMO in RP.[29,30]

In all patients FAF changes were more obvious and extended to the periphery beyond the clinically evident paravenous chorioretinal changes. In some 'milder' cases only hypo-autofluorescence was evident rather than additional surrounding increased signal. SD-OCT imaging over the PPCRA lesions have shown thinning of the choroidal, RPE, outer retinal[8] and inner retinal layers.[31] The RPE may be the primary layer affected given the aforementioned hypo-autofluorescence. However, Bartesilli demonstrated choroidal thinning in a 25 years old Japanese with early PPCRA, in areas where RPE was unaffected associated with visible overlying thinning of the entire outer retina[32] suggesting that in the early/mild stages of PPCRA choroidal thinning precedes development of definite RPE atrophy. It was hypothesised that decreased choroidal perfusion secondary to choroidal thinning may lead to insufficient metabolic supply for the outer retinal structures leading to thinning and atrophy of the photoreceptors first and then the RPE later. In contrast, Ahmed et al, showed a thickened cystic retinal nerve fibre layer on SD-OCT in a 79 years old woman with uniocular PPCRA which they believed supported a vascular aetiology rather than an RPE based cause.[33] We found no such changes in our series.

Previously reported visual field findings have ranged from normal to severe constriction – often associated with the severity of observed retinal changes, and usually corresponding to the areas of retinal atrophy [23,34]. In our cohort, perimetry was performed in only 7 cases and ranged from normal, to enlarged blind spot, to peripheral visual field defects. We did not observe a definite progression in visual field loss over time in our cohort.

A wide range of ERG abnormalities have been documented in PPRCA, from normal to undetectable responses,[8] but mostly using older or non-standard ERG methods. In our series ISCEV-standard full-field ERGs in most showed evidence of generalised retinal dysfunction with a similar degree of rod and cone system involvement, and significant inter-

ocular ERG asymmetry was common. Generalised photoreceptor dysfunction occurred in the majority but some showed evidence of additional or predominant inner retinal dysfunction. In contrast, patients with RP typically have ERG evidence of predominant rod photoreceptor dysfunction (rod-cone dystrophy), with a high degree of inter-ocular symmetry. One patient (case 21) had evidence of generalised inner retinal dysfunction affecting rod and cone On-bipolar function. Similar but more severe On-bipolar dysfunction may be associated with melanoma-associated retinopathy and some cases of presumed autoimmune retinopathy [35-37]and it is tempting to speculate a post-inflammatory or autoimmune aetiology. There are isolated accounts of PERG findings in PPCRA including reports of absent responses [7] and PERG N95 loss suggesting retinal ganglion cell dysfunction.[23] In our series there was a high incidence of PERG P50 reduction, varying in severity and including cases of unilateral and asymmetrical macular dysfunction. It is notable that EOG abnormality was broadly in keeping with DA ERG a-wave reduction, suggesting generalised dysfunction of the photoreceptor/RPE interface rather than primary or selective generalised RPE dysfunction, as has been reported in some other forms of asymmetrical retinopathy such as acute zonal occult outer retinopathy (AZOOR).[38]

Our study has several inherent limitations given its retrospective nature, with other weaknesses including the limited visual field data. It has many strengths including being a large series, with high quality multi-modal imaging and ISCEV standard ERGs in the majority of patients, and serial assessments over time.

In this large series of patients with PPCRA we show that most patients with PPCRA retain stable vision over time, with minimal if any definite evidence of structural or functional progression. There was no strong evidence of a genetic basis and we observed that inter-ocular structural and functional asymmetry is common.

REFERENCES

1. Obata R, Yanagi Y, Iriyama A, Tamaki Y. A familial case of pigmented paravenous retinochoroidal atrophy with asymmetrical fundus manifestations. *Graefe's archive*

