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Patients with an Acute Zonal Occult Outer Retinopathy-like Illness Rapidly Improve with Valacyclovir Treatment

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Introduction

There are a group of patients with acute vision loss that share one or more clinical features that include patchy or zonal visual field loss, photopsias, outer retinal or photoreceptor dysfunction, asymmetric electroretinographic abnormalities, vitreous cells, an antecedent flu-like illness, and a nearly normal fundus examination. In 1993 Gass described a series of such patients and suggested the term, acute zonal occult outer retinopathy (AZOOR), and Fletcher in 1988 had described other patients with acute idiopathic blind spot enlargement and no disc edema.^{1–6} Retinal vascular narrowing and retinal pigment epithelial atrophy similar to retinitis pigmentosa may develop in later stages.⁷ The visual field loss is often permanent, and the second eye may become involved within several years.^{2, 4, 6–8} The underlying etiology of these AZOOR-like illnesses is not known, but both autoimmunity and a viral etiology have been suggested.^{9–11}

Herpes-family virus is highly prevalent,¹² and seroconversion can be asymptomatic.¹³ Autopsy studies have established that latent herpes virus is present in virtually every organ system.¹⁴ New and highly sensitive laboratory testing has shown that otherwise immunocompetent patients may develop subacute disease with viral reactivation. This may be due to subclinical immunosuppression where specific immunological cells and signals in the innate and acquired immune system that normally suppress viral reactivation and shedding are affected.^{15–16} These observations have given rise to the concept of subacute herpetic viral infections with significantly greater variance in the clinical manifestations than

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previously appreciated.^{17–18} For example, patients that originally did not meet all the diagnostic criteria for herpetic encephalitis, but had some of the symptoms with less severity, seemed to respond to antiviral medication and were eventually found to have increased viral loads after DNA polymerase chain reaction (PCR) testing of the cerebral spinal fluid.^{14, 19}

We encountered three patients with clinical features suggestive of AZOOR and considered the possibility of a subacute herpes virus infection analogous to that described in other central nervous system disorders. These patients were treated with oral valacyclovir, and their cases are described.

Methods

A retrospective case series was assembled from the charts of three patients who were informed prior to treatment regarding the off-label use of the medication, lack of randomized clinical trial data to support its efficacy, and potential adverse effects. Subjects underwent eye exams that included slit-lamp examination, dilated retinal biomicroscopy and indirect ophthalmoscopy, optical coherence tomography, Goldmann visual field testing, and electroretinography. Patients were given 3-grams of oral valacyclovir daily for 1-week and then 1-gram daily for an additional 3-weeks. The medication was then tapered over 1-month.

Results

Case 1

A 26-year old male experienced a flu-like illness and over two weeks noticed rapid, progressive vision loss in both eyes. He was otherwise healthy, and an outside MRI and CBC were normal. On examination, his visual acuity was 20/20 in both eyes. The spectacle refraction was -4.00 OU. His intraocular pressures were 9 and 15 mmHg. His anterior segment exam was unremarkable. A dilated fundus exam showed healthy optic discs, retinal vessels, maculas, and foveas (Figure 1A, B). There were 1+ and trace vitreous cells in the right eye and left eye respectively. A Goldmann visual field revealed severe constriction of all isopters in the right eye. Defects in the left eye included scotomas and an enlarged blind spot (Figure 1 C, D). An electroretinogram demonstrated mild depression of the scotopic dim flash in the right eye relative to the left eye (Figure 1I).

He was given the presumptive diagnosis of bilateral AZOOR and started on valacyclovir as described in the methods. His vision stabilized immediately and began to improve within a few days. Visual field testing confirmed improvement at 1-week (Figure 1E, F). In the next four weeks, the right visual field expanded significantly, leaving only a modest depression inferiorly (Figure 1H). Subtle retinal pigment epithelial atrophy became apparent in the zone corresponding to his field loss (Figure 1J). The left visual field also normalized. He has not had a recurrence in the last three-years and his visual fields remain stable.

Case 2

A 14-year old female was referred for evaluation of longstanding pigmentary retinopathy and unilateral vision loss in her right eye. She felt her peripheral vision had gradually

decreased six months prior to presentation, and that her night vision had worsened. She was otherwise healthy. An outside MRI was normal. There was no family history of inherited eye disease. On examination, her visual acuity was 20/30 in the affected right eye and 20/20 in the asymptomatic left eye. The intraocular pressures were 13 and 9 mmHg. Her anterior segment exam was unremarkable. A dilated fundus exam showed waxy pallor of the disc in the right eye and a normal disc in the left eye. (Figure 1A, B) The right fundus showed attenuated arterioles and patchy pigmentary changes in the peripheral retina with bone spicule-like pigmentation. There were mild vitreous cells in the right eye. Goldmann visual field testing demonstrated only a 10-degree I4e isopter in the right eye with a dense ring scotoma of the V4e (similar to figure 2D). This contrasted sharply with her normal left eye. The left fundus appeared normal and demonstrated a normal 60–80-degree I4e isopter in the left eye (data not shown). OCT imaging revealed extensive loss of the photoreceptor layer in the right eye but was normal in the asymptomatic left eye (Figure 1H). These findings were consistent with a unilateral retinitis pigmentosa phenotype or a late stage AZOOR-like illness. She refused electroretinography studies.

