ORIGINAL ARTICLE

From A... to... Z(OOR): The Clinical Spectrum of Acute Zonal Occult Outer Retinopathy

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ABSTRACT

Acute idiopathic blind spot enlargement (AIBSE) is often caused by Acute Zonal Occult Outer Retinopathy (AZOOR), an outer retinal disease. We report two illustrative cases of AZOOR. The first one was a 21-year-old white female who presented with a scotoma and “shimmering lights” in her left eye. In the second case, a 73-year-old white female was referred for evaluation of a “bitemporal hemianopsia” that started years prior, with no clinical significant photopsias. To our knowledge, case two is the longest documented duration of bilateral, progressive, and chronic, idiopathic, enlargement of the blind spot (CIBSE) documented in the English language ophthalmic literature.

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Acute zonal occult outer retinopathy; enlarged blind spot; ellipsoid zone; autofluorescence

Case one

A 21-year-old Caucasian female presented to the emergency room with an acute onset of a “dark area” in the temporal vision of her left eye (OS) associated with “shimmering lights”. Her past general history was remarkable for asthma and migraine. She reported an episode of cystitis three weeks before presentation, associated with fever.

On examination, visual acuity was 20/20 in both eyes (OU) with normal anterior segment and fundus examination (Figure 1A). Pupils were equal with no relative afferent pupillary defect (RAPD). Colour vision testing was normal. Automated visual field testing (Figure 1B) was unremarkable in the right eye (OD), but showed an enlarged blind spot OS. Optical coherence tomography (OCT) of the macula was normal OD. There was disruption of the peripapillary ellipsoid zone OS (Figure 1C). Fundus autofluorescence (FAF) was normal OD, but showed a halo of peripapillary hyperautofluorescence OS (Figure 1D).

Fluorescein angiography (FA) showed hyperfluorescence in this same area which persisted in the late phases of the angiogram. Indocyanine green angiography (ICGA) was significant for hypofluorescence more evident in the late phases, up to 30 minutes (Figure 1E-H). A diagnosis of AZOOR was made based on multimodal imaging findings, positive ophthalmic and systemic history, and exclusion of other entities. The patient was treated with oral steroids (prednisone 1 mg/kg/day for 10 days followed by taper) with resolution of symptoms, the visual field defect and the multimodal ocular imaging abnormalities.

Case two

A 73-year-old white female was referred to the neuro-ophthalmology service at Houston Methodist Hospital for evaluation of an asymmetrical possible “bitemporal hemianopsia” OU that progressively became worse over seven years. The retina service

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Figure 1. A. Colour fundus photography was normal in both eyes. B. Humphrey 30–2 visual field is unremarkable in the right eye while showing enlarged blind spot in the left eye. C. Macular OCT of the left eye showing disruption of the peripapillary ellipsoid zone on the right side. D. Fundus autofluorescence (FAF) is normal OD, but shows a halo of peripapillary hyperautofluorescence OS. E–F. Fluorescein angiography (FA) showing hyperfluorescence in this same area and remains evident in the late phases of the angiogram. G–H. Indocyanine green angiography (ICGA) is significant for hypofluorescence more evident in the late phases, up to 30 minutes.

has been following the patient previously for early dry form of age-related macular degeneration (ARMD). Past medical history was significant for severe migraines that stopped six years ago and hypothyroidism treated with levothyroxine replacement.

On examination, the visual acuity was 20/20 OU. The pupils were equal and reactive with no RAPD. Intraocular pressure measurements were 17 mm Hg OD and 16 mm Hg OS. Colour plates were correctly identified in 14/14 plates bilaterally. Slit-lamp examination was within normal limits, with no vitreous cells. Dilated ophthalmoscopy showed significant peripapillary retinal pigment epithelium (RPE) atrophy around the optic nerve aligning with her blind spot enlargement OU (Figure 2A). The remainder of the fundus exam was normal OU except for scattered macular drusen. Cup-to-disk ratio was 0.4 in each eye, with no

rim pallor. There was no active disease and no vasculitis. There was no papilloedema seen in either eye.

