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Prevalence of anti-retinal antibodies in Acute Zonal Occult Outer Retinopathy (AZOOR): a comprehensive review of 25 cases

Cynthia X. Qian^{*,1}, Angeline Wang^{*,2}, David L. DeMill¹, Thiran Jayasundera¹, Kari Branham¹, Maria Fernanda Abalem¹, Naheed Khan¹, and John R. Heckenlively¹

¹Department of Ophthalmology and Visual Sciences, University of Michigan Medical School, Ann Arbor, Michigan, United States.

²Department of Ophthalmology and Visual Sciences, University of Wisconsin Medical School, Madison, Wisconsin, United States.

Abstract

Purpose—To perform a comprehensive review and to investigate the presence and role of autoimmune antibodies in 25 cases of acute zonal occult outer retinopathy (AZOOR) identified using the classification originally proposed by J.Donald Gass.

Design—Observational case series

Methods

Setting: Institutional

Study Population: Twenty-five patients were identified by characteristic symptoms (abrupt onset of photopsias, followed by large scotomata at or connected to the blind spot), ocular findings (paucity of pigmentary changes with no sign of vitreous inflammation and abnormal electroretinogram in at least one eye,) and a negative family history for retinitis pigmentosa.

Observation Procedures: Patients underwent a full comprehensive ophthalmologic exam fundus retinography, Goldmann kinetic visual field (GVF), and full-field electroretinogram (ffERG). Blood samples were also obtained to verify for the presence of anti-retinal antibodies by Western blot analysis.

Main outcome measures: Clinical presentation, best-corrected visual acuity (BCVA), fundus abnormalities, visual field defects, ffERG changes and presence of anti-retinal antibodies.

Results—Sixteen patients (64%) presented with photopsias, 56% (14/25) with night blindness, and 56% (14/25) with loss of peripheral vision. 64% (16/25) of cases were bilateral. All patients demonstrated retinal vascular attenuation, optic nerve head pallor, and mottling of RPE. The most

Corresponding Author: John R. Heckenlively, University of Michigan / W.K. Kellogg Eye Center Address: 1000 Wall Street, Ann Arbor, MI. 48105. jrheck@med.umich.edu, Phone: 734-763-0438, Fax: 734-764-3906.

*The authors contributed equally to this manuscript.

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common visual field changes included enlargement and expansion of the blind spot extending into large pericentral or other types of scotomata (64%). Both scotopic and photopic fERG values were abnormal and affected to a similar degree in our patients. Nine patients (36%) had a greater than 20% asymmetry in ERG values between the two eyes. All patients had anti-retinal antibodies on Western blot with an average of 6.6 bands.

Conclusion—Evidence suggests that AZOOR is a unique form of autoimmune retinopathy and retinal manifestation suggests possible anti-retinal antibody leakage from the disc margin with spread of immune products under the retina resulting in large scotomata that connect to the optic nerve head.

Keywords

autoimmune; AZOOR; autoimmune retinopathy; enlarged blind spots; retinal degeneration

Introduction

Acute zonal occult outer retinopathy (AZOOR) was first described in 1993 by J. Donald Gass as a syndrome with rapid loss of one or more extensive zones of outer retinal function.

¹ The initial 13 patients he reported were mostly young females who presented with photopsias associated with progressive scotomata, profound electroretinographic abnormalities in one or both eyes and minimal fundusoscopic changes. ¹⁻³

Subsequently in 2002, Dr. Gass, Agarwal, and Scott further characterized 51 AZOOR patients who were followed for at least three years. ⁴ In this study, the patients presented with photopsias and visual field defects with highly variable patterns and sizes of field defects. The most common defects were enlarged blind spots and large scotomata connecting to blind spots. (Figure 1) In many cases, there were visible zones of pigment epithelial atrophy and retinal vessel narrowing.

