Unilateral pigmentary retinopathy : a retrospective case series

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Abstract:

Purpose: To review the clinical characteristics of patients with unilateral pigmentary retinopathy (UPR).

Methods: The cohort of 42 patients was identified retrospectively. All had undergone full-field (ERG) and pattern (PERG) electroretinography, with 13 additionally having multifocal electroretinography (mfERG). The clinical findings, fundus photographs, and fundus autofluorescence (AF) images were reviewed.

Results: All index eyes showed ERG evidence of generalized photoreceptor dysfunction with most showing a similar degree of rod and cone involvement. However, the fellow eyes were reported as normal at fundus examination, there were bilateral but asymmetrical ERG abnormalities in 8 patients and a further 4 patients had PERG evidence of macular dysfunction in the fellow eye. A relevant medical history or the diagnosis of an ophthalmologic entity that might be related to the unilateral fundus changes was ascertained in 15 cases (~36%) including AZOOR, trauma, systemic malignancy or autoimmune disease, retinal vasculitis, presumed pregnancy-related choroidal ischemia and meningitis. Two patients had a family history of retinitis pigmentosa (RP) (4.8%).

Conclusion: The underlying etiology in most cases of unilateral pigmentary retinopathy cannot accurately be identified but is unlikely to be heritable. Aspects of the history clearly suggest an acquired disorder in some patients. Twenty-five patients (60%) with non-genetic UPR did not adhere to the pattern of rod greater than cone dysfunction as noted in RP. The pattern of rod>cone dysfunction seen in true RP is not a feature of most patients with UPR.

Key words: Acute Zonal Occult Outer Retinopathy, ERG**,** ocular trauma, retina, unilateral pigmentary retinopathy, uveitis

Introduction

Pigmentary retinopathy is a frequent feature of retinitis pigmentosa (RP, rod-cone dystrophy), a highly heterogeneous group of heritable photoreceptor degenerations with a prevalence of approximately 1 in 4000 (Berson 1993). Despite the extensive genetic heterogeneity, there are common clinical features that include intra-retinal pigment migration, optic disc pallor and attenuated retinal blood vessels. Patients usually present with nyctalopia or peripheral visual field loss or, rarely, with reduced visual acuity (VA).

RP is usually bilateral, and although there are reports of "unilateral RP" in the literature, there are only two genetically confirmed cases (Sim et al. 2018; Mukhopadhyay et al. 2011). One recent study described 14 cases of "unilateral RP", bringing the total number of cases in the literature to less than 100 since 1865, but without genetic confirmation of the diagnosis (Farrell et al. 2009). However, there are several acquired retinal disorders with fundoscopic features that mimic RP, including those arising on a post-traumatic or post-inflammatory basis and unilateral "pseudo retinitis pigmentosa" has previously been reported in association with choroidal melanoma (Lommatzsch et al. 1988); ocular trauma (Bastek et al. 1981); forceps related birth trauma (Mann 1957); drug toxicity (chloroquine (Thaler et al. 1973); cephaloridine (Turut & Malthieu 1980); oral contraceptive (Giovannini & Consolani); diffuse unilateral sub-acute neuroretinitis (DUSN) (Raymond et al. 1978); and ocular toxoplasmosis (Silveira et al. 1989). It is a long-standing concept that unilateral RP is a diagnosis of exclusion (François & Verriest 1952) and most reported

cases show no evidence or suggestion of inheritance (Farrell et al. 2009; Kolb & Galloway 1964; Cordier et al. 1966; Kandori et al. 1968; Carr & Siegel 1973; Bozin & Stangos 1972; Pearlman et al. 1976; Thaler et al. 1980; Contestabile et al. 1992; Spadea et al. 1998; Chen et al. 2006). A familial incidence from 16 to 35.7% has been suggested (Farrell et al. 2000; Joseph 1951), but without molecular confirmation. Thus, the term atypical unilateral pigmentary retinopathy or atypical retina degeneration sometimes called "unilateral pigmentary retinopathy (UPR)" is usually more appropriate than unilateral RP.

The present study reports 42 patients with UPR, the largest series to date. Detailed electrophysiological and clinical assessments were used to establish the nature and severity of retinal dysfunction and the incidence of possible subclinical involvement in the fellow eye.

Methods

The research adhered to the tenets set forth in the Declaration of Helsinki and approval of the local Ethics Committee was obtained (Research Management Committee, Moorfields Eye Hospital).

The records of all patients referred to Moorfields Eye Hospital Department of Electrophysiology for investigation of UPR or possible unilateral RP between January 2008 and March 2011 were retrospectively reviewed. The objective was to study a cohort of patients who had clinical features of unilateral RP clinically in the index eye and all fellow eyes were symptom free with normal vision acuity and normal fundus examination at baseline.

Forty-two patients were ascertained, comprising 31 females and 11 males. Patients found to have inner retinal vascular pathology (e.g. central retinal artery or vein occlusion), or those lacking adequate clinical details were excluded. A family history, medical history including drug history, any previous history of trauma, a full history of visual symptoms, and visual acuity in both eyes were recorded.

In female participants, if the clinical presentation was compatible with, but not necessarily typical of, carrier status for X-linked retinitis pigmentosa, both RP2 and RP3 (RPGR) were sequenced for the full coding region and intron-exon boundaries using Sanger sequencing. The RPGR-ORF15 exon was sequenced in four overlapping PCR reactions as previously described (Chakarova et al. 2006).

Retinal photographs were not available for review in 5 externally referred patients but adequate description of the fundus appearance was available from the referral letters. Fundus autofluorescence (FAF) imaging was available for 16 patients; visual field data for 25 patients.

Electrophysiological assessment included full field electroretinography (ERG) to assess generalized retinal function, performed to incorporate and exceed the standards of the International Society for Clinical Electrophysiology of Vision (Marmor et al. 2009) and pattern ERG (PERG) to assess macular function (Holder 2001; Bach et al. 2012).

Approximately equal rod and cone involvement was defined by the ratio “Scotopic b-wave /Photopic b-wave” equal to a range interval of 0.8 - 1.2.

Rod >Cone involvement was defined by the ratio “Scotopic b-wave /Photopic b-wave” <0.8

Cone >Rod involvement was defined by the ratio “Scotopic b-wave /Photopic b-wave” >1.2

Multifocal ERG (mfERG) (Hood et al. 2012) was performed in 13 patients. Longitudinal electrophysiological data were available in 12 patients with follow up periods of between 22 and 128 months (median 52 months).

Results.

The clinical findings in the 42 patients are summarized in Table 1 and the final diagnoses in Table 2.

A relevant medical history/diagnosis was reported in 15 of 42 patients. Ten patients out of 42 patients had a diagnostic evaluation for uveitis or an autoimmune-type retinopathy (complete blood count, erythrocyte sedimentation rate, kidney test, urine analysis, syphilis serology, serum calcium, serum angiotensin-converting enzyme (ACE) and chest x ray). Two patients had other investigations, one had a tuberculin skin test, and another a rheumatoid factor test.

Patients with relevant medical history: Seven had a probable inflammatory or post-inflammatory etiology including one with a history of vasculitis in the fellow eye (case 32); one with presumed auto-immune retinopathy in association with rheumatoid arthritis (case 30) and one with a history of meningitis (case 22). Four patients carried a diagnosis of Acute Zonal Occult Outer Retinopathy (AZOOR; cases 31, 35, 36 and 42) because of photopsia, enlarged blind spot, visual field loss and altered outer retinal function on ERG (Gass 1993; Jacobson et al. 1995; Francis et al. 2005; Mrejen et al. 2014). Genetic testing in case 36 (with bilateral ERG abnormalities) revealed no alteration in 105 genes associated with retinal degeneration. Other associations included presumed choroidal ischemia associated with recent pregnancy (case 21) and a history of ocular trauma (cases 9, 15, 23 and 37). One patient had possible autoimmune retinopathy (case 26), with a relatively

sudden onset of visual loss in the right eye prior to being diagnosed with uterine carcinoma, but anti-retinal antibody screening was not available. There was definite evidence of genetically determined disease, and thus of true RP, in only 2 patients. One (case 7) is a member of a pedigree with confirmed autosomal dominant RP (RP1) consequent upon a heterozygous mutation in *ORF1* (p.R677X), and has previously been reported;[2] all affected relatives had bilateral disease including the patient's dizygotic twin. In this patient (case 7), multifocal, pattern ERG, full-field ERG, fundus examination and autofluorescence imaging were unambiguously normal in the unaffected eye.

The other (case 34, Fig 3) is an obligate carrier of XLRP with a heterozygous mutation in *RPGR* (RP3.pR412X; c.1234C>T). No relevant association could be confirmed in the remaining 28 (66.5%) patients. There were no disease-causing mutations found in female participants that would suggest their retinopathy were due to carrier status for XLRP.

a) Clinical findings (see Table 1)

The mean age at electrophysiological investigation was 40 years; the mean follow-up was 32 months (range: 1-120 months) for those 29 patients for whom follow-up data were available. All patients had UPR at presentation; all fellow eyes were symptom-free with normal visual acuity and normal fundus examination at baseline. VA in the affected eyes ranged from 20/16 to counting fingers (CF). Thirteen patients had VA 20/20 or better in the affected eye, 10 had a VA of 20/30 and19 worse than 20/30 including 8 with 20/125 or worse.

Five patients were asymptomatic and UPR was found at routine optometric examination. No definite diagnosis could be established in 3 of these 5 patients. Eighteen patients presented with reduced visual acuity, 14 during or after the 4th decade of life. Visual field constriction was revealed

by automated or confrontation perimetry in 24 of 28 patients tested. The defects were mostly peripheral with severe constriction in 4 patients (cases 3, 9, 10 and 14). Nineteen patients reported visual field loss as a symptom. Nyctalopia was not a prominent feature with only 4 patients admitting difficulty under reduced lighting conditions. Photopsia was reported by 14 patients but was not associated with a specific diagnosis.

The fundoscopic features in the abnormally pigmented eyes were similar to those associated with RP in 37 of 42 cases, including intra-retinal bone spicule pigment deposition and/or RPE changes such as pigmentary dispersion with perivascular pigment cuffing, granular pigmentary disturbance or punched out atrophic RPE lesions. The 5 other patients had pigmentary changes less typical for RP, with granular pigmentary disturbances without bone spicules (most of 4 of them had a relevant medical history: of trauma, cases 15, 23 and 37 and of possible auto-immune retinopathy, case 26 and one had no definite medical history, case 20).

The pigmentary alterations were characterized as mild (irregularity of pigment in the RPE in restricted segments with or without associated intra-retinal bone spicule pigmentation confined to some areas of the retinal periphery); moderate (widespread abnormalities in the periphery with extensive changes in retinal pigmentation including the mid-periphery outside the vascular arcades) or severe (widespread pigmentation with additional changes inside the temporal vascular arcades). Regarding the spread and localization of pigmentary alterations, one could not differentiate cases with presumable diagnostic based on relevant medical history from those with no definite diagnostic.

-<u>Patients with mild fundus changes</u> (n=12):

Patients with relevant medical history: One patient had a family history of dominant RP (*ORF1* mutation) with fundus changes restricted to the pre-equatorial fundus (case 7), and a small area of bone spicules was present in an obligate carrier for XLRP (case 34; Fig 3). One patient (case

26; possible paraneoplastic/ autoimmune syndrome) had no bone spicule deposition at presentation but developed pigmentary changes associated with widespread mid-zone and peripheral choriocapillaris atrophy during a 4-year follow-up period.

One patient with severe changes in the index eye (see below) had perivascular sheathing in the fellow eye at presentation that progressed to paravenous pigmentation at follow-up (case 32).

Patients with no definite medical history: A definite diagnosis could not be reached in the other 9 patients with mild pigmentary changes.

-<u>Patients with moderate pigmentary changes</u> (n=14):

Patients with relevant medical history: Eleven eyes with moderate pigmentary changes in the mid peripheral zone could be related to a presumed concomitant inflammatory disorder (case 30) or AZOOR (cases, 31, 35 and 42), meningitis (case 22) or trauma (cases 15 and 37).

-<u>Patients with severe pigmentary changes</u> (n=16):

Patients with relevant medical history: Inflammatory change was present in one patient (the fellow eye of case 32), and two had a history of ocular trauma (cases 9 and 23).

<u>Other clinical features</u>:

There were distinct areas of excessive pigmentation in 6 patients that were restricted to a single sector or hemisphere with changes within the arcades. Patients with no definite medical history: There was a crescent-shaped or sectorial area of pigmentation nasally in three eyes (cases 13,

19, 27 and 28); one patient had clumps of pigment superiorly and peripapillary in the mid peripheral fundus with some bone spicules associated with chorioretinal scarring (case 20). Patient with relevant medical history:

Considering other signs often associated typically with RP, 20 patients had disc pallor; 24 had attenuated vessels; and 2 had cystoid macular edema (Table 1).