for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie. 2006;244(7):874-877.
2. Brown TH. RETINO-CHOROIDITIS RADIATA. *The British journal of ophthalmology.* Dec 1937;21(12):645-648.
3. Noble KG, Carr RE. Pigmented paravenous chorioretinal atrophy. *American journal of ophthalmology.* 1983;96(3):338-344.
4. Johansen J, Lund-Andersen C, Autzen T. Pigmented paravenous chorioretinal atrophy. *Acta ophthalmologica.* 1988;66(4):474-477.
5. Kukner AS, Yilmaz T, Celebi S, Aydemir O, Ulas F. Pigmented paravenous retinochoroidal atrophy. A literature review supported by seven cases. *Ophthalmologica. Journal international d'ophtalmologie. International journal of ophthalmology. Zeitschrift fur Augenheilkunde.* Nov-Dec 2003;217(6):436-440.
6. Lessel MR, Thaler A, Heilig P. ERG and EOG in progressive paravenous retinochoroidal atrophy. *Documenta ophthalmologica. Advances in ophthalmology.* 1986;62(1):25-29.
7. Murray AT, Kirkby GR. Pigmented paravenous retinochoroidal atrophy: a literature review supported by a unique case and insight. *Eye Lond Engl14 Pt.* 2000;5 SRC - GoogleScholar:711-716.
8. Huang H-B, Zhang Y-X. Pigmented paravenous retinochoroidal atrophy (Review). *Experimental and therapeutic medicine.* 2014;7(6):1439-1445.
9. Foxman SG, Heckenlively JR, Sinclair SH. Rubeola retinopathy and pigmented paravenous retinochoroidal atrophy. *American journal of ophthalmology.* May 15 1985;99(5):605-606.
10. McKay GJ, Clarke S, Davis JA, Simpson DAC, Silvestri G. Pigmented paravenous chorioretinal atrophy is associated with a mutation within the crumbs homolog 1 (CRB1) gene. *Investigative ophthalmology & visual science.* 2005;46(1):322-328.
11. Chakarova CF, Papaioannou MG, Khanna H, et al. Mutations in TOPORS cause autosomal dominant retinitis pigmentosa with perivascular retinal pigment epithelium atrophy. *American journal of human genetics.* Nov 2007;81(5):1098-1103.
12. Small KW, Anderson W, Jr. Pigmented paravenous retinochoroidal atrophy: Discordant expression in monozygotic twins. *Archives of Ophthalmology.* 1991;109(10):1408-1410.
13. McCulloch DL, Marmor MF, Brigell MG, et al. ISCEV Standard for full-field clinical electroretinography (2015 update). *Documenta ophthalmologica. Advances in ophthalmology.* Feb 2015;130(1):1-12.
14. Bach M, Brigell MG, Hawlina M, et al. ISCEV standard for clinical pattern electroretinography (PERG): 2012 update. *Documenta ophthalmologica. Advances in ophthalmology.* Feb 2013;126(1):1-7.
15. Constable PA, Bach M, Frishman LJ, Jeffrey BG, Robson AG. ISCEV Standard for clinical electro-oculography (2017 update). *Documenta ophthalmologica. Advances in ophthalmology.* Feb 2017;134(1):1-9.
16. Hood DC, Bach M, Brigell M, et al. ISCEV guidelines for clinical multifocal electroretinography (2007 edition). *Documenta ophthalmologica. Advances in ophthalmology.* Jan 2008;116(1):1-11.
17. AG HGaR. *Paediatric electrophysiology: a practical approach.* Berlin: Springer-Verlag; 2006.
18. de Pavert SA. van A single amino acid substitution (Cys249Trp) in Crb1 causes retinal degeneration and deregulates expression of pituitary tumor transforming gene Pttg1. *J Neurosci Off J Soc Neurosci.* 2007;27 SRC - GoogleScholar:564-573.