The improvement in imaging techniques over time has allowed for a new era in defining and describing this condition. Loss or irregularity of the inner segment-outer segment (IS/OS) boundary can be found in scotomatous areas and can be demonstrated by optical coherence tomography (OCT). ⁵⁻⁷ Retinal red free and fundus autofluorescence (FAF) image may also reveal retinal pigment epithelium (RPE) alterations. (Figure 1) ^{8,9} Mrejen et al. recently performed a comprehensive review of AZOOR emphasizing the value of a multimodal imaging approach. ⁹ They described in detail the outer retinal demarcation line of lesion progression and the trizonal appearance of subacute or chronic lesions on FAF, OCT and indocyanine green (ICG) imaging. ⁹

Despite being first described more than 20 years ago, the etiology of AZOOR remains elusive and is undergoing constant redefinition. Gass proposed an infectious viral process that first involves the peripapillary area with progressive advancement. ¹ Jampol and Becker postulated a genetics-driven autoimmune and inflammatory basis for a spectrum of separate disease entities including AZOOR and other white dot diseases such as multiple evanescent white dot syndrome (MEWDS), multifocal choroiditis and panuveitis (MFC-PU), and punctate inner choroidopathy (PIC). ^{10,11} Other mechanisms such as toxic retinopathy

10,12,13 or fungal infiltration^{14–16} have also been considered. In this report, we investigated 25 patients with AZOOR in order to better establish natural history and to further elucidate the role of autoimmunity in their disease.

Methods

The University of Michigan institutional review board, following the tenets of the Declaration of Helsinki, approved this study.

A retrospective chart review of all consecutive patients with AZOOR seen between January 2004 and June 2013 was conducted at the Retinal Dystrophy Clinic of the Kellogg Eye Center (University of Michigan).

Patients were selected based on the strict criteria for AZOOR as reported by Gass.^{1,4} These selection criteria included: sudden onset of visual symptoms, enlarged blind spots or large scotomatous areas connected to the blind spot, asymmetry of findings, and abnormal fERG in the presence of a normal fundus examination. Family history was obtained by a genetic counselor looking for a history of retinal degeneration and autoimmune disorders in the family pedigree. Cases with family history of retinitis pigmentosa were excluded.

The patients underwent a full comprehensive ophthalmic exam, including: best-corrected visual acuity (BCVA) using a Snellen chart, slit-lamp biomicroscopic examination, dilated fundus examination with a 78-diopter (Volk Optical Inc, Mentor, OH) lens, and indirect ophthalmoscopy with a 20-diopter (Volk Optical Inc, Mentor, OH) lens. Patients were also evaluated using standardized GVF with I-4-e, III-4-e, IV-4-e targets (Goldmann, Haag Streit, Koeniz, Switzerland), fERG (UTAS-3000, LKC Technologies, Gaithersburg, MD) following the ISCEV standard¹⁷ and fundus retinography. Kinetic visual field testing was preferred over static perimetry because the latter typically measures central field, and often misses the larger scotomata seen in AZOOR patients. The electroretinographic a- and b-wave amplitudes were reported in each eye in microvolts and as a percentage of mean normal to put any loss in perspective. (Table 1) Fundus autofluorescence (FF450, Carl Zeiss, Germany) and spectral-domain OCT (Heidelberg Engineering, Heidelberg, Germany) were analyzed when available.

Outcome measures included investigation of scotoma size and pattern of visual field loss. Unilateral versus bilateral visual field loss was also noted. The severity and types of electroretinographic changes, presence of fundus lesions or changes, time of onset of symptoms as best recollected by the patient to first visit were recorded.

Western blot analysis

Most AZOOR patients have a number of clinical findings overlapping with autoimmune retinopathy presentation. These include a sudden onset of symptoms in otherwise healthy patients, abnormal ERGs, and no abnormalities on fundus examination except in long standing cases. We therefore considered it prudent to check patients for anti-retinal antibodies by Western blot analysis. (Figure 2) After informed consent, serum and blood samples were obtained, processed, and stored at -80°C until studied. As control subjects, 10

healthy volunteers with normal ERGs and no family history of autoimmune diseases were recruited. Normal donor bovine retinal tissue was used. The latter retinal extracts were used as a means for reproducibility validation. Samples were suspended in phosphate-buffered saline, 1mM phenylmethylsulfonyl fluoride (PMSF), protease inhibitor cocktail and sonicated. Thirty micrograms of each lysate was heated for 10 minutes at 80°C in sample buffer with dithiothreitol, followed by sodium dodecyl sulfate–polyacrylamide gel electrophoresis. Proteins were transferred to nitrocellulose membrane and were incubated overnight with patients' serum at 1:100 dilution. The membrane was washed and incubated with anti-human IgG–tagged horseradish peroxidase, and proteins were detected using a chemiluminescent detection kit (SuperSignal West Pico; Thermo Scientific Pierce, Rockford, Illinois) and were then exposed to film.¹⁸