Longitudinal clinical data:

Most patients had stable VA when re-examined within 36 months of presentation, but worsening central vision was documented in 4 cases (Table 1). Six patients were monitored over longer periods of between 48 - 120 months; VA was stable in 3 (cases 10, 35 and 42) but there was worsening in cases 8 (20/30 - 20/40 over 84 months), 22 (20/30 - 20/60 over 120 months) and 26 (20/20 - 20/80 over 48 months).

The fundus and FAF findings were stable in 9 of 10 UPR eyes monitored over periods of 3-10 years. One patient with bilateral presumed AZOOR (case 36) showed progressive atrophic changes in the vicinity of the vascular arcades and bilaterally increased AF at the macula, with additional evidence of macular and peripapillary punctate laser lesions sustained when the patient sought treatment abroad. Case 32, monitored over 9 years, had evidence of uveitis and perivascular sheathing in the fellow eye at presentation and developed paravenous pigmentation soon afterwards (stable for the last 5 years). Case 42 developed peripapillary lesions in the fellow eye at 8 years follow-up (see below).

b) Electrophysiology and imaging.

Imaging:

FAF imaging was performed in 16 patients. A high-density parafoveal ring of increased AF was present in 7 patients (cases 6, 7, 26, 27, 35, 36 and 42). Additionally, there was marked loss of AF along the arcades and peripapillary area in case 26 (fig 1A-B) and foci of low density AF outside the arcades in case 27 (fig 1C). Fundus AF was reduced outside the vascular arcades in 13 patients. One patient had streak-like areas of decreased AF in the macular region (case 37; fig 1D).

Electrophysiology:

Normal values for ISCEV-standard pattern (PERG) and full-field ERGs are presented in Table 3.

Generalized retinal function.

Index eyes:

The electrophysiological data are summarized in Figure 2 (A-D). The data were compared against previously published normative values with age-related adjustment applied to elderly patients (Vincent et al. 2013). Bright flash dark-adapted (DA 10.0) ERG a-waves, an index of rod photoreceptor function, ranged from undetectable to mildly reduced in the abnormally pigmented eye (10 cases) or were significantly asymmetrical (Figure 2A); there was proportionate reduction in b-waves with no patient showing post-phototransduction or inner retinal dysfunction (Figure 2A). Photopic 30Hz flicker (LA 3.0 30Hz) ERG amplitudes fell below the normal range in 38 cases, including 7 with undetectable responses, and were significantly lower than the fellow eye in the remaining 4 cases (Figure 2B). Peak-time delays, in keeping with generalized cone system dysfunction (N=26), ranged from 1 to 12ms above the upper limit of normal for age; peak times were at the upper limit

of normal in 6 patients and normal in 10 patients (Figure 2C). The ERGs showed rod and cone abnormalities of similar magnitude in 26 patients; the rod system more affected than the cone system in 15 patients; and a predominant cone system abnormality in the remaining patient. Most of the patients with a similar degree of rod and cone system involvement had milder overall dysfunction than those with a rod-cone pattern of dysfunction. Table 2 brings a short summary for the data of electrophysiology for both groups: "no definite" vs. "relevant medical history". Patients with electrophysiology's data showing 'rod and cone abnormalities of similar magnitude' and 'rod system more affected than the cone system' were found in both groups either 'with' or 'without relevant medical history'. Interestingly, patients with the diagnosis of AZOOR, or ocular trauma or no definite diagnosis (non-genetic causes of RP) did not have the characteristic rod-cone abnormality as noted in RP patients on electrophysiological testing but rather had a similar degree of involvement of cone and rods in many cases. Twenty-five patients (60%) with non-genetic UPR did not adhere to the pattern of rod greater than cone dysfunction as noted in RP (Table 2).

Fellow eyes:

ERGs suggested generalized sub-clinical retinal dysfunction in the fellow eye in only 8 cases (Fig 2). Three had approximately equal rod and cone involvement that was milder than in the index eye, including the carrier of X-linked RP (case 34; Fig 3), a patient with presumed AZOOR (case 36) and case 10 (etiology unknown). One patient had mild generalized loss of cone system function (case 2) and one had cone dysfunction with mild rod involvement but a history of retinal vasculitis (case 32**;** ERGs undetectable in the index eye). Cases 26 (possible carcinoma associated retinopathy) and cases 16 and 33 (diagnoses unknown) had evidence of a mild generalized loss of rod photoreceptor function with

severe dysfunction in the index eyes. Two patients had borderline or mild full-field ERG abnormalities associated with high myopia (case 23) or incomplete mydriasis (case 5), not clinically significant.

Macular function.

Macular function was assessed bilaterally using pattern ERGs (N=42) and multifocal ERGs (N=13). PERG P50 (Fig 2D) was undetectable in 14 of the index eyes, subnormal in 14 and borderline in 3, in keeping with differing degrees of macular involvement. Eleven patients had a normal PERG suggesting sparing of macular function. Multifocal ERGs (mfERG) were abnormal in the index eye in 13/13 cases and revealed paracentral dysfunction in 8 cases with relatively preserved central responses (cases 8, 9, 20, 21, 35, 36, 38 and 41), including 3 with a normal PERG P50 component. Five patients with undetectable PERGs had widespread mfERG attenuation (7, 13, 32, 39 and 42), being worst over the central area in all but one patient (case 42) who retained a residual central mfERG response. Four of the patients in whom FAF imaging had been performed had electrophysiological evidence of macular involvement without associated FAF change.

Pattern ERG P50 was mildly subnormal in 4 fellow eyes (cases 22, 29, 39 and 42; Fig 2E), and of borderline amplitude for age in 3 fellow eyes (cases 2, 12 and 30). Paracentral mfERG attenuation with central sparing occurred in 1 fellow eye in which the pattern ERG P50 component was normal (case 32).

Longitudinal data.

Longitudinal ERG data were available in 12 patients, with 8 having periods of between 3 and 10.7 years (mean 5.1 years) follow-up (cases 3, 8, 21, 26, 31, 32, 33, and 42). Full-field and pattern ERGs in case 42 showed worsening in the index eye over a 2- to 8-year period (fig 6E). Initially severely abnormal ERGs in case 31 became undetectable over 10 years and there was PERG evidence of worsening macular function. Full-field ERGs in the index eyes of all other cases remained stable, but the PERG and mfERG in case 26 showed progressive attenuation in keeping with worsening macular dysfunction and the ERGs in the fellow eye showed rapid deterioration over 2 years, unlike the gradual progression usually associated with a genetic etiology. There was progressive generalized cone system dysfunction in the fellow eye of case 33 and PERG evidence of worsening macular function in the fellow eye of case 30 (follow-up 29 months).

c) Illustrative cases.

Case 34

A 39-year-old female was an obligate carrier for X-linked RP, her son being diagnosed with the pR412X (c.1234C>T) mutation in *RPGR* (RP3). Visual acuity and color vision were normal in both eyes. Right fundus examination was normal (Fig 3A). The left fundus showed some focal (infero-nasal) bone spicules and pigmentary dispersion with perivascular pigment cuffing (Fig 3B). The mild intensity and the focal localization of the pigmentary changes appearance in this case was compatible with RP. Although in RP, progressive bone-spicule pigment changes develop throughout the peripheral retina and involves in advanced cases the posterior pole.

ERG showed mild generalized rod system dysfunction in each eye of approximately equal severity. Cone-mediated ERGs were bilaterally abnormal but were asymmetrical, with the left eye worse than the right (Fig 3C).

Case 15

A 17-year-old male was referred with poor vision confined to his right eye since early childhood. There was a family history of red-green color deficiency and 'lazy eye', but not of RP. Best-corrected visual acuity was 20/200 on the right; 20/20 on the left. The fundus of the right eye showed subtle pigmentary changes in the nasal and supero-temporal periphery associated with attenuated retinal vessels (Fig 4A); the left eye fundus was normal (Fig 4B). This case differs from RP for lacking of bones spicules.

ERGs were undetectable from the right eye, in keeping with severe generalized loss of photoreceptor function, but were completely normal in the fellow eye (Fig 4C). No definitive diagnosis could be reached. There was a history of direct ocular trauma in childhood, which is likely to be causative, but the slim possibility that the right eye fundus abnormalities may relate to a congenital TORCH syndrome (Toxoplasmosis, Rubella, Cytomegalovirus and Herpes simplex infections) cannot be excluded.

Case 35

A 37-year-old woman was referred by her optician for investigation of sudden onset of visual field defect and photopsias in her right eye. Visual acuities were 20/20 unaided bilaterally. There was no relevant family history. The right fundus showed subtle mid-peripheral pigmentary

changes nasally-superior and inferior in the periphery associated with attenuated retinal vessels and a few bone spicules (Fig 5A). The pigmentary changes were of moderate intensity and compatible with RP, although of focal localization.

FAF imaging revealed irregular arcs of increased signal at the posterior pole inside the arcades and patchy hypoautofluorescence inferiorly (Fig 5B). The left fundus and FAF image were normal (Fig 5C & D). Full field ERG showed generalized rod and cone dysfunction in the right eye (Fig 5E). Pattern ERG was mildly subnormal with multifocal ERGs being severely reduced over paracentral areas but displaying relative central sparing (Fig 5F). Left eye electrophysiology was normal. The clinical presentation and findings are consistent with AZOOR (Mrejen et al. 2014).

Case 42

A 40-year-old woman was referred for investigation of field loss and photopsias in her right eye. Visual acuities were 20/20 unaided bilaterally. There was no relevant family history. The right fundus showed mid-peripheral RPE depigmentation with a few bone spicules and yellowish peripapillary chorioretinal scars (Fig. 6A).

FAF imaging revealed a parafoveal ring of hyperautofluorescence and widespread patchy hypoautofluorescence over eccentric areas (Fig 6B). The left fundus was normal at presentation (Fig 6C). Full field ERG showed moderately severe generalized rod and cone dysfunction in the right eye (Figure 6E). The findings are in keeping with AZOOR. Pattern ERG was markedly subnormal with multifocal ERGs showing no definite response other than a subnormal central response (data not shown). Left eye electrophysiology was normal. During an 8-year follow-up period she developed almost complete loss of peripheral retinal function (ERG) in the index eye with pattern ERG showing worsening (Fig 6E but some

sparing of central retinal function). Electrophysiology in the fellow eye remained normal at 8-year follow up even though inflammatory peripapillary chorioretinal lesions appeared (Fig 6D).

Discussion

This report describes the findings in 42 patients with UPR**.** There was difficulty in establishing an etiology in many patients but, importantly, a family history suggesting a heritable cause was present in only 2 of the patients. The observation that a genetic diagnosis could be reached in only 2 cases is consistent with previous studies of atypical that have suggested a high incidence of acquired disease (Spadea et al. 1998; Chen et al. 2006; Joseph 1951). Detailed electrophysiological testing showed generalized retinal dysfunction in the eye with pigmentary changes that varied in severity. Although all fellow eyes were asymptomatic and had normal fundus examination at presentation, subclinical abnormalities of generalized retinal function were present in 8 of 42 patients. Subclinical macular dysfunction was observed in a similar number, but usually independent of the full-field ERG findings, highlighting the importance of appropriate testing.

Several disorders were associated with UPR. The largest groups were presumed AZOOR (9.5%) and a history of trauma (9.5%), mostly associated with severe ERG abnormalities; it is possible that the incidence of trauma may be higher given that some patients may have sustained head or ocular injury as infants or children with no record or recollection of the trauma. AZOOR was a presumed diagnosis based on clinical symptoms, visual fields defects, electrophysiological findings and non-specific chorioretinal features; there is currently no “gold-standard”

diagnostic test for AZOOR. Other conditions included inflammatory eye disease and possible paraneoplastic syndrome. One patient had presumed choroidal ischemia associated with recent pregnancy; mfERG abnormalities have previously been described in a patient with preeclampsia; the retinal dysfunction is likely secondary to RPE dysfunction and choroidal ischemia (Kwok 2001). Patients with RP, a disorder generally considered to be bilateral and relatively symmetrical, usually present with night blindness but photopsias are frequently reported (Bittner et al 2009). It is uncommon for RP patients to present with visual acuity loss, without accompanied symptoms such as night blindness or visual field loss. Visual acuity loss in RP patients usually occurs late in the course of the disorder (Heckenlively 1988; Weleber 1994).