19. Chen MS, Yang CH, Huang JS. Bilateral macular coloboma and pigmented paravenous retinochoroidal atrophy. *The British journal of ophthalmology.* 1992;76(4):250-251.
20. Small KW, Anderson WB. Pigmented paravenous retinochoroidal atrophy. Discordant expression in monozygotic twins. *Archives of ophthalmology (Chicago, Ill. : 1960).* 1991;109(10):1408-1410.
21. Yamaguchi K, Hara S, Tanifuji Y, Tamai M. Inflammatory pigmented paravenous retinochoroidal atrophy. *The British journal of ophthalmology.* 1989;73(6):463-467.
22. Haustrate FM, Oosterhuis JA. Pigmented paravenous retinochoroidal atrophy (PPRA). *Documenta ophthalmologica. Advances in ophthalmology.* 1986;63(3):209-237.
23. Batioglu F, Atmaca LS, Atilla H, Arslanpençe A. Inflammatory pigmented paravenous retinochoroidal atrophy. *Eye (London, England).* 2002;16(1):81-84.
24. Karussis D, Petrou P. The spectrum of post-vaccination inflammatory CNS demyelinating syndromes. *Autoimmunity reviews.* 2014;13(3):215-224.
25. Stübgen J-P. A literature review on optic neuritis following vaccination against virus infections. *Autoimmunity reviews.* 2013;12(10):990-997.
26. Sudarshan S, Huang EHZ, Lim PL, Leo YS, Lim SA. A case of post-vaccination optic neuritis: coincidence or causative? *Eye (London, England).* 2012;26(11):1498.
27. Hildebrand GD, Taylor D, Thompson D, Russell-Eggitt I. A clinical classification system for paravenous pigmentary chorioretinal atrophy (PPCRA) in childhood. *J Am Assoc Pediatr Ophthalmol Strabismus JAAPOS15 e.*21(2011 SRC - GoogleScholar).
28. Fishman GA, Maggiano JM, Fishman M. Foveal lesions seen in retinitis pigmentosa. *Archives of ophthalmology (Chicago, Ill. : 1960).* 1977;95(11):1993-1996.
29. Heckenlively JR, Solish AM, Chant SM, Meyers-Elliott RH. Autoimmunity in hereditary retinal degenerations. II. Clinical studies: antiretinal antibodies and fluorescein angiogram findings. *The British journal of ophthalmology.* 1985;69(10):758-764.
30. Strong S, Liew G, Michaelides M. Retinitis pigmentosa-associated cystoid macular oedema: pathogenesis and avenues of intervention. *The British journal of ophthalmology.* Jan 2017;101(1):31-37.
31. Junqueira DLM, Lopes FSS, Biteli LG, Prata TS. Pattern of inner retinal layers involvement in pigmented paravenous retinochoroidal atrophy as determined by SD-OCT: case report. *Arquivos brasileiros de oftalmologia.* 2013;76(6):380-382.
32. Barteselli G. Fundus autofluorescence and optical coherence tomography findings in pigmented paravenous retinochoroidal atrophy. *Canadian journal of ophthalmology. Journal canadien d'ophtalmologie.* 2014;49(6):e144-146.
33. Ahmed AS, Rishi P. A rare presentation of pigmented paravenous retinochoroidal atrophy. *Oman journal of ophthalmology.* 2015;8(1):47-49.
34. Parafita M, Diaz A, Torrijos IG, Gomez-Ulla F. Pigmented paravenous retinochoroidal atrophy. *Optometry and vision science : official publication of the American Academy of Optometry.* 1993;70(1):75-78.
35. Berson EL, Lessell S. Paraneoplastic night blindness with malignant melanoma. *American journal of ophthalmology.* Sep 15 1988;106(3):307-311.
36. Alexander KR, Fishman GA, Peachey NS, Marchese AL, Tso MO. 'On' response defect in paraneoplastic night blindness with cutaneous malignant melanoma. *Investigative ophthalmology & visual science.* Mar 1992;33(3):477-483.
37. Robson AG, Richardson EC, Koh AH, et al. Unilateral electronegative ERG of non-vascular aetiology. *The British journal of ophthalmology.* Dec 2005;89(12):1620-1626.

38. Francis PJ, Marinescu A, Fitzke FW, Bird AC, Holder GE. Acute zonal occult outer retinopathy: towards a set of diagnostic criteria. *The British journal of ophthalmology*. Jan 2005;89(1):70-73.

LEGENDS

FIGURE 1: Color fundus photography and fundus autofluorescence imaging of Patients 1, 3, 4, 15, 13, and 19 with PPCRA.

Top and second rows: Patients 1 and 3 with bilateral asymmetrical PPCRA and paravenous hypoautofluorescence on fundus autofluorescence (FAF) imaging surrounded by linear hyperautofluorescence (Type 1 pattern). Third and fourth rows: Patients 4 and 15 with bilateral asymmetrical PPCRA, to a different degree on color fundus photography compared to FAF, with Type 1 FAF pattern. Fifth and sixth rows: Patients 13 and 19 demonstrating localised areas of retinal disturbance with normal chorioretinal paravenous area in between lesions (Type 2 FAF pattern).

FIGURE 2:Comparison of main dark adapted electroretinogram (DA) ERG and light adapted electroretinogram (LA ERG) amplitude parameters in 16 patients that underwent ISCEV-std testing.

Comparison of LA 30 Hz ERG peak times (N=16) case 22 is excluded (ERGs performed at a different institution.

Supplementary File.doc

Figure 3 (Supplementary): Color fundus photography, fundus autofluorescence imaging, and optical coherence tomography of Patients 9, 11, 14, 16, and 17 with PPCRA.

Figure 4 (Supplementary): Color fundus photography, fundus autofluorescence imaging, and optical coherence tomography of Patients 3, 9, 12, and 23 with PPCRA.

Figure 5 (Supplementary): Serial color fundus photography over time in Patients 9 and colour fundus photos of Patient 5 with PPCRA.

Figure 6 (Supplementary): Color fundus photography, fundus autofluorescence imaging, optical coherence tomography, and static visual fields of Patient 2 with PPCRA.

Figure 7 (Supplementary): Interocular differences in ISCEV-std full fields ERG parameters and serial ERGs in cases in cases 3, 8, 7 ,21