Results

We evaluated 25 patients that fit the criteria for AZOOR as outlined above. Patients presented with similar histories, but the history of disease activity varied from occurring many years previously to recent onset. Patient findings are detailed in Table 1. The mean age was 46.3±11 years old (range 14 to 81 years) and 84% of patients (21/25) were female. Age of symptom onset ranged from age 12 to age 71 (mean 51.1±19.7 years). Time of onset of symptoms to examination in our clinic varied from 4 months to 20 years. 64% of patients had personal or family histories of autoimmune disorders. None of the patients or their families had a history of retinitis pigmentosa. Macular function better than or equal 20/40 in at least one eye was present in 84% of patients. All patients had retinal vascular attenuation, optic nerve head pallor, and mottling of RPE. While diffuse retinal atrophy could be seen in affected areas, only two cases with longer duration had bone-spicule like pigment patches in the areas of scotomata.

All 25 (100%) AZOOR patients were positive for presence of anti-retinal antibodies (average 6.6 bands) on Western blot, compared to an average of 4.2 bands when compared to 25 consecutive autoimmune retinopathy patients, and 0–2 bands for normal controls.

Clinically, the AZOOR patients presented with similar patterns of findings with a rapid onset that included photopsias (64%), night blindness (56%), and loss of peripheral vision (56%). Nine (36%) patients had visual changes in one eye, while 64% had visual changes in both. (Table 1)

Characteristic visual field changes included enlarged blind spots and expansion of blind spots extending into large pericentral or other scotomata in 64% of patients. (Figure 1) Visual field defects often corresponded to changes seen in red free or autofluorescence photos. (Figure 1B) Asymmetric generalized constriction of fields was seen in nine patients (36%). (Table 1)

All patients manifested retinal dysfunction on electroretinography, either monocularly or binocularly. Nine patients (36%) had a greater than 20% asymmetry in ERG values between the two eyes. Under scotopic conditions, the mean a-wave value was 47.6±22.8% that of normal controls and the b-wave value was 43.3±27.4% of normal controls. Average photopic

b-wave value amongst patients was $44 \pm 28.9\%$ of normal database while combined response was decreased to a mean of $45.1 \pm 24.6\%$ and $49.1 \pm 29.5\%$ for a- and b-waves respectively. (Table 1)

Discussion

AZOOR has been a difficult disease to understand due to its unclear etiology, the lack of diagnostic biomarkers, and the paucity of initial retinal changes to help confirm that AZOOR. This has led to confusing the diagnostic delineation between AZOOR and a multitude of other conditions that possess similar findings. The diagnosis is made by recognizing a common disease pattern including the abrupt onset of photopsias, scotomata, nyctalopia and vision loss in previously normal patients without history of retinitis pigmentosa. Retinal abnormalities are confirmed by abnormal full field electroretinogram, all the more remarkable in the face of a lack of discernible changes on funduscopy.

Specialized equipment, i.e. an electroretinogram and kinetic perimetry greatly assist in establishing the diagnosis, but these instruments are not found in many clinics. The most helpful diagnostic sign is an enlargement of the blind spot. (Figure 1) A minority of cases (10%) have large peripheral confluent scotomata, which Gass hypothesized was because the anterior retina was thinner giving easier access to a serum-borne damaging agent.⁴

Several studies, including this paper, show that abnormal photopic and scotopic ERGs are common in AZOOR.³ The photoreceptor functional loss in addition to the pattern of damage emanating from the optic nerve rim, seen on visual field and in autofluorescence studies raise the possibility that anti-retinal antibodies may be breaking through the blood-retinal barrier at the optic canal retina junction, and may be a key component in causing enlargement of the blind spot. Autoantibodies spreading across the subretinal space in many patients likely result in the scotomata connecting to the blind spot. The subretinal damage can be seen as hypofluorescent patches on autofluorescence or with hyperfluorescent RPE staining that corresponds to scotomata noted on visual fields. (Figure 1C) The presumed leakage of immune products into the subretinal space may be one of the main events initiating large blind spots, a distinguishing feature of AZOOR.

Until this study, there has been no clear underlying etiology; however, anti-retinal antibodies were abundantly present in all our cases. (Table 1) Each of our patients demonstrated a varying number of bands and mixture of different anti-retinal antibodies on Western blots, implying that different retinal cell types were likely targeted, giving each individual a unique set of anti-retinal antibody composition.