The prevalence of nyctalopia in the present series was less than 10%, and 45% of the patients had reduced visual acuity as a presenting symptom. Photopsias and acuity loss may occur in inflammatory, paraneoplastic or autoimmune mediated retinopathy (Heckinlively et al. 2006) and are common in AZOOR (Gass et al. 2002; Francis et al. 2005), which is often unilateral at presentation (Gass et al. 2002; Monson & Smith 2011). Overall, the unilaterality and the constellation of symptoms do not favor a diagnosis of RP but **an atypical retina degeneration**. However, obligate carriers of X-linked RP may have markedly asymmetrical fundus appearance and ERGs (Jacobson et al. 1989), similar to one patient in the present series. Only one other patient (case 7; RP1) had a relevant family history including a dizygotic twin with bilateral disease and molecular confirmation of the mutation.

The nature of the pigmentary changes in the current series did not reliably predict the diagnosis or functional phenotype. Intra-retinal pigmentary deposition, RPE depigmentation, disc pallor and vessel attenuation can occur in RP depending of the stage of the disease, but are not pathognomonic (Hamel 2006)**.**

Possible mechanisms evolved on RP appearance, particularly bone spicules pigment deposition, have been studied in murine model for human RP. After the loss of all photoreceptor cells, the outer retina successively degenerates, leading to a direct contact of inner retinal vessels triggering migration of retinal pigment epithelium (RPE) cells along the contacting vessels towards the inner retina. These mislocalized RPE cells partially seals the vessels by tight junction linkage and deposits extracellular matrix perivascularly. Also, the vascular endothelium develops fenestrations similar to the RPE-choroid interface forming pigmented cell clusters outlining retinal capillaries or bones spicules (Jaissle et al. 2010). Therefore, one may explain the appearance of bone spicule pigments in the eyes of patients with inflammatory etiology or trauma by the loss of photoreceptor cells even if the cause remains idiopathic, as being the trigger event.

Three patients had unilateral hypopigmentation similar to that described in older literature as "RP sine pigmento" (Pearlman et al. 1976; Jacobson & Stephens 1962), but which is unlikely to be a distinct diagnostic entity. Fundus examination and/or FAF imaging revealed restricted abnormality in 6 cases, none with a definite diagnosis. A parafoveal ring of increased FAF can be associated with RP (Robson et al. 2003; Popovic et al. 2005; Murakami et al. 2008; Robson et al. 2011) but is usually bilateral with high inter-ocular symmetry (Robson et al. 2003); a ring was present in only 7 of the 42 patients in the present series and was always unilateral. FAF rings are not pathognomonic and can occur in other retinal disorders (Kurz-Levin et al. 2002; Jarc-Vidmar et al. 2003; Ebenezer et al. 2005; Tsang et al. 2007; Fleckenstein et al. 2009).

The asymmetrical nature of the fundus abnormality was reflected in the full-field ERGs in all 42 cases. Patients with RP typically demonstrate a high degree of inter-ocular ERG symmetry (Marmor et al. 1993)**,** but heterozygote carriers of X-linked RP, can have marked interocular asymmetry both in electrophysiology and in fundus appearance (Jacobson et al. 1989) thought to reflect random X-chromosome inactivation

(lyonization). Further, as a rod-cone dystrophy, the dysfunction in RP is primarily in the rod system with consequent cone involvement and with rod ERGs being more abnormal than cone ERGs. A minority (35.7%) of cases in the current study manifested rod greater than cone-mediated ERG abnormalities, including the patient with RP1 (case 7). In severe or end-stage RP, full-field ERGs may be undetectable (Jacobson & Stephens 1962) but this occurred in only five cases including one with inflammatory disease and a history of uveitis in the fellow eye (case 32). ERGs in the fellow eye of this patient showed greater cone than rod system dysfunction including flicker ERG delay; similar changes, although not diagnostic, are a common non-specific manifestation of inflammatory retinal disease (Robson et al. 2005). Full-field ERGs were stable in both eyes of 5 of 8 patients monitored over 3-10 years and in 1 eye in the other 3; a high proportion of patients with typical RP show significant deterioration over similar periods (Birch et al. 1999). Others have also reported the affected eye in UPR to show a progressive loss of peripheral retinal function that cannot be attributed to aging alone, with large variations in the rate of decline (Potsidis et al. 2011).

Unilateral ERG abnormalities are often present in inflammatory disease, but can also occur in presumed auto-immune mediated retinal dysfunction (Francis et al. 2005; Robson et al. 2005). The concept of non-malignancy related autoimmune retinopathy has been proposed by several authors, and anti-retinal antibodies have been identified (Mantel et al. 2008; Heckenlively et al. 2000; Weleber et al. 2005). Two groups describe a similar "auto-immune retinopathy" characterized by mostly normal fundi, normal FAF and predominantly cone-system dysfunction (Mantel et al. 2008; Heckenlively et al. 2000). Others describe retinal pigmentary deposition and atrophy with a predominance of rod dysfunction on ERG testing (Heckenlively et al. 2000). Whether the presence of anti-retinal antibodies is causative, or is an epiphenomenon consequent upon retinal degeneration, remains unclear (Mantel et al. 2008).

Macular dysfunction could neither be predicted from the fundus appearance nor from the nature of the full-field ERG changes in either the index or fellow eyes, highlighting the need for PERG or mfERG as an objective index of macular function. One patient with a normal PERG had multifocal ERG evidence of paracentral macular dysfunction; the mfERG can reveal details of spatial distribution not accessible with PERG, the latter being dominated by central macular function. The additional use of large-field PERGs, although not part of the present study, can give additional spatial information that can be of value in a patient unable to perform mfERG (Lenassi et al. 2012).

The normally pigmented fellow eyes were all asymptomatic in the present series, and any sub-clinical ERG abnormalities were mild (8 patients). Some have suggested that UPR may indicate relatively benign disease (Thaler et al. 1980); others that loss of peripheral retinal function is more rapid in affected eyes with a greater delay in the cone ERG peak time (Potsidis et al. 2011). Asymmetrical RP cannot be excluded with absolute certainty in this series, as illustrated by unilateral expression of RP1 in case 7, but overall seems unlikely. One possible cause of UPR is mosaicism, such that a somatic mutation occurs during embryonic development within a cell that is a precursor for cells in one retina or part of one retina, but not affecting the other (Poduri et al. 2013) or, alternatively, the individual may be a chimera composed of cells from two distinct zygotes one harboring a relevant mutation (Yu et al. 2002). The difficulty in obtaining retinal tissue *in vivo* makes it difficult to test these hypotheses.

To conclude, appropriate and comprehensive clinical and electrophysiological testing determines both the nature and severity of retinal dysfunction in patients with UPR, and ascertains whether the fellow eye is involved. The etiology remains enigmatic with only a minority of clinically relevant associations found in this survey; the disorder is ‘idiopathic’ in most patients.

References:

Bach M, Brigell MG, Hawlina M et al (2013): ISCEV standard for clinical pattern electroretinography (PERG): 2012 update. Doc Ophthalmol **126**:1–7.

Bastek JV, Foos RY, Heckenlively JR (1981): Traumatic pigmentary retinopathy. Am J Ophthalmol **92**:621–624.

Berson EL (1993): Retinitis Pigmentosa. The Friedenwald Lecture. Invest Ophthalmol Vis Sci **34**:1659–1676.

Birch DG, Anderson JL & Fish GE (1999): Yearly rates of rod and cone functional loss in retinitis pigmentosa and cone-rod dystrophy. Ophthalmology **106**:2582–68.

Bittner AK, Diener-West M & Dagnelie G (2009): A survey of photopsias in self-reported retinitis pigmentosa: location of photopsias is related to disease severity. Retina **29**:1513–1521.

Bozin I & Stangos N (1972): Does unilateral pigmentary retinopathy exist? A propos of 2 further cases. Ophthalmologica **165**:402–408.

Carr RE & Siegel IM (1973): Unilateral retinitis pigmentosa. Arch Ophthalmol **90**:21–26.

Chakarova CF, Cherninkova S, Tournev I et al (2006): Molecular genetics of retinitis pigmentosa in two Romani (Gypsy) families. Mol Vis **12**:909-14.

Chen H, Wu D, Huang S & Jiang F (2006): Unilateral retinitis pigmentosa with amblyopia in the fellow eye. Graefes Arch Clin Exp Ophthalmol **244**:1701–1704.

Contestabile MT, Plateroti R, Carlesimo SC et al (1992): Atypical retinitis pigmentosa : a report of three cases. Ann Ophthalmol **24**:325–334.

Cordier J, Reny A& Seigneur JP (1966) : Unilateral retinitis pigmentosa. Bull Soc Ophtalmol Fr **66**:224–227.

Ebenezer ND, Michaelides M, Jenkins SA et al (2005): Identification of novel RPGR ORF15 mutations in X-linked progressive cone-rod dystrophy (XLCORD) families. Invest Ophthalmol Vis Sci **46**:1891–1898.

Farrell DF (2009): Unilateral retinitis pigmentosa and cone-rod dystrophy. Clin Ophthalmol **3**:263–270.

Fleckenstein M, Charbel Issa P, Fuchs HA et al (2009): Discrete arcs of increased fundus autofluorescence in retinal dystrophies and functional correlate on microperimetry. Eye **23**:567–575.

Francis PJ, Marinescu A, Fitzke FW et al (2005): Acute zonal occult outer retinopathy: towards a set of diagnostic criteria. Br J Ophthalmol **89**:70–73.

Francois J & Verriest G (1952) : Retinopathie pigmentaire unilaterale. Ophthalmologica **124**:65–88.

Gass JD, Agarwal A & Scott IU (2002): Acute zonal occult outer retinopathy: a long-term follow-up study. Am J Ophthalmol **134**:329–939.

Gass JD (1993): Acute zonal occult outer retinopathy. Donders Lecture: The Netherlands Ophthalmological Society, Maastricht, Holland, June 19, 1992. J Clin Neuroophthalmol **13**:79–97.

Giovannini A & Consolani A (1979): Contraceptive-induced unilateral retinopathy. Ophthalmologica **179**:302–305.

Granse L, Ponjavic & Andreason S (2004): Full-field ERG, multifocal ERG and multifocal VEP in patients with retinitis pigmentosa and residual central visual fields. Acta Ophthalmol Scand **82**:701–706.

Hamel C (2006): Retinitis Pigmentosa. Orphanet J Rare Dis **11**:40.

Heckinlively JR, Aptisauri N, Holder GE (2006): Autoimmune retinopathy, CAR and MAR syndromes. In: Arden GB, Heckenlively JR (ed.) Principles and Practice of Clinical Electrophysiology of Vision. Cambridge: MIT Press 691–698.

Heckenlively JR, Fawzi AA, Oversier J et al (2000): Autoimmune retinopathy. Patients with antirecoverin immunoreactivity and panretinal degeneration. Arch Ophthalmol **118**:15251–533.

Heckenlively JR. (1988): Retinitis Pigmentosa. Philadelphia: JB Lipincott 226–227.

Holder GE (2001): Pattern ERG and an integrated approach to the visual pathway diagnosis. Prog Ret Eye Res **20**:531–561.

Hood DC, Bach M, Brigell M al (2012): ISCEV Standard for clinical multifocal electroretinography (2011 edition). Doc Ophthalmol **124**:1–13.

Jacobson SG, Morales DS, Sun XK, et al (1995) : Pattern of retinal dysfunction in acute zonal occult outer retinopathy. Ophthalmology **102**:1187–1198.

Jacobson SG, Yagasaki K, Feuer WJ, Roamn AJ (1989): Interocular asymmetry of visual function in heterozygotes of X linked retinitis pigmentosa. Exp Eye Research **48**:679–691.41.

Jacobson JH & Stephens G (1962): Unilateral retinitis pigmentosa sine pigmento. Arch Ophthalmol **67**:456–458.

Jaissle GB1, May CA, van de Pavert SA et al (2010): Bone spicule pigment formation in retinitis pigmentosa: insights from a mouse model. Graefes Arch Clin Exp Ophthalmol **248**:1063-70.

Jarc-Vidmar M, Kraut A & Hawlina M (2003): Fundus autofluorescence imaging in Best's vitelliform dystrophy. Klin Monatsbl Augenheilkd **220**:861–867.

Joseph R (1951): Unilateral retinitis pigmentosa. Br J Ophthalmol **35**:98–113.

Kandori F, Tamai A & Watanabe T (1968): Two cases of unilateral pigmentary degeneration

Nippon Ganka Gakkai Zasshi **72**:489–496.

Kolb H & Galloway NR (1964): Three cases of unilateral pigmentary degeneration. Br J Ophthalmol **48**:471–479.

Kurz-Levin MM, Halfyard AS, Bunce C et al (2002): Clinical variations in assessment of bull's-eye maculopathy. Arch Ophthalmol **120**:567–75.

Kwok AK, Li JZ, Lai TY et al (2001): Multifocal electroretinographic and angiographic changes in pre-eclampsia. Br J Ophthalmol **85**:111–112.