Humphrey visual fields (HVF) showed an enlarged blind spot OU (OD > OS). Cranial magnetic resonance imaging (MRI) was normal. Serial automated visual field tests showed slow progression of the enlargement of the blind spots OU over seven years (Figure 3A–B).

Repeat MRI of head was normal. OCT of the retinal nerve fibre layer showed no optic atrophy of disc oedema but the peripapillary retina showed changes at the level of the RPE and the ellipsoid OU (Figure 2B–C). Full-field flash electroretinogram (FERG) was negative for any 30-Hz cone b-wave implicit time delay changes (Figure 2D). Multifocal ERG (mfERG), with 103 test spots in the central 67 degrees, showed decreased temporal

Figure 2. Colour fundus photography shows significant peripapillary retinal pigment epithelium (RPE) atrophy around the optic nerve aligning with her blind spot enlargement in both eyes. B. OCT of the showing peripapillary outer retina and IS/OS junctional disruption OU. C. OCT RNFL showing normal-borderline total optic nerve RNFL thickness OU. D. Full-field flash electroretinogram (FERG) is negative for any 30-Hz cone b-wave implicit time delay changes OU. E-F. Multifocal ERG multifocal signals with 38% less foveal amplitude OD but an essentially normal mfERG OS.

Figure 3. A-B. Humphrey visual fields (HVF) showing progressive temporal visual field loss OU (OD > OS) over seven years.

parafoveal signals with 38% less foveal amplitude OD than OS (Figure 2E-F). A diagnosis of AIBSES secondary to atypical AZOOR was made.

Discussion

Acute zonal occult outer retinopathy (AZOOR) was first described by Gass in 1992 as an idiopathic syndrome characterised by sudden loss of outer retinal function associated with photopsia

with minimal or no fundoscopic changes initially and electroretinographic abnormalities affecting one or both eyes.¹ In his series of 13 patients, affected individuals were typically young, more frequently female and otherwise healthy, but some of those experienced a previous viral-like illness. Visual acuity was minimally affected and in a small percentage of patients, other signs were noted, such as vitreous cells or relative afferent pupillary defect. Fundoscopic examination was

normal in the early stage of the disease although most patients developed areas of retinal pigment epithelium (RPE) changes, such as atrophy or pigment clumping, vascular retinal attenuation, and eventually choroid atrophy when followed over time.^{1,2} In 1995, Gass and Stern described acute annular outer retinopathy (AAOR) as a variant of AZOOR.³ Patients with AAOR, like individuals with AZOOR, have acute visual field loss, but unlike AZOOR, fundus examination showed a grey intraretinal ring corresponding to the edge of the scotoma. The ring progressively enlarged, leaving zones of RPE depigmentation.

Gass speculated that AZOOR, acute idiopathic blind spot enlargement (AIBSE), multiple evanescent white dot syndrome (MEWDS), acute macular neuroretinopathy (AMN), punctate inner choroidopathy (PIC), and multifocal choroiditis (MFC) were a cluster of conditions named “white dot” syndromes or “AZOOR complex” disorders. Later, Herborn described these conditions as primary inflammatory choriocapillaropathies, supposedly caused by a presumed inflammatory process disturbing perfusion of the choriocapillaris leading to the functional disturbance in the outer retina.⁴ Indeed, it is not clear whether AZOOR should be considered part of this spectrum of diseases, or if AIBSE, MEWDS, AMN, PIC, MFC share a similar etiology. Although these disorders could manifest as or even be precipitating factors of AZOOR, most patients do not proceed to develop AZOOR. Nevertheless, there is consensus that electrophysiological assessment is essential in establishing diagnosis.⁵ Recently, Mrejen et al. proposed a classification of AZOOR based on clinical fundus and modern multimodal imaging.⁶ The characteristic findings observed by the authors on fundus photography, spectral-domain optical coherence tomography (SD-OCT), fundus autofluorescence (FAF), fluorescein angiography (FA) and indocyanine green angiography (ICG) might be helpful in distinguishing AZOOR from white dot syndromes as a specific entity. The etiology of AZOOR is still unclear and two hypotheses have been presented. Gass postulated that a virus or another infectious agent infects retinal photoreceptors, but the disease results when an autoimmune response is mounted against the infected cells.² Jampol and Becker gave evidence that

inflammatory eye manifestations may be due to the interplay of genetic predisposition to autoimmune diseases, environmental triggers, and immune pathways.⁷