A question that commonly arises is: given the perception that the retina is an immune privileged site where tight junctions of the endothelium and the RPE basement membrane are purported to inhibit antibody penetration, how do the antibodies reach the retina? It is known that inflammation disrupts the tight junctions of the RPE.^{19–21} In the case of AZOOR, it is highly likely that the blood retinal barrier may be breached at the optic nerve rim, allowing the anti-retinal antibodies to gain access to the subretinal space where they are toxic to the photoreceptors and the RPE. Since autofluorescence studies often show

damaged RPE emanating from the disc rim matched to similarly shaped scotomata on visual field, it can be hypothesized that this subretinal leakage of anti-retinal antibodies originates at the disc rim and is a unique feature in AZOOR (Figure 1). Some patients also have a normal zonal withdrawal of the peripapillary RPE, which might open up subretinal access to circulating antibodies. It is possible that the macula may present with tight junctions and zonula occludens particular to its location and more impermeable to this effect and hence may also be relatively spared in comparison.

The mechanisms by which anti-retinal autoantibodies are present is unknown. A minority of patients have other autoimmune diseases while others give a history of head trauma or a prodromal viral infection. There are also reports of immune-mediated retinal diseases such as MEWDs or multifocal choroiditis preceding onset of symptoms. There may have been release of retinal antigens that may result in an autoimmune response.¹⁰

In many patients, AZOOR is a self-limiting disease and becomes quiescent, typically after six months.⁴ The history of onset and the current immediate history of progression are important in understanding if the disease is active. We found that most patients who undergo progression give clear histories that their vision is deteriorating. The presence of anti-retinal antibodies is helpful diagnostically, although they do not distinguish active from inactive cases. If immunosuppressive treatment is undertaken, it is important to evaluate the patients for active disease with repeat functional tests such as GVF and fERG. This approach allows treatment effects to be validated, since the clinical signs of AZOOR remain even after the disorder becomes inactive. Currently there are no biomarkers for autoimmune retinopathy that are known to help in tailoring the treatment regimen.

In summary, the current study suggest that AZOOR is a form of autoimmune retinopathy in which the pattern of visual field damage may be strongly influenced by peripapillary leakage of anti-retinal antibodies into the subretinal space. This information is useful in designing future biomarkers to survey the level of autoimmune activity in the condition, which in turn may help tailor and gauge the effect of an immunologic treatment regimen for AZOOR.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement/Disclosure

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Figure 1- Representative multimodal imaging of 3 patients presenting with Acute zonal occult outer retinopathy

Selected cases to illustrate the testing and imaging findings of 3 patients presenting with typical AZOOR findings as defined by the criteria originally defined by Gass et al. These correspond to patients listed in Table 1 and identified with their laboratory identification number

Top row: Case 1 is patient 1024, a 42-year-old woman who presented with progressive two-and-a-half year history of decreased visual acuity and distortion of fine print, OD worse than OS. The Goldmann visual fields showed enlarged blind spots and peripheral scotomata

OS>OD. Fundus examination showed no overt lesions and mild vascular attenuation; the autofluorescence (AF) demonstrated RPE damage emanating from the discs OU. Western blot showed five anti-retinal antibody bands in the human test lane.

Middle row: Case 2 is patient 5448, a 58-year-old man who presented with a two-year history of bilateral peripheral visual field loss and central vision blurring. He had a family history of diabetes and connective tissue disease. His autofluorescence was remarkable for RPE damage emanating from focal points of the optic disc, which correspond exquisitely well to the color fundus photographs and the outline of his GVF. He had four anti-retinal antibody bands on Western blot.

Bottom row: Case 3 is patient 861, a 63-year-old lady with a one-year history of visual distortion OS>OD. Goldmann visual field testing showed full isopters, but with pericentral scotomatous regions OU, consistent with the areas of atrophy in her fundus. Fundus color photographs and autofluorescence show areas of diffuse RPE loss corresponding to the visual field scotomata. The pattern of RPE damage OU was suggestive that toxic immune products leaked from the disc margins and spread into the subretinal space. There were minimal pigmentary deposits in the areas of RPE atrophy. She had eight anti-retinal immunoreactive bands on Western blot

Figure 2- Examples of normal western blot results on peripheral blood samples of normal subjects

Left: HR: human retina; BR: bovine retina, KDa: kilodaltons

Table 1-

Clinical information on all 25 patients with acute zonal occult outer retinopathy