Lenassi E, Robson AG, Hawlina M, Holder GE (2012): The value of two-field pattern electroretinogram routine clinical electrophysiologic practice. Retina **32**: 588–599.

Lommatzsch PK, Jensen OA, Prause JU, Bauke G (1988): Pseudoneuritis pigmentosa in malignant melanoma of the choroid. Klin Monatsbl Augenheilkd **193**:69–74.

Mann I (1975): Developmental abnormalities of the eye. 2nd ed. London: BMA 141.

Mantel I, Ramchand KV, Holder GE et al (2008): Macular and retinal dysfunction of unknown origin in adults with normal fundi: evidence for an autoimmune pathophysiology. Exp Mol Pathol **84**:90–101.

Marmor MF, Fulton AB, Holder GE al (2009): ISCEV standard for full field clinical electroretinography (2008 update) Doc Ophthalmol **118**:69–77.

Marmor MF, Aguirre G, Arden G, et al (1983): Retinitis pigmentosa: a symposium on terminology and methods of examination. Ophthalmology **90**:126–131.

Monson DM & Smith JR (2011: Acute zonal occult outer retinopathy. Surv Ophthalmol **56**:23–35.

Mrejen S, Khan S, Gallego-Pinazo R et al (2014):Acute zonal occult outer retinopathy : a classification based on multimodal imaging. JAMA Ophthalmol **132**:1089–1098.

Mukhopadhyay R, Holder GE, Moore AT, Webster AR (2011): Unilateral retinitis pigmentosa occurring in an individual with a germline mutation in the RP1 gene. Arch Ophthalmol **129**:954 –956.

Murakami T, Akimoto M, Ooto S et al (2008): Association between abnormal autofluorescence and photoreceptor disorganization in retinitis pigmentosa. Am J Ophthalmol **145**:687–694.

Pearlman JT, Saxton J & Hoffman G (1976): Unilateral retinitis pigmentosa sine pigmento. Br J Ophthalmol **60**:354–360.

Poduri A, Evrony GD, Cai X, Walsh CA (2013): Somatic mutation, genomic variation, and neurological disease. Science **341**:1237758.

Popovic P, Jarc-Vidmar M & Hawlina M (2005): Abnormal fundus autofluorescence in relation to retinal dysfunction in patients with retinitis pigmentosa. Graefes Arch Clin Exp Ophthalmol 243:1018–1027.

Potsidis E, Berson EL & Sandberg MA (2011): Disease course of patients with unilateral pigmentary retinopathy. Invest Ophthalmol Vis Sci **52**:9244–9249.

Raymond LA, Gutierrez Y, Strong LE et al (1978): Living retinal nematode (filarial-like) destroyed with photocoagulation. Ophthalmology

85:944–949.

Robson AG, Richardson EC, Koh AHC et al (2005): Unilateral electronegative ERG of non-vascular aetiology. Br J Ophthalmol **89**:1620–1626.

Robson AG, El-Amir A, Bailey C et al (2003): Pattern ERG correlates of abnormal fundus autofluorescence in patients with retinitis pigmentosa and normal visual acuity. Invest Ophthalmol Vis Sci **44**:3544–3550.

Robson AG, Tufail A, Fitzke FW et al (2011): Serial imaging and structure-function correlates of high density rings of fundus autofluorescence in retinitis pigmentosa. Retina **31**:1670–1679.

Silveira C, Belfort R Jr, Nussenblatt R et al (1989) : Unilateral pigmentary retinopathy associated with ocular toxoplasmosis. Am J Ophthalmol **107**:682–684.

Sim PY, Jeganathan VSE, Wright AF, Cackett P. (2018): Unilateral retinitis pigmentosa occurring in an individual with a mutation in the CLRN1 gene. BMJ Case Rep [Epub ahead of print].

Spadea L, Magni R, Rinaldi G et al (1998) : Unilateral RP clinical and electrophysiological report of four cases. Ophthalmologica **212**:350–354.

Thaler A, Heilig P & Wiesflecker J (1980): Unilateral pigmentary degeneration of the retina. Klin Monatsbl Augenheilkd **176**:203–206.

Thaler A, Heilig P & Slezak H (1973): Chloroquine retinopathy and unilateral sectoral pigmentary degeneration of the retina. Klin Monatsbl Augenheilkd **163**:172-6.

Tsang SH, Vaclavik V, Bird AC et al (2007): Novel phenotypic and genotypic findings in X-linked retinoschisis. Arch Ophthalmol **125**:259–67.

Turut P & Malthieu D (1980): The ocular toxicity of cephaloridine - A clinical and experimental study J Fr Ophtalmol **3**:401–408.

Vincent A, Robson AG, Neveu MM et al (2013): A phenotype-genotype correlation study of X-linked retinoschisis. Ophthalmology; **120**:1454–1464.

Weleber RG, Watzke RC, Shults WT et al (2005): Clinical and electrophysiologic characterization of paraneoplastic and autoimmune retinopathies associated with antienolase antibodies. Am J Ophthalmol **139**:780–794.

Weleber R (1994): Retinitis Pigmentosa and allied disorders. Ryan S (ed.) Retina, 2nd ed. Mosby St Louis: MO 335–466.

Yu N, Kruskall MS, Yunis JJ et al (2002): Disputed maternity leading to identification of tetragametic chimerism. N Engl J Med. **346**:1545–1552.

Figure 1: (A and B): Case 26. Possible autoimmune retinopathy. Fundus autofluorescence (FAF) of the affected right eye shows marked hypo-autofluorescence in the peripapillary region and along the arcades. There is decreased AF outside the arcades with a ring of hyper-autofluorescence in the macular region. The asymptomatic left eye shows increased AF along the arcades, in the peripapillary region and outside the arcades inferiorly. (C): Case 27. No definite diagnosis. Left eye FAF shows areas of focal hypo-autofluorescence outside the arcades (pin-points). They correspond to hyperpigmented areas seen on fundus examination. Case 37. (D): History of trauma. FAF in the left eye shows streak-like areas of decreased AF in the macular region.

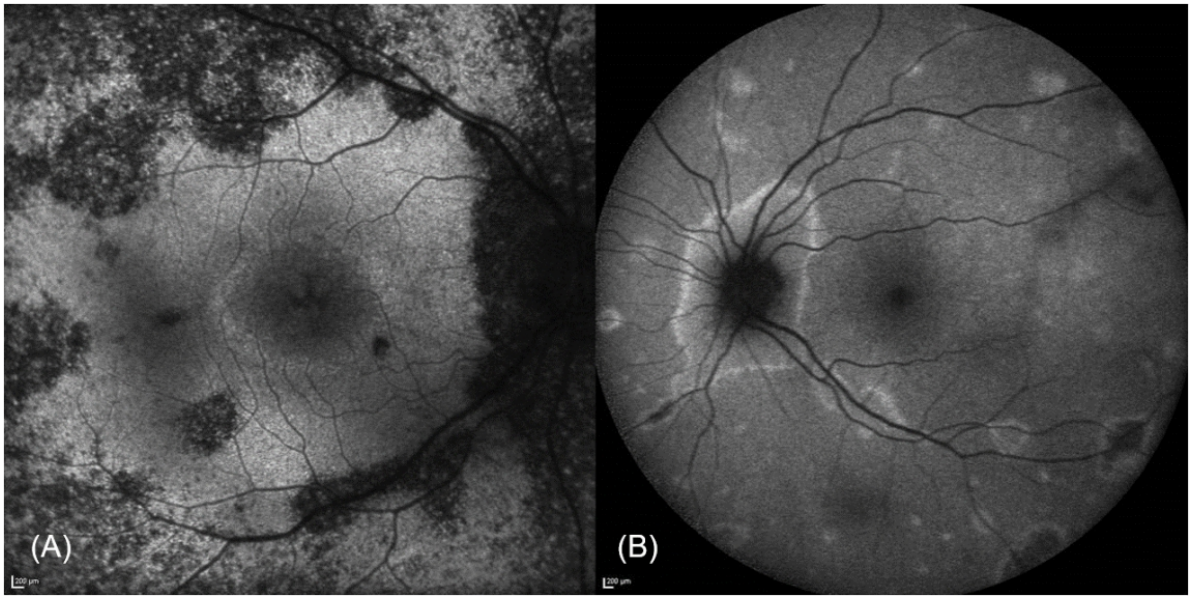


Figure 1 A & 1B: Case 26. Possible autoimmune retinopathy. Fundus autofluorescence (FAF) of the affected right eye shows marked hypo-autofluorescence in the peripapillary region and along the arcades. There is decreased AF outside the arcades with a ring of hyper-autofluorescence in the macular region. The asymptomatic left eye shows increased AF along the arcades, in the peripapillary region and outside the arcades inferiorly.

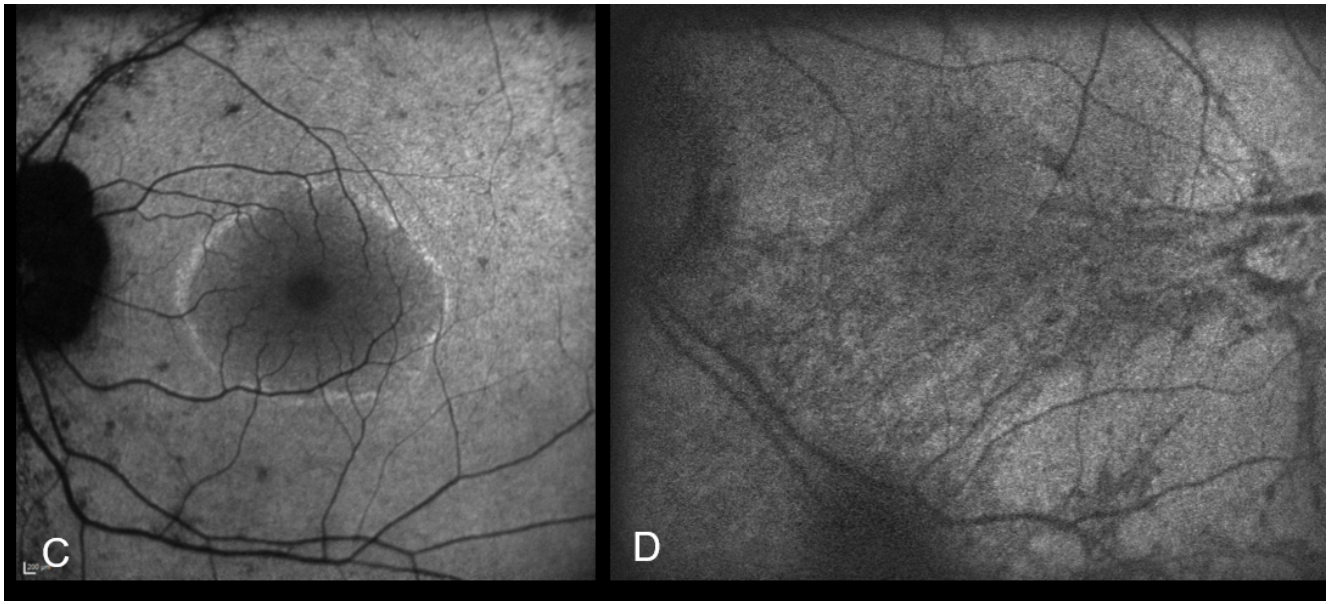


Fig. 1 C: Case 27, No definite diagnosis. Left eye FAF shows areas of focal hypo-autofluorescence outside the arcades (pin-points). They correspond to hyperpigmented areas seen on fundus examination; Fig D: Case 37, History of trauma. FAF in the left eye shows streak-like areas of decreased AF in the macular region.

Figure 2. Summary of the main full-field ERG and pattern ERG parameters in patients with UPR. A) Amplitudes are expressed as a percentage of the lower limit of normal for the dark adapted bright flash ERG a and b-waves (sc a-wave and sc b-wave) and for light adapted 30Hz flicker ERG and single flash cone ERG (ph b-wave). Amplitude data is shown for the 42 eyes with abnormal pigment and for the 8 fellow eyes that manifested an ERG abnormality. Amplitude data in the remaining 34 eyes with normal ERGs are omitted for clarity. B) Light adapted (LA) 30Hz flicker ERG amplitude is shown for all affected and fellow eyes; C) Flicker ERG implicit time is shown for all affected and fellow eyes. D) Pattern ERG P50 is plotted for eyes with and without abnormal pigment; the lower limit of normality is 2μV (broken line). Although some normal values appear small, they fall within the normal range for age, which varied considerably (see Table 1).