Our two cases are complementary and illustrative of the spectrum of the disorder. Our first case was a young patient who had photopsias at onset. Her findings improved after prompt treatment. In contrast, our second case was an elderly woman with progression over seven years and referred as a possible bitemporal hemianopsia with negative neuroimaging. Our case two is interesting because of the bilateral visual field deficits and lack of specific physical findings besides significant peripapillary atrophy OU. Peripapillary atrophy can be associated with a number of conditions including post-papilledema, high myopia, presumed ocular histoplasmosis syndrome, glaucoma, and can even be seen as a normal aging variant. However, none of these alternative conditions were present in our patient: the brain MRI was negative, IOPs were normal, no documented disc oedema was observed, normal aging would not explain the visual fields and patient did not need any correction with glasses.

Although classically AZOOR is thought to occur in a young female with photopsias and an enlarged blind spot or other zonal visual field defect, our second case highlights what we believe are differences across a spectrum of zonal occult and non-occult retinopathies. The debate about AZOOR and other similar occult or non-occult retinopathies centres on whether one is a “lumper” or a “splitter”. For our cases, if a “lumper” approach is taken, then perhaps the two cases are representative examples along a spectrum of AZOOR from typical (case one) to atypical (case two). However, if a “splitter” approach is taken, then perhaps case one would be better characterised as typical AZOOR and case two as a form of progressive chronic (rather than acute as in AIBSE) idiopathic blind spot enlargement syndrome (CIBSES).

There are two prior long-term follow-up case series that has alluded to this “lumper” approach with documentation showing step-wise progression of blind spots in AZOOR patients. Gass showed 2 out of 51 patients had step-wise progression of blind spots after being followed for a median of

96 months (range of 36–420 months)²; Saito reported 1 out of 38 patients had at least 30% worsening vision loss after being followed for a median of 31 months (range of 6–132 months).⁸ Only one case study documented detailed progression of worsening AZOOR over a 13-year period.⁹ This 55-year-old patient continued to develop significant retinal atrophy and decreased visual acuity in one eye, with no improvement despite immunomodulators or antivirals, for 13 years.

Regardless of whether one is a “lumper” or “splitter”, we emphasise that there is a spectrum of presentations of retinal pathology mimicking neuro-ophthalmic disease. It should also be highlighted that, although the median age for typical AIBSES is mid-30’s^{2,10}, the chronic progressive AZOOR patients documented in literature (our second case and reference 16) both are older. To our knowledge, our case two is the longest documented progression of blind spot enlargements bilaterally with subsequent development of peripapillary atrophy ophthalmoscopically OU.

Salgado et al¹¹, previously reported a case of pseudo-bitemporal hemianopia in a 67-year-old woman in whom brain MRI scan was normal with no signs of chiasmal compression. The fundus examination and mfERG in this case were both unremarkable. During follow up, after four years, atrophic peripapillary changes were noted bilaterally and repeated mfERG now showed abnormal topography bilaterally with severely reduced activity in the nasal retinas of both eyes corresponding to the temporal hemifields.

The fundus examination is usually normal in the early stage of AZOOR, but our older patient did show significant peripapillary RPE atrophy later in her course. The most frequently reported retinal abnormalities include RPE changes, such as RPE depigmentation, retinitis pigmentosa-like changes with or without cystoid macular oedema (CME), white annular ring or other non-specific abnormalities.¹⁰

Zonal visual field loss is a characteristic finding of AZOOR and a visual field test is strongly recommended to confirm the diagnosis. A wide variety of visual field defects are reported in AZOOR, but the most frequent is an enlarged blind spot with central scotoma. Fundus fluorescein angiography is often normal when the fundus examination is

unremarkable and the most frequent abnormality is related to RPE changes when clinically appreciated. Less frequently vascular changes can be observed, such as retinal vascular staining and/or leakage, narrowed retinal vessels, delayed choroidal filling, CME, optic disc staining. ICG has not been extensively studied, but it usually shows hypofluorescence of the clinical lesion or eventually hypofluorescent areas unrelated to the lesion. However, ICG is typically normal when the fundus is normal. FAF can be normal but hypofluorescent areas correspond to areas of RPE atrophy with or without a hyperfluorescent border. SD-OCT shows a loss or irregularity of the photoreceptor inner segment/outer segment (IS/OS) junction (ellipsoid) in areas of retina corresponding to scotoma or in areas with reduced multifocal electroretinography (mfERG) response. Other SD-OCT findings are attenuation or loss of the outer nuclear layer, irregularity of the RPE and/or decreased retinal thickness.¹²