Lab ID	Age/ Sex	Onset	Initial VA OD/OS	Laterality	Family Hx AI Disease	Goldmann visual field	Dilated Fundus Examination	Bands WB	ERG (in μ V, % normal mean)					
									Photopic		Scotopic	Mixed		
									A-WAVE	B-WAVE		A-WAVE	B-WAVE	
480	14/F	12 yrs	20/70 20/400	Bilateral	Astmda (GM) Tdyroid (Mt)	PCS, EBS, contraction OU	Vasc atten, diffuse retinal atrophy OU, no pg	10	13 (33%) OD, 9 (23%) OS	58 (36%) OD, 51 (31%) OS	<5 (<2%) OD, <5 (<2%) OS	32 (15%) OD, 23 (11%) OS	57 (15%) OD, 56 (15%) OS	
848	49/F	29 yrs	20/20 20/20	Unilateral	None	PCS OS, EBS OS, mild contraction OS	Perivascular pg OS, patchy RPE thinning OS	10	24 (62%) OD, 12 (31%) OS *	105 (64%) OD, 38 (23%) OS *	159 (57%) OD, 47 (17%) OS *	105 (50%) OD, 40 (19%) OS *	208 (52%) OD, 59 (15%) OS *	
861	42/F	39 yrs	20/20 20/20	Bilateral	Thyroid (Pt, Mt, S)	EBS OU, CS OU, temporal scotoma OS	Vasc atten, mild temporal optic atrophy OU	8	11 (28%) OD, 16 (41%) OS	31 (19%) OD, 55 (34%)OS	36 (13%) OD, 91 (33%) OS *	18 (9%) OD, 86 (41%) OS *	62 (16%) OD, 2 (1%) OS	
906	51/F	50 yrs	20/60 20/40	Bilateral	RA (Mt), Asthma (S), Thyroid (S)	EBS OU, CS OD, PS OU, mild contraction OD>OS	Blonde fundus, patches of atrophy superiorly OU	10	21 (54%) OD, 22 (56%) OS	18 (11%) OD, 87 (53%) OS *	55 (20%) OD, 26 (9%) OS	97 (46%) OD, 93 (44%) OS	127 (37%) OD, 133 (24%) OS	
910	42/F	32 yrs	20/15 20/15	Unilateral	None	PCS OS	Vasc atten OS, equatorial pg OS	10	42(107%) OD, 26 (67%) OS *	152 (93%) OD, 108 (66%) OS *	334 (120%) OD, 178 (64%) OS *	243 (115%) OD, 135 (64%) OS *	469 (117%) OD, 283 (70%) OS *	
1024	63/F	63 yrs	20/25 20/200	Bilateral	None	EBS OU, multiple scotomata OD, PCS OS	Pale optic nerve, diffuse retinal loss OU, RPE pg OS	6	15 (38%) OD, 23 (59%) OS *	53 (33%) OD, 71 (44%) OS	86 (31%) OD, 76 (27%) OS	79 (37%) OD, 82 (39%) OS	120 (30%) OD, 119 (30%) OS	
2040	58/F	49 yrs	20/400 20/20	Bilateral	None	CS OD, mild contraction OU	No pg, peripapillary atrophy, flat fovea OU	10	19 (49%) OD, 39 (100%) OS *	43 (26%) OD, 120 (74%) OS *	103 (37%) OD, 216 (78%) OS *	76 (36%) OD, 173 (82%) OS *	189 (47%) OD, 355 (89%) OS *	
3035	47/F	46 yrs	20/30 20/20	Bilateral	None	Temporal scotomata OU	RPE thinning, fine pg, focal atrophy OU	8	19 (49%) OD, 19 (49%) OS	110 (67%) OD, 99 (61%) OS	99 (36%) OD, 105 (38%) OS	58 (27%) OD, 91 (43%) OS	157 (40%) OD, 209 (53%) OS	
3076	50/F	33 yrs	20/20 20/20	Bilateral	Thyroid (Mt)	PCS OD, contraction ring OS	RPE depigmentation and equatorial atrophy OU, no pg	6	30 (56%) OD, 23 (59%) OS	124 (76%) OD, 116 (71%) OS	218 (78%) OD, 160 (58%) OS *	125 (59%) OD, 141 (67%) OS	353 (90%) OD, 339 (86%) OS	
3179	35/F	27 yrs	20/15 20/20	Bilateral	Thyroid (S) Raynaud (Mt)	EBS OU, scattered scotomata OD, PCS OS	Scattered white dots, sheathed vessels OU, no pg	10	30 (77%) OD, 26 (67%) OS	105 (64%) OD, 101 (62%) OS	135 (49%) OD, 108 (39%) OS	111 (53%) OD, 98 (46%) OS	248 (63%) OD 253 (64%) OS	
3180	48/F	46 yrs	20/20 20/30	Unilateral	Fib (Pt), Poly (Ft)	CS OS	Sheathing retinal arterioles OS, diminished foveal reflex OS, no pg	6	32 (82%) OD, 17 (44%) OS *	175(107%) OD, 31 (19%) OS *	331 (119%) OD, 215 (77%) OS *	22 (10%) OD, 17 (8%) OS	418 (106%) OD, 265 (67%) OS *	
3439	55/F	53 yrs	20/20 20/30	Unilateral	Thyroid (Pt, Mt)	Moderate contraction OU	Peripheral retinal/RPE atrophy OU, CME OS, no pg	6	10 (26%) OD, <5 (13%) OS	20 (12%) OD, 5 (3%) OS	38 (14%) OD, 11 (4%) OS	47 (22%) OD, NR (0%) OS *	60 (15%) OD, NR (0%) OS	
3556	73/F	71 yrs	20/25 20/30	Bilateral	Psoriasis (B)	EBS OU, contraction OU	Choroidal loss, bare sclera, subretinal pg OU	2	5 (13%) OD, 10 (26%) OS	15 (9%) OD, 40 (25%) OS	41 (15%) OD, 125 (45%) OS *	54 (26%) OD, 128 (61%) OS *	80 (20%) OD, 183 (47%) OS *	
3626	29/F	28 yrs	20/40 20/30	Bilateral	None	Multiple scotomata OD, mild contraction OU	None	10	35 (90%) OD, 29 (74%) OS	163(100%) OD, 139 (85%) OS	239 (83%) OD, 232 (83%) OS	201 (95%) OD, 155 (73%) OS *	378 (96%) OD, 308 (78%) OS	
3634	55/F	55 yrs	20/15 20/25	Bilateral	None	Scattered scotomata OU	Blonde fundus, mild atrophy OU, no pg	2	17 (44%) OD, 54 (34%) OS	84 (52%) OD, 54 (34%) OS	203 (73%) OD, 245 (88%) OS	137 (65%) OD, 158 (75%) OS	277 (70%) OD, 303 (77%) OS	