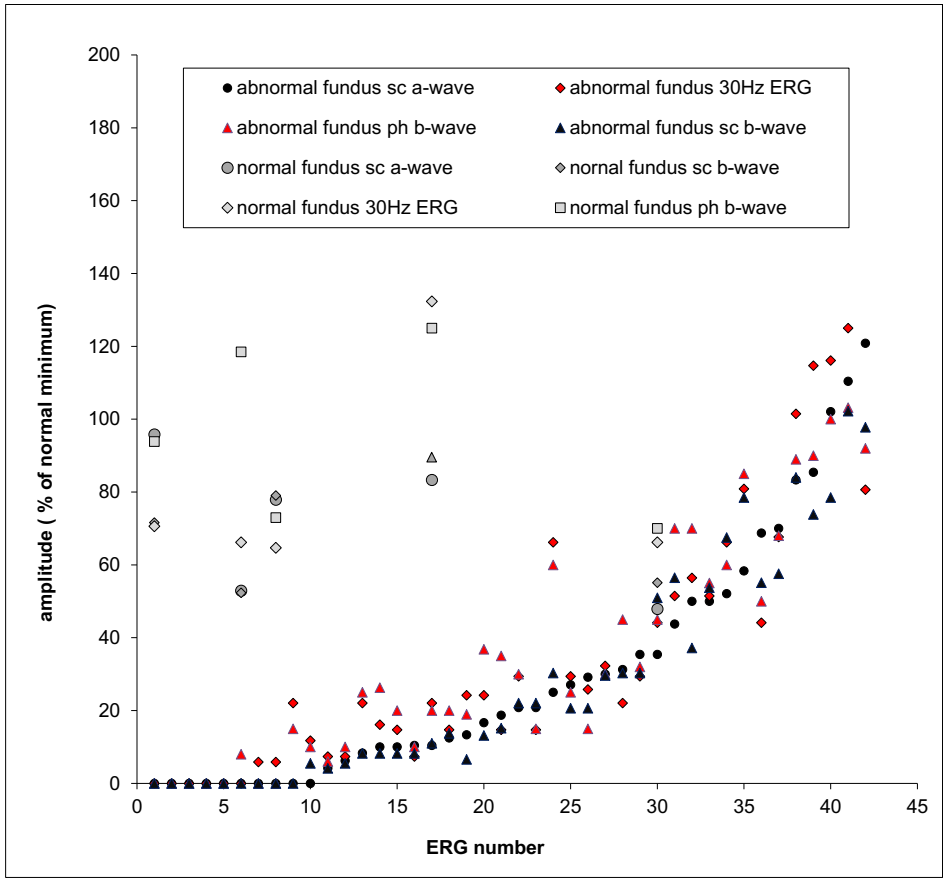
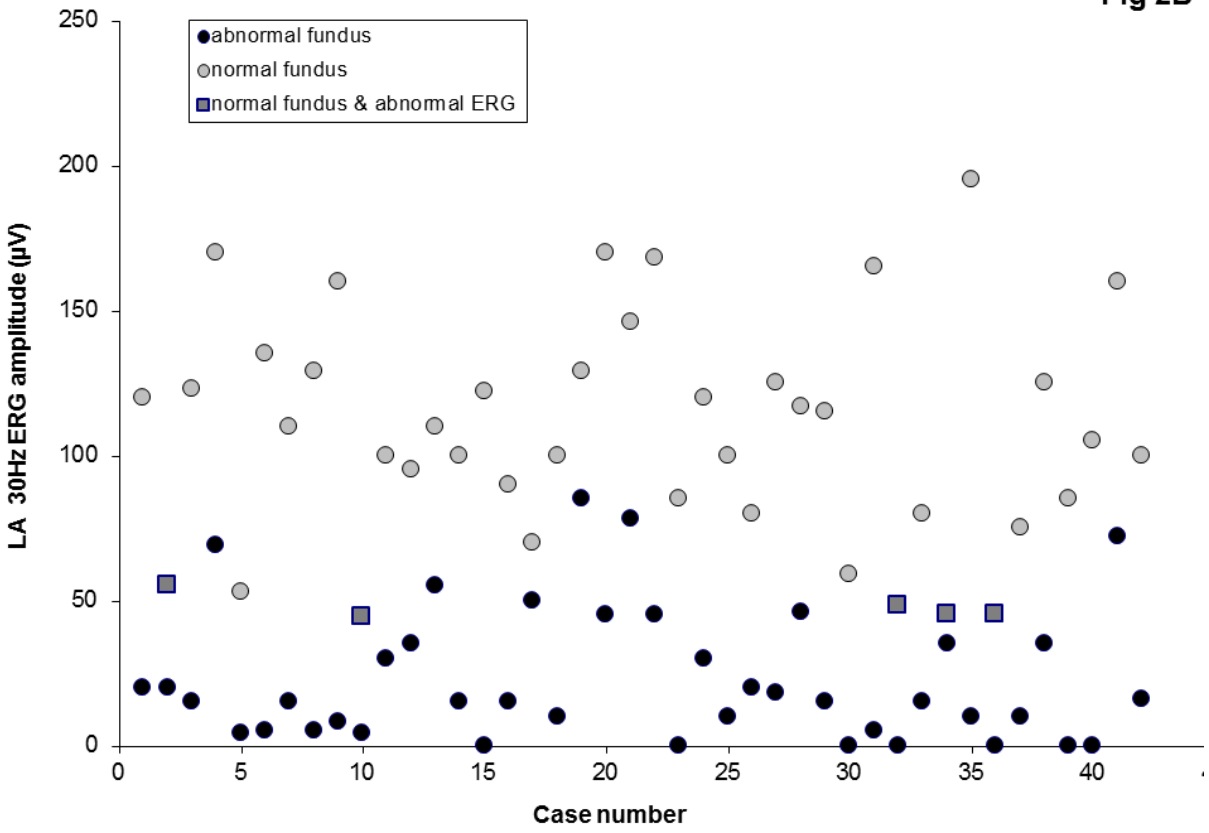

abnormal fundus sc a-wave
abnormal fundus 30Hz ERG
abnormal fundus ph b-wave
abnormal fundus sc b-wave
normal fundus sc a-wave
nornal fundus sc b-wave
normal fundus 30Hz ERG
normal fundus ph b-wave
amplitude (% of normal minimum)
ERG number
0
20
40
60
80
100
120
140
160
180
200
0
5
10
15
20
25
30
35
40
45

Fig 2B


abnormal fundus
normal fundus
normal fundus & abnormal ERG
LA 30Hz ERG amplitude (μV)
250
200
150
100
50
0
0
5
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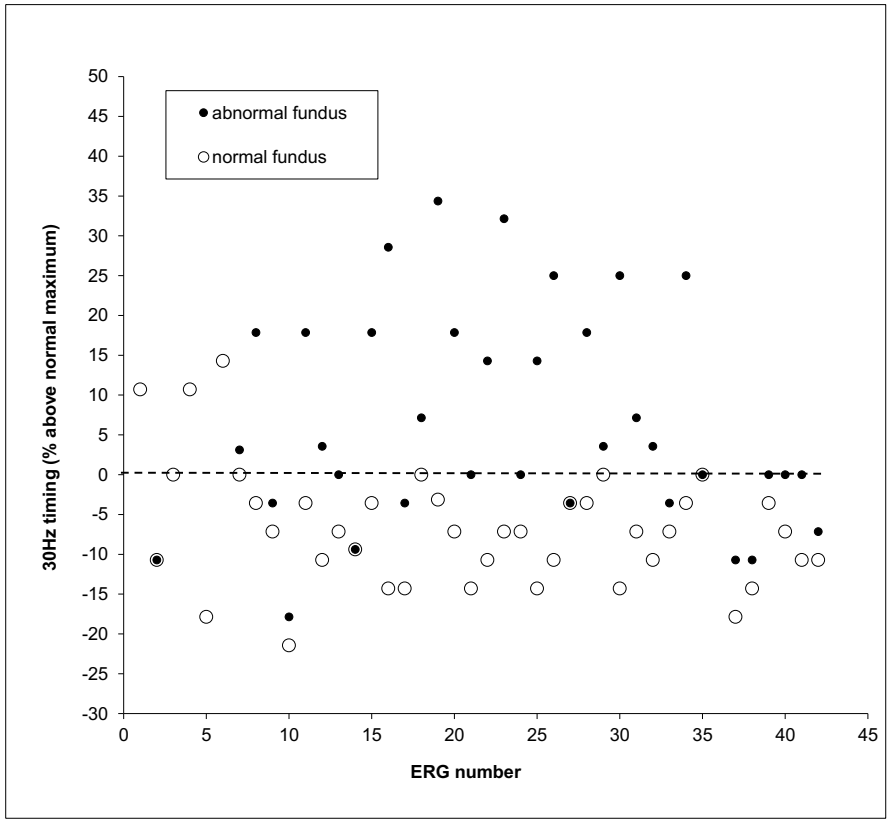
25
30
35
40
Case number


abnormal fundus
normal fundus
30Hz timing (% above normal maximum)
ERG number
50
45
40
35
30
25
20
15
10
5
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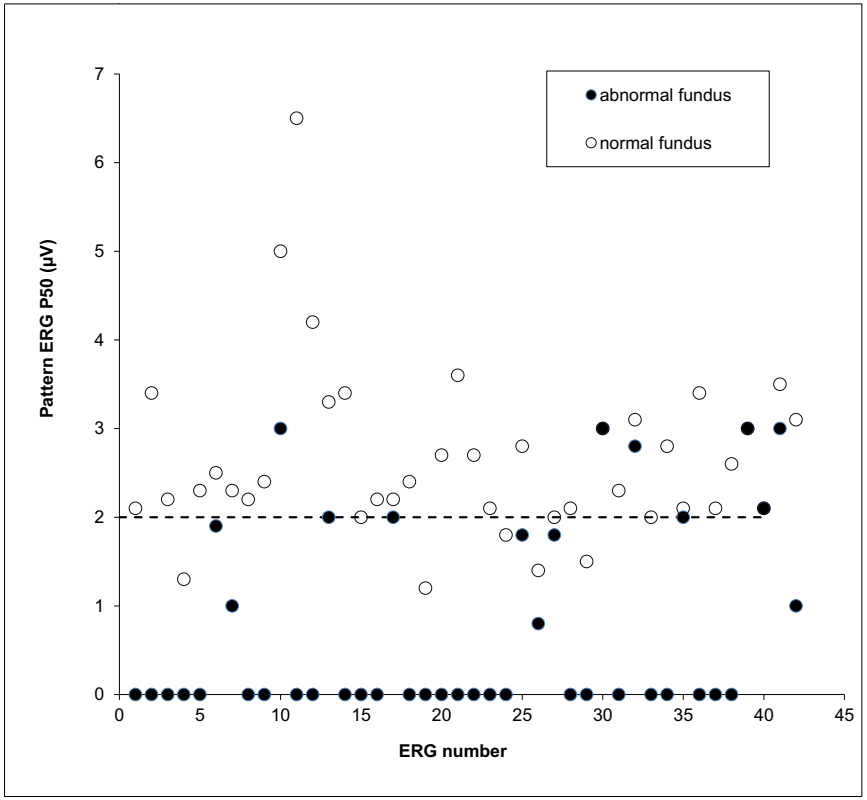
abnormal fundus
normal fundus
Pattern ERG P50 (μV)
ERG number
0
1
2
3
4
5
6
7
0
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10
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20
25
30
35
40
45

Figure 3: Case 34. Obligate carrier for X-linked RP. (A): Normal fundus in the uninvolved fellow eye. (B): The left eye fundus shows bone spicule pigmentary deposition in the infero-nasal quadrant (C): ERGs show generalized rod and cone dysfunction bilaterally but worse in the index left eye with PERG evidence of mild macular involvement in the index eye. Representative normal traces are shown for comparison in row 3. Dark-adapted (DA) responses are shown for flash strengths of 0.01 cd.s/m2 (DA 0.01) and 10.0 cd.s/m2 (DA 10.0). Light-adapted (LA) ERGs are shown for flash strength 3.0 cd.s/m2 (LA 3.0 30 Hz and LA 3.0 2 Hz). See text and Tables 1 & 2 for further detail.