Abnormalities of the cone outer segment tip (COST) line have been reported in AZOOR.¹³ COST line has been recognised in SD-OCT images as a thin, highly reflective line between the IS/OS junction and the RPE.¹⁴ The characteristic features described in the recent original investigation by Mrejen et al. included a demarcating line of the progression at the level of the outer retina and a trizonal pattern of sequential involvement of the outer retina, RPE and choroid, as well as frequent zonal progression.⁶ Those RPE and choroidal changes were all detected by a multimodal imaging including fundus photography, SD-OCT, FAF, FA and ICG and they may be attributed to the death of photoreceptors. FERG is a widely performed test for the diagnosis of AZOOR, although this test produces a single waveform and only recruits from the rods and cones in the peripheral retina. Thus, the full field ERG is usually normal in AZOOR. The most frequent abnormality is a delay in the cone system, showing as a decrease in 30-Hz (pure cone) response. If available, mfERG documents the extent and localisation of central field loss. A reduction in the light rise on electro-oculogram can be also noted. Because most patients present with electrophysiologic abnormalities, most authors seem to question a diagnosis of AZOOR if ERG is negative, but may only suggest there is

no peripheral retina involvement. However, unusual cases with typical features of AZOOR and seemingly normal wavelengths on electroretinograms have been reported.¹⁵ In addition, some authors consider the FERG is rarely needed to confirm the diagnosis of AZOOR with the advent of modern ophthalmic imaging.¹⁶

Our first patient showcases the utility of a multi-modal imaging algorithm for diagnosis. Her OCT macula, FAF and FA all corroborated the AZOOR diagnosis. Our second patient's diagnosis was more elusive, and required ruling out multiple other entities (compressive mass, optic nerve neuropathy) to arrive at AZOOR.

Her FERG from the peripheral retina was negative due to the zonal nature of AZOOR presentations, while her mfERG from the central retina showed waveform discrepancies consistent with visual field deficits. Her OCT RNFL showing diagnostic, bilateral IS/OS junction disruption, significant peripapillary RPE atrophy on fundus exam and zonal visual field findings strongly suggest AZOOR as her diagnosis.

No treatment has been proven to be effective in improving the symptoms or recovering the visual field loss. Systemic corticosteroids are the most commonly attempted therapy. Recently, Chen et al. speculated that AZOOR may be an inflammatory disease and that aggressive systemic steroid therapy at an early stage may reverse the natural course of the disease, minimising secondary RPE and choroidal changes and improving visual outcome.¹⁷ However, in most patients the diagnosis is delayed and the treatment may not help outer retinal tissue recovery in time if significant tissue damage has already occurred. Given the second hypothesis of a presumed viral aetiology, oral antiviral agents, such as acyclovir and valacyclovir, have been employed in combination with a tapering dose of systemic corticosteroids. Other antimicrobial drugs, including sulfadiazine/trimethoprim and anti-fungal agents, and non-corticosteroid systemic immunosuppressive in association with steroids have been reported in the treatment of some cases of AZOOR.¹⁰

In summary, these two cases show the diverse range of patients and clinical manifestations that may make the diagnosis of AZOOR difficult. AZOOR should be considered a disease of neuro-ophthalmic interest with variable clinical

presentations: from an acute visual field defect mimicking optic neuritis, to a (pseudo)bitemporal hemianopia mimicking a chiasm compression. The authors suggest performing a mfERG and other retinal multimodal imaging, particularly OCT and fundus AF, in cases of unilateral or bilateral enlarged blind spot of unknown origin. We also propose that there is a chronic equivalent of AIBSES, CIBSES which may be on the spectrum of AZOOR.

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