Lab ID	Age/ Sex	Onset	Initial VA OD/OS	Laterality	Family Hx AI Disease	Goldmann visual field	Dilated Fundus Examination	Bands WB	ERG (in μ V, % normal mean)				
									Photopic		Scotopic	Mixed	
									12 (31%) OS				
3712	18/F	17 yrs	20/20 20/15	Bilateral	Asthma (Pt, Mt, S), RA (Mt), Fib (Mt)	EBS OD, scotomata, contraction OD	Retinal/RPE atrophy OU, scars, central atrophy OD	10	11 (28%) OD, 27 (69%) OS *	17 (10%) OD, 128 (79%) OS *	13 (5%) OD, 191 (69%) OS *	47 (22%) OD, 139 (66%) OS *	28 (7%) OD, 264 (67%) OS *
3776	57/F	47 yrs	20/25 20/40	Bilateral	Fib (Pt)	EBS OU, PCS OD, ring OS	Paracentral atrophy OU, no pg	2	15 (38%) OD, 33 (85%) OS *	57 (35%) OD, 84 (52%) OS *	143 (51%) OD, 227 (82%) OS *	115 (55%) OD, 164 (78%) OS *	194 (49%) OD, 262 (67%) OS *
3816	60/M	59 yrs	20/200 20/100	Bilateral	Fib (S)	EBS OU, contraction OS>OD	Cryo scars OU, RD scars OS, no pg	6	14 (36%) OD, 16 (41%) OS	34 (21%) OD, 38 (23%) OS	140 (50%) OD, 63 (23%) OS *	82 (39%) OD, 54 (26%) OS	206 (52%) OD, 107 (27%) OS *
3952	36/F	34 yrs	20/25 20/20	Bilateral	SLE (GM)	EBS, contraction OU, scattered scotomata OD	Diffuse retinal atrophy OU; minor bone spicule-type pg OD	4	7 (18%) OD, 6 (15%) OS	9 (6%) OD, 7 (4%) OS	<5 (<2%) OU	17 (8%) OD, 22 (10%) OS	20 (5%) OD, 15 (4%) OS
3954	52/F	40 yrs	20/30 20/40	Unilateral	Thyroid (Pt)	EBS OS, mild contraction OS	Mottled RPE OD, posterior pole scar OS, no pg	2	32 (82%) OD, 20 (51%) OS *	109 (67%) OD, 77 (47%) OS	190 (68%) OD, 108 (39%) OS *	175 (83%) OD, 118 (56%) OS *	372 (95%) OD, 248 (63%) OS *
4454	38/F	26 yrs	20/25 20/160	Unilateral	None	PCS OS, severe contraction	Depigmented spots OU, mild pigmentary changes, CME OS	4	43 (110%) OD, 4 (10%) OS *	188(115%) OD, 43 (26%) OS *	390 (140%) OD, NR (0%) OS *	329 (156%) OD, NR (0%) OS *	594 (151%) OD, NR (0%) OS *
4486	51/M	49 yrs	20/400 20/20	Unilateral	RA (S)	EBS OD, CS OD scattered PCS/PS, contraction OD	Optic disc pallor OD, no pg	4	9 (23%) OD, 40 (102%) OS *	19 (12%) OD, 226(138%)OS *	150 (54%) OD, 288 (104%) OS *	83 (39%) OD, 252 (119%) OS *	260 (66%) OD, 504 (128%) OS *
4488	51/F	47 yrs	20/40 20/40	Bilateral	Asthma (Pt), Raynaud (Pt), Thyroid (Pt)	contraction, multiple scotomata OU, CS OS.	Diffuse retinal atrophy, lack of pigment OU, CWS OS.	6	10 (26%) OD, 11 (28%) OS	21 (13%) OD, 28 (17%) OS	59 (21%) OD, 19 (7%) OS	72 (34%) OD, 46 (22%) OS	110 (28%) OD, 75 (19%) OS
4505	81/M	71 yrs	20/50 20/250	Bilateral	None	EBS OD, severe contraction OS	Patches of pg OU	2	<5 (<13%) OD, NR (0%) OS	11 (7%) OD, NR (0%) OS	28 (10%) OD, NR (0%) OS	47 (22%) OD, NR (0%) OS *	95 (24%) OD, NR (0%) OS *
5448	58/M	56 yrs	20/40 20/40	Bilateral	CTD (S), DM2 (Mt,Ft)	Moderate contraction OU, EBS OU	Retinal atrophy, exudates, peripapillary subretinal pg OU	4	9 (23%) OD, 11 (28%) OS	26 (16%) OS, 35 (22%) OS	77 (28%) OD, 103 (37%) OS	79 (37%) OD, 111 (53%) OS	131 (33%) OD, 165 (42%) OS