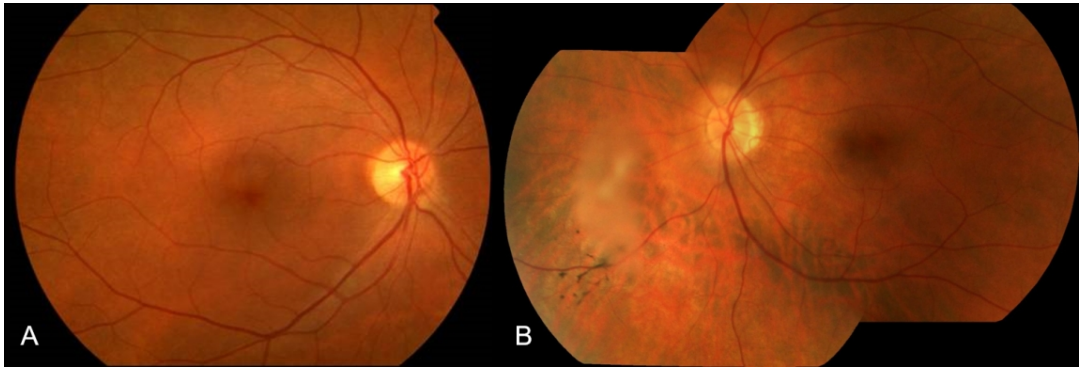

Figure 3 A & 3B: Case 34. Obligate carrier for X-linked RP. (A): Normal fundus in the uninvolved fellow eye. (B): The left eye fundus shows bone spicule pigmentary deposition in the infero-nasal quadrant

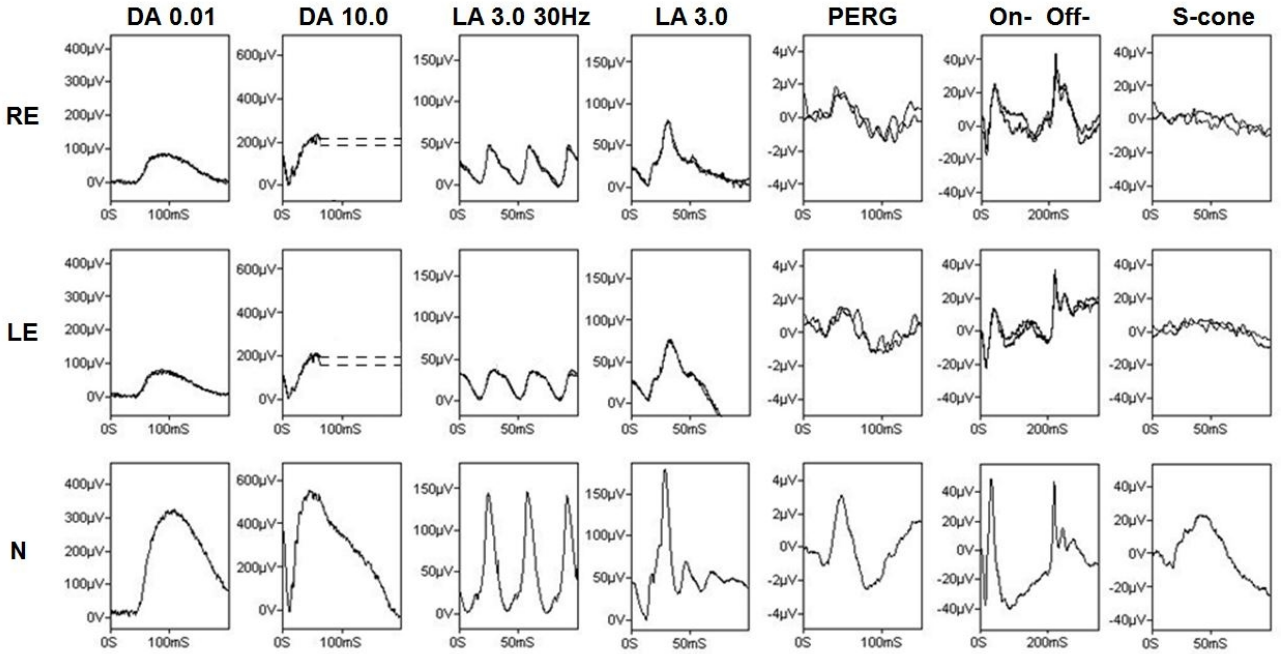

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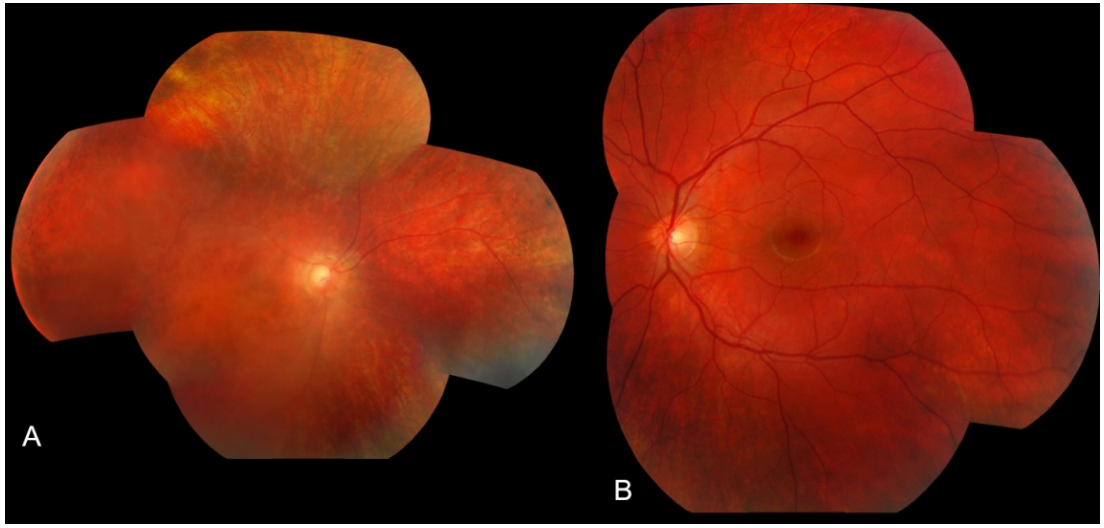
Figure 4: Case 15. History of ocular trauma. (A): The right eye fundus shows subtle pigmentary changes nasally and supero-temporally in the periphery associated with attenuated retinal vessels. (B): The normal left eye fundus. (C): Right eye full-field ERGs are undetectable consistent with global loss of rod and cone photoreceptor function and PERG evidence of severe macular involvement. Left eye findings are normal. ERGs are as shown in Fig 3. See text and Tables 1 & 2 for further detail.



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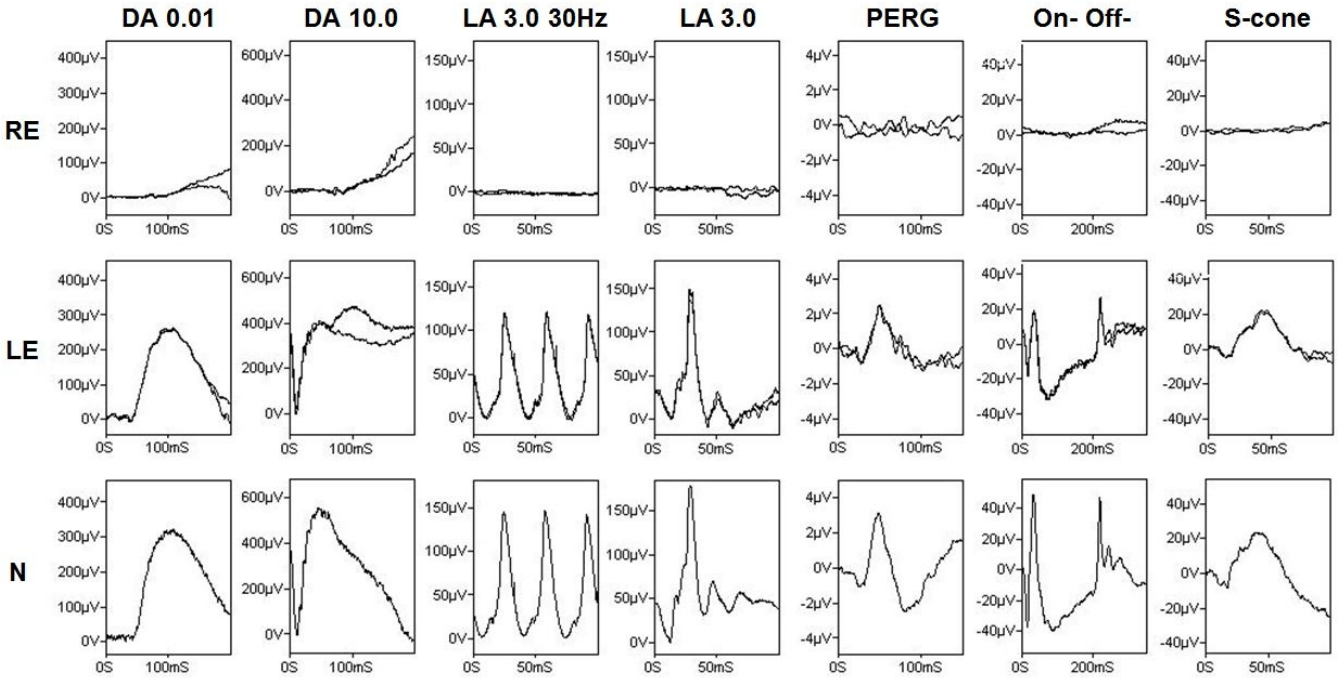

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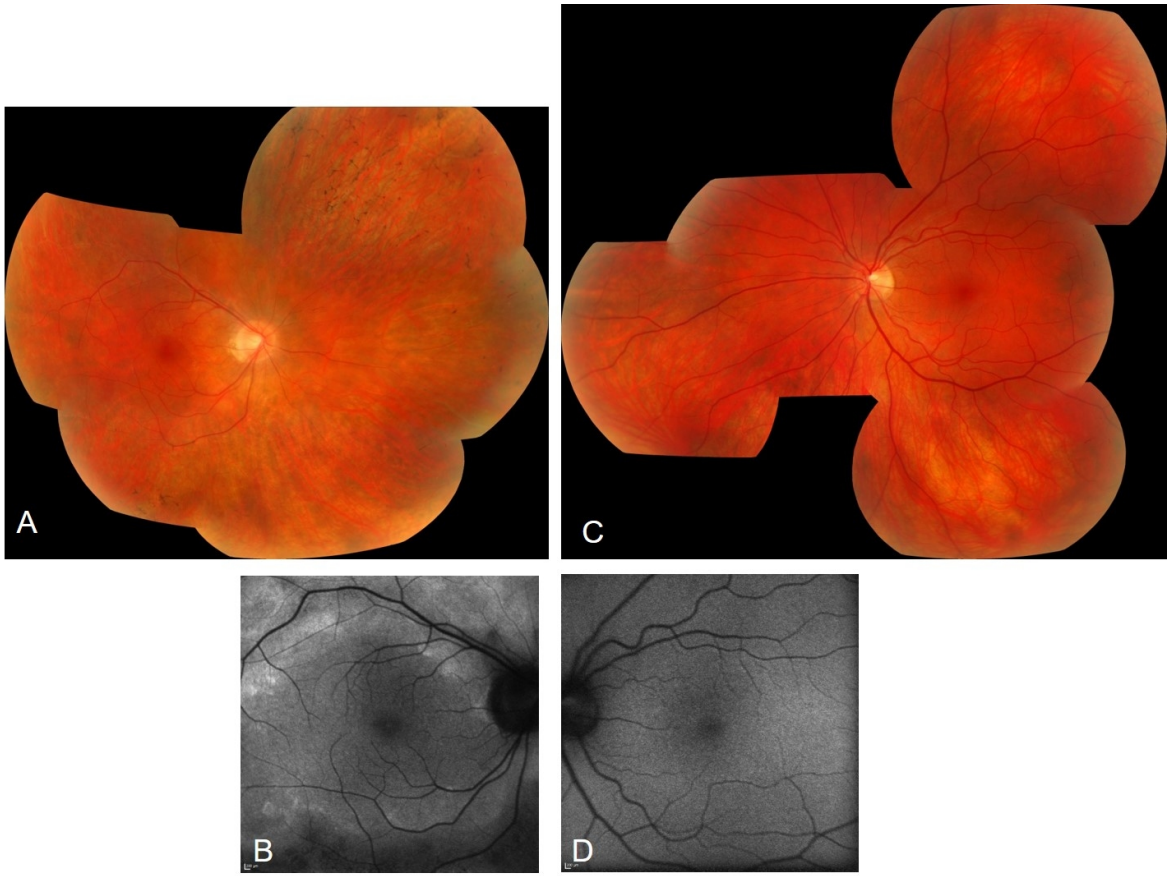
325x179mm (96 x 96 DPI)

Figure 5: Case 36, AZOOR. (A): The fundus of the right eye shows subtle pigmentary changes nasally and in the mid-periphery associated with attenuated retinal vessels; (B) there is a ring of increased AF at the posterior pole within the arcades surrounded inferiorly by an area of reduced AF. (C, D): The left eye fundus and FAF are normal. (E): Right eye ERGs show generalized rod and cone photoreceptor dysfunction with PERG evidence of mild macular involvement. ERGs are as shown in Fig 3. See text and Tables 1 & 2 for further detail. (F): Multifocal ERGs from the RE show mild central and severe paracentral macular involvement; left eye findings are normal. Note different amplitude scales for right and left eyes.

AZOOR: acute zonal occult outer retinopathy.



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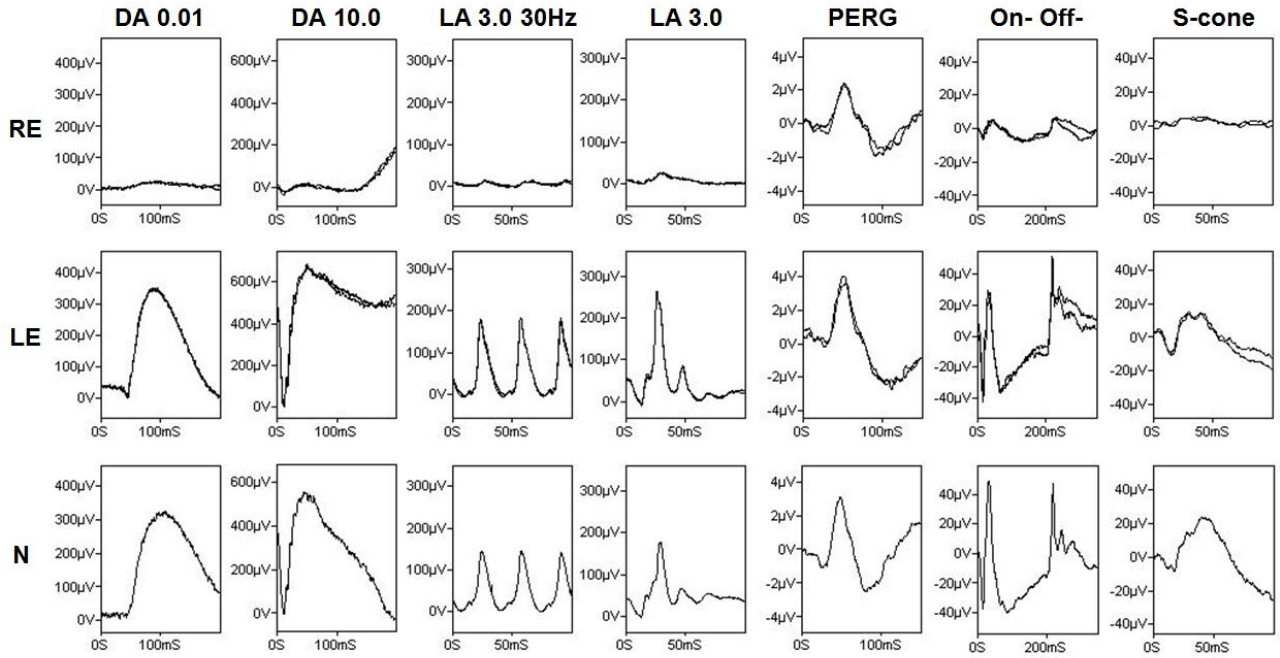


Figure 5: Case 36, AZOOR. (E): Right eye ERGs show generalized rod and cone photoreceptor dysfunction with PERG evidence of mild macular involvement. ERGs are as shown in Fig 3. See text and Tables 1 & 2 for further detail.

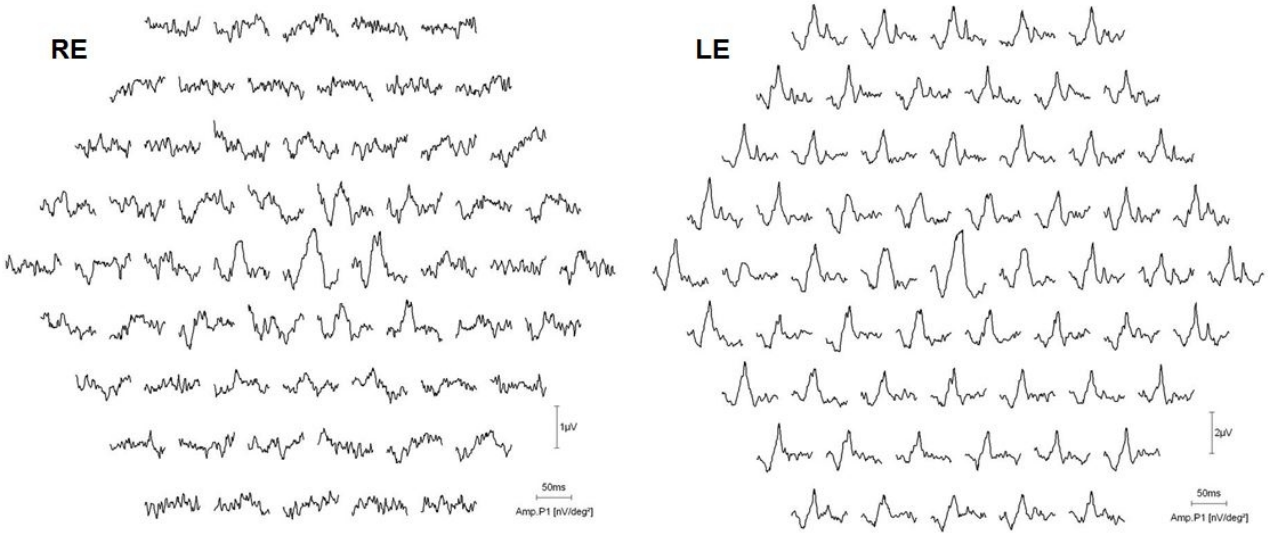
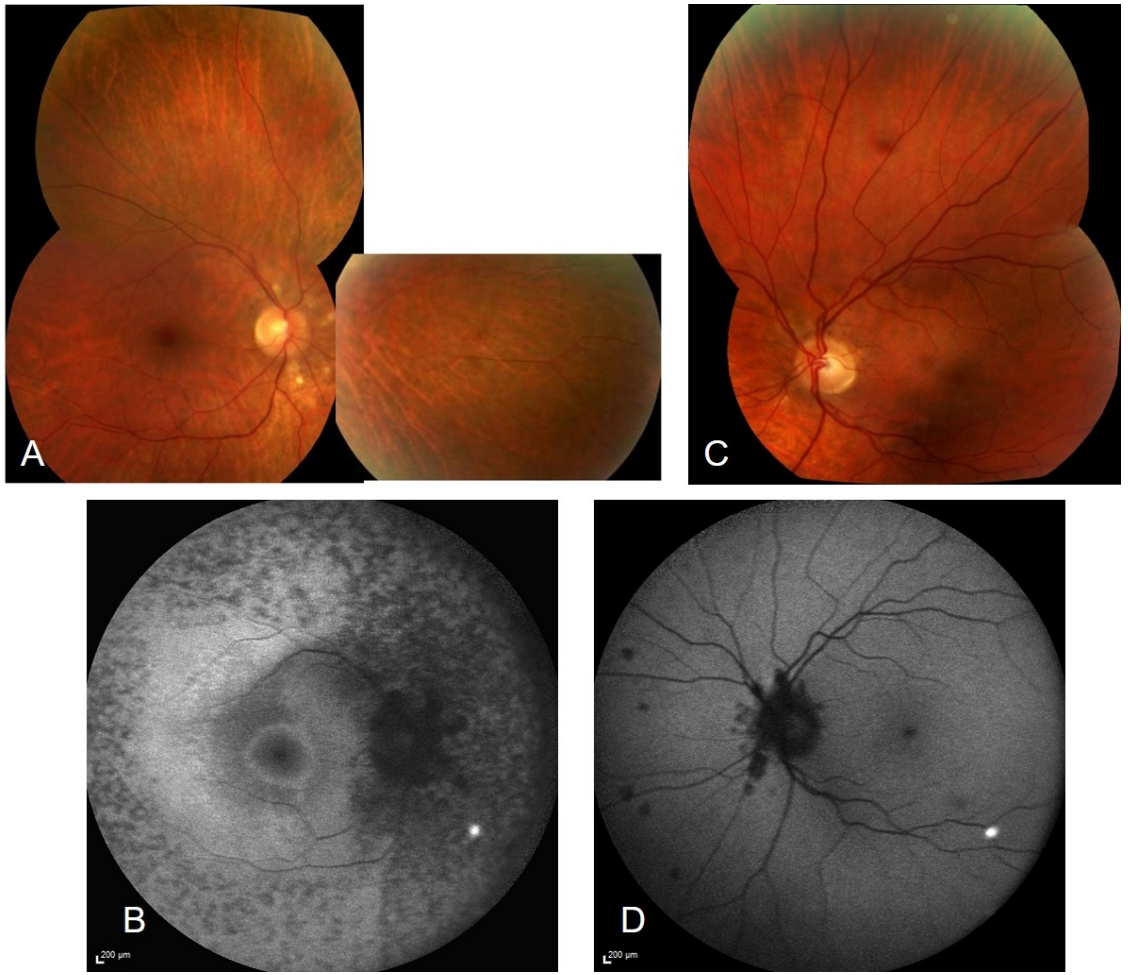


Figure 5: Case 36, AZOOR. (F): Multifocal ERGs from the RE show mild central and severe paracentral macular involvement; left eye findings are normal. Note different amplitude scales for right and left eyes. AZOOR: acute zonal occult outer retinopathy.

Figure 6: Case 42, AZOOR. (A): The fundus of the right eye shows pigmentary changes in the periphery associated with attenuated retinal vessels and peripapillary chorioretinal scars. (B): There is a ring of increased AF at the posterior pole within the arcades with a widespread area of reduced AF in the periphery. (C & D): The left eye fundus is normal and FAF shows peripapillary changes associated with small areas of hypo-fluorescence in nasal retina. (E): Right eye full-field ERGs in 2004 show generalized rod and cone dysfunction with additional inner retinal involvement. PERG shows marked macular involvement. At 4 follow-up visits between 2006 and 2012 right eye ERGs were undetectable; left eye findings remained normal and stable throughout. ERGs are as shown in Fig 3. See text and Tables 1 & 2 for further detail.



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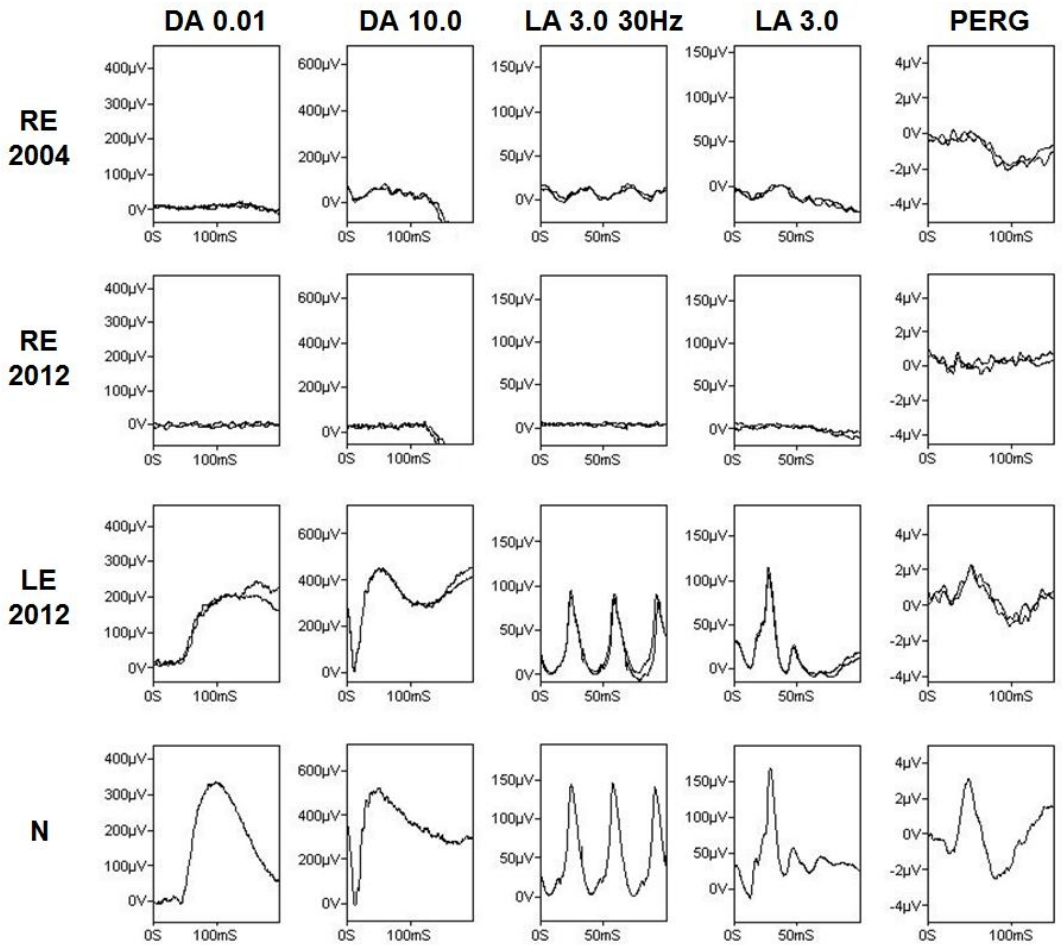

Figure 6: Case 42, AZOOR. (E): Right eye full-field ERGs in 2004 show generalized rod and cone dysfunction with additional inner retinal involvement. PERG shows marked macular involvement. At 4 follow-up visits between 2006 and 2012 right eye ERGs were undetectable; left eye findings remained normal and stable throughout. ERGs are as shown in Fig 3. See text and Tables 1 & 2 for further detail.