Normal ERG range for a-wave and b-wave: Photopic conditions a-wave normal range: 23–54 μ V; b-wave normal range 95–230 μ V. Scotopic b-wave normal range is 180 to 375 μ V. Combined response a-wave normal range: 120–301 μ V; bwave normal range: 230–555 μ V. Normal mean ERG values were calculated by averaging the upper and lower limits of the normal range. The percentage of the normal mean for each patient was recorded in parentheses.

* = μ V asymmetry between eyes 20%.

Immunoreactive bands refers to anti-retinal antibody activity on Western blot.

Abbreviations:

AI: Autoimmune; B: Brother; CME: Cystoid macular edema; Cryo: Cryotherapy; CS: Central Scotoma; CTD: Connective Tissue Disease; DA: Dark Adaptation; EBS: Enlarged blind spot; ERG: Electroretinogram; Ft: Father; F: Female; Fib: Fibromyalgia; GVF: Goldmann Visual Field, GM=Grandmother; GF=Grandfather; Hx: History; M: Male; Mt: Mother; PCS: paracentral scotoma, Pg: Pigment deposits; Poly: Polymyositis; PS: Peripheral scotoma; Pt: Patient; RA: Rheumatoid arthritis; Raynaud: Raynaud’s disease; Ring: Ring scotoma; RPE: Retinal pigment epithelium; S: Sister; SLE: Systemic lupus erythematosus; Thyroid: Thyroid disease, VA: Visual acuity; Vasc atten: vascular attenuation; WB: Western blot.