Table 1: Clinical characteristics in 42 patients with unilateral pigmentary retinopathy (UPR).

Table 2: Final diagnoses of the 42 patients with unilateral pigmentary retinopathy (UPR).

Table 3: Normal values for ISCEV-standard pattern (PERG) and full-field ERGs.

Table 1. The clinical findings in 42 patients with unilateral pigmentary retinopathy.

No/ age/sex	Follow-up in months (M)	Presenting VA - recent VA	Symptoms	Ocular trauma history	Relevant medical history and familial history	Fundus	Disc pallor	Attenuated vessels	Field defect
1/ 55/ F	36M	20/30	symptomatic field loss	-	-	+ mild	+	+	reduced
2/ 48/ F	0	20/20	symptomatic visual loss nyctalopia	-	-	* marked scarring on fundus examination.	N/A	N/A	N/A
3/ 20/ F	36M	20/20-20/30	symptomatic field loss photopsias	-	-	RP typical aspect	+	+	+++ severe constriction
4/ 21/ F	0	20/30	symptomatic field loss	-	-	RP typical aspect	+	+	+
5/ 65/ F	18 M	20/30	symptomatic visual loss nyctalopia for 3 years	-	-	+ peripheral retina mottled appearance	0	+ possibly slight alteration	++ constriction
6/ 50/ F	14 M (dg 10 yrs ago)	20/400	symptomatic field loss	-	-	++ CME	+	+	++ Humphrey

7/ 60/ F	0	20/20	symptomatic visual loss	-	family history of RP1	+ pigmentary dispersion with perivascular pigment cuffing	+	+	+
8/ 37/ F	84M	20/30 - 20/40	symptomatic field loss	-	-	++	+	+	+ Humphrey
9/ 17/ F	19M	20/40	symptomatic field loss photopsias	bilateral periorbital hemorrhage at child birth.	ANCA-ve ESR nlr	++ pigmentary dispersion with perivascular pigment cuffing	+	+	+++ Humphrey fields constricted to 15°
10/ 38/ F	96M	20/125	symptomatic field loss 4 years after onset nyctalopia	-	-	+++ extensive pigmented retinopathy, pigmentary dispersion with perivascular pigment cuffing + granular pigmentary disturbance in periphery.	+	+	+++ demonstrating function within 20° central field
11/ 35/M	5M	20/40	symptomatic field loss + photopsias	-	consanguinity (parents related), 6 siblings unaffected	++ pigmentary dispersion with perivascular pigment cuffing, bone-spicules.	0	0	++
12/ 46/ F	4M	20/40	symptomatic field loss central vision symptomatic visual loss photopsias	-	-	+ + mid-periphery pigmentary changes	0	0	N/A

13/ 49/ F	6M	20/16	asymptomatic	-	-	+ sectorial retinal pigmentation nasally with punched out atrophic RPE lesion, bone-spicules	0	0	+
14/ 52/ F	5M	20/30	symptomatic field loss central loss symptomatic visual loss photopsias	-	-	++ pigmentary dispersion with perivascular pigment cuffing	+	0	+++ demonstrating function within 10° central field
15/ 17/M	0	20/200	symptomatic visual loss since childhood	trauma age 4	TORCH congenital infections?	+ pigmentary changes in the nasal and supero-temporal periphery associated with attenuated retinal vessels, no bone spicules	+	+	N/A
16/ 49/F	4M	20/80	visual loss photopsias floaters	-	-	* fundus pigmentation	N/A	N/A	N/A
17/ 32/	0	20/80	symptomatic reduced vision over 1 yr	-	-	+ patchy pigmented disturbances	+	+	N/A
18/ 27/ F	0	20/250	symptomatic visual loss	left eye optic neuropathy (2 years previously). MRI brain: white matter lesions consistent with demyelination / CSF :	-	++ pigmentary dispersion with perivascular pigment cuffing	+	+	N/A

				unmatched oligoclonal bands.					
19/ 50/ F	7M	20/30	asymptomatic	-	-	+ heavily clumped pigmentation in crescent shaped patch nasally, perivascular pigment cuffing, bone-spicules	0	0	N/A
20/ 45/ F	4M	20/30	symptomatic visual loss retinal scarring noticed few years ago	-	--	+ + punched out atrophic RPE lesions superiorly and peripapillary .	+	+	+ Humphrey
21/ 41/ F	8M	20/20	photopsias	-	secondary to choroidal ischemia in pregnancy?	*unilateral retinal pigmentation noted 5 years ago	N/A	N/A	N/A
22/ 24/M	120M	20/30-20/60	photopsias	-	meningococcal meningitis at 14 yo	+ mid peripheral pigment dispersion, peripapillary atrophy	0	+	function within 50° on confrontation
23/ 53/ F	0	20/125	symptomatic visual loss	trauma age 7	-	+ + *peripapillary atrophy	N/A	N/A	N/A
24/ 31/M	0	20/20	*N/A	-	-	+	0	0	VF defects

25/ 55/ F	4M	20/40	asymptomatic	-	Inflammatory blood tests -ve	++ pigmentary dispersion with perivascular pigment cuffing, bone-spicules.	0	0	VF defects
26/ 44/ F	48M	20/20 - 20/80	photopsias	-	uterine carcinoma Inflammation tests –ve*.	+ mild changes at presentation then developed pigmentary dispersion with perivascular pigment cuffing, granular pigmentary disturbances. no bone spicules, CME.	0	0	N/A
27/ 37/ F	1M	20/20	amaurosis fugax 6 - 8 years ago. Since then unilateral visual disturbance. MRI scan - ve.	-	-	+++ peripapillary, supero-nasal and nasal pigmentary dispersion (crescent-shaped hyperpigmentary changes) that extended beyond the vascular arcades with perivascular pigment cuffing, bone-spicules.	0	+	VF constriction+
28/ 34/M	7M	20/250	visual loss for many years	-	longstanding hearing problems. poor vision one eye since childhood. 8 siblings unaffected. No-consanguinity.	+++ localized area of punched out atrophic RPE lesions nasally spreading towards the periphery; pigment dispersion (or crescent-shaped pigmentation)	+	+ nasally	full confrontation, Humphrey N/A
29/ 62/ F	0	20/80	*N/A	N/A	N/A	*RP typical aspect	N/A	N/A	N/A
30/ 41/M	3M	20/200	visual loss	-	optic neuritis diagnosed 8 years ago, resolved. No further details about it. Possible rheumatoid	+ mid-periphery RPE changes; pigment migration (bones spicules), pigmentary dispersion with	+	+	N/A

					arthritis	perivascular pigment cuffing			
31/ 19/ F	36M	20/40 - 20/60	photopsias	-	AZOOR	+ mid-periphery pigmentary changes with perivascular pigment cuffing, (perivenous)	0	0	field loss
32/ 13/ F	36M	20/400 - PL	visual loss	-	post inflammatory, paravascular sheathing fellow eye. routine inflammatory tests -ve	+ mild changes that progressed to extensive diffuse RPE atrophy; pigmentary dispersion with perivascular pigment cuffing	0	0	N/A
33/ 37/ F	30M	20/30	photopsias visual loss field loss nyctalopia migrainous	-	-	+ pigmentary dispersion with perivascular pigment cuffing, bones spicules supero and infero temporally	0	0	reduced to 20^0 on confrontation.
34/ 39/ F	0	20/20	asymptomatic	-	carrier of X-linked RP. Son has pArg412X (c.1234C>T) in *RPGR*.	+ inferior nasal bone spicules, pigmentary dispersion with perivascular pigment cuffing	0	0	VF full on confrontation
35/ 37/ F	48M	20/20	photospias, photosensitivity field loss	-	AZOOR Brain CT-scan normal (migraine)	+ mid-periphery RPE depigmentation with a few bone spicules and yellowish peripapillary chorioretinal scars	+	+	field loss in extreme edges of the field, unchanged 4 years later.

36/ 27/M	7M	20/20-20/80	photopsias field loss	-	AZOOR	+ nasal and mid-periphery pigmentary changes	0	+- mild	field loss
37/ 27/ F	0	CF	visual loss	trauma 3 years ago, profound unilateral visual loss since then.	-	+ peripheral retinal depigmentation and subretinal fibrotic tissue. no bones spicule.	0	0	N/A
38/ 33/F	2M	20/30	photopsias	-	parents first cousins. Brain CT-scan and orbits normal	+ peripheral pigmentary changes (inferior retina)	+	+	superior visual field loss
39/ 56/ F	4M	20/40	visual loss field loss	-	-	+++ widespread retinal degeneration, bones spicules	+	+	-
40/ 53/M	0	20/60	visual loss	-	+	++ mid peripheral pigmentary changes	+	+	field loss
41/31/M	43M	20/20	asymptomatic	-	-	+ bone spicules	++	+	field loss
42/40/F	108M	20/20	field loss	-	AZOOR	+ mid-peripheral RPE depigmentation with a few bone spicules and yellowish peripapillary chorioretinal scars.	0	+	field loss

N: normal ; N/A: not available or incomplete**.** If only one value in the VA column visual acuity remained unchanged between presentation and last follow-up.

Visual fields: - normal; + peripheral loss; ++ confluent mid-zone loss, +++ severe mid-zone and peripheral loss

Fundi: - normal; + peripheral changes; ++ peripheral and mid-zone changes; +++ advanced retinitis pigmentosa. RP: retinitis pigmentosa. CME: cystoid macular edema.

*Symptoms not reported for 2 patients. Details of fundus examination not available for 5 patients. AZOOR: acute zonal occult outer retinopathy.

Table 2: Final diagnoses of the 42 patients with unilateral pigmentary retinopathy (UPR).

Diagnoses	**Number of patients (n=42) (%)**	**Patient Number**	**Fundoscopic features similar to RP (%)**	**Electrophysiology**		
				rods, cones abnormalities of similar magnitude	**rods more affected than the cones**	**predominant cones abnormality**
Relevant Medical History	15 (35.7%)		11 (26%)	11 (26%)	3 (7%)	1 (2%)
Inherited disease: (Genotype if known)						
RP1 (ORF1)	1	7			case 7	
RP3 (RPGR)	1	34		case 34		
Ocular Trauma history	4	9,15,23,37	cases 15, 23, 37 (without bone	cases 9,15,23,37		

			spicules)			
<u>Possible Inflammatory Etiology</u>:						
AZOOR	4	31,35,36, 42		cases 31,35,36,42		
Vasculitis (in fellow eye)	1	32		case 32		
Presumed auto-immune retinopathy (rheumatoid arthritis)	1	30				case 30
History of meningitis	1	22			case 22	
Presumed autoimmune retinopathy	1	26	case 26 (without bones spicule)s		case 26	
Presumed choroidal ischaemia (recent pregnancy)	1	21		case 21		
No definite diagnosis	27 (64.3%)		26 (62%)	15 (36%)	12 (29%)	0 (0%)

Table 3: Normal values for ISCEV-standard pattern (PERG) and full-field ERGs.

Electrophysiological parameter	Age of patient	
	<50 years	**≥ 50 years**
Pattern ERG P50 amplitude (µV)	2.0	1.5
DA 0.01 (rod ERG) amplitude (µV)	140	80
DA 11.0 (bright flash ERG) amplitude (µV):		
a-wave	240	150
b-wave	350	200
LA 3.0 (single flash cone ERG) amplitude (µV):		
a-wave	29	19
b-wave	101	95
LA 3.0 30Hz (flicker ERG) :		
peak time (ms)	28	32
amplitude (µV)	70	62

Normal values for ISCEV-standard pattern (PERG) and full-field ERGs.

The lower limits of normal amplitude and upper limits of timing are shown for the main electrophysiological parameters in two adult age groups (a control group of 60 healthy subjects aged under 50 years and 19 subjects that were older). The limits of normality for ERG analysis were defined as the maximum peak time or minimum amplitude obtained in the control group, plus or minus 5% of the reference interval (the maximum value minus minimum value within the control group), to minimize false positives.

Percentiles for the main ERG parameters (Vincent at al., 2013) are added.

DA: dark-adapted; LA: light-adapted; µV: microvolts ; ms: milliseconds.