The patient returned 30 months later complaining of acute, progressive vision loss over the last two weeks, in what had been her normal left eye, similar to what she had experienced in her right eye. She also reported a flu-like illness and a “pink” left eye one-month prior. On examination, her visual acuity had deteriorated to hand motions in the right eye and 20/60 in the left eye. The intraocular pressures were 13 mmHg in both eyes. Her anterior segment examination was normal. The optic discs and fundus exam appeared similar to her prior examination. There were no pigmentary changes in her newly symptomatic left eye. There were no posterior uveitis findings. Goldmann visual field testing, however, revealed three new central scotomas in the left eye (Figure 2C). There were no changes in the right eye visual field or OCT.

Recurrent AZOOR in the fellow eye was suspected, and she was started on valacyclovir as described in the methods. She reported that her vision stabilized immediately and improved during the first week of treatment. There was resolution of a central scotoma in the left eye on visual field testing at 1-week (Figure 1E). Within 1 month of treatment, her symptoms improved along with her visual acuity, which returned to a 20/60 in the right eye and improved to 20/25 in the left eye. Goldmann visual field testing also showed the left eye central scotomas had disappeared (Figure 1G), and she was tapered off the valacyclovir. She has not had any recurrences during her 18-month follow-up.

Case 3

A 37-year old healthy female presented to the emergency department when she noticed dark spots with a few photopsias in her right eye for the past week. She did not report any floaters, pain, photophobia, or amaurosis. There was no family history of inherited eye disease. She was healthy without an antecedent viral infection, migraines, diabetes, or hypertension. On examination, her visual acuity was 20/25 in the right eye and 20/20 in the left eye. The intraocular pressures were 16 and 15 mmHg. There was no relative afferent pupillary defect. Her anterior segment exam showed only mild conjunctival injection. A

dilated fundus exam was unremarkable. The next day she complained of increased black spot size and she was referred to our service.

The vision in her symptomatic right eye decreased to 20/40 but remained 20/20 in her left eye. The fundus exam showed only a few small cuticular drusen and no evidence of a neovascular membrane (Figure 3A, B). There were no signs of a posterior uveitis, vitreous detachment, retinal tear or retinal detachment. Fluorescein angiography was normal. A multifocal electroretinogram, however, showed decreased amplitudes in the right eye but normal waveforms in the left eye (Figure 3C). Goldmann and Humphrey visual field (insert) testing revealed scotomas in the central 10 and 30 degrees of the right visual field (Figure 3E). The visual fields were normal in the asymptomatic left eye (Figure 3D). Although the left eye optical coherence tomography was also normal, the affected right eye imaging suggested asymmetric reflectivity of the outer nuclear layer in the area corresponding to the scotoma (Figure 3F). There was no photoreceptor loss at the disc.

She was started on valacyclovir and reported that the dark spots began to disappear within the first few days of treatment, and were completely gone at her 1-month follow-up. Examination confirmed her visual acuity returned to 20/20 in the left eye and the central scotomas resolved (Figure 3G). Since stopping valacyclovir over a year ago, she has not had a recurrent episode.

Discussion

Here we report three patients with clinical features of an AZOOR-like illness that presented with acute, progressive vision loss that immediately reversed and showed significant resolution at 1-week and 1-month. Two patients had an antecedent flu-like illness, mild conjunctivitis, and vitreous cells. All had an essentially normal appearance of the recently affected retina, but distinct areas of visual field loss confirmed by testing. One presented with bilateral findings and another with findings of late stage AZOOR in their fellow eye. Photoreceptor dysfunction was apparent in all three patients, either detected on optical coherence tomography or asymmetric electrophysiologic abnormalities.²⁰ Two of the patients developed late pigmentary changes similar to that described in late AZOOR.⁷ All three patients, however, demonstrated a dramatic and rapid clinical response to valacyclovir, with improvement in subjective symptoms, visual acuity, and visual field testing as soon as 1-week.

This study is limited by its retrospective nature, the small number of subjects, and the absence of virologic evidence of a specific viral infection. Further, the retrospective study design does not include controls. Nevertheless, it is interesting to note that in Case-2, where she previously lost significant retinal function in her first eye, valacyclovir treatment seemed to prevent a similar course in her fellow eye. It is not possible to know with certainty whether the visual improvement was due to valacyclovir or the natural history of the disease in these three patients. Infrequent improvement in visual field testing has been reported in some suspected AZOOR patients without treatment,⁷ but not with such rapidity as we observed in these cases. The dramatic response of these three patients suggests that a trial of valacyclovir may be warranted in some cases of idiopathic field loss and a normal retinal

appearance. The ideal dosage of valacyclovir is not known, but 3 g per day for 1-week followed by 1 g per day for 3-weeks and a taper over 1-month was effective in these cases.

A possible viral etiology was suggested for AZOOR in a previous study, but intravenous acyclovir treatment did not show any benefit.⁷ Valacyclovir is an esterified prodrug of acyclovir with much higher bioavailability, especially in the vitreous.²¹ In retinal infections, oral valacyclovir may provide sufficient ocular penetration for treatment of acute retinal necrosis.^{22–23} In relatively noninflammatory conditions such as these AZOOR-like illnesses where the blood-retinal barrier seems to be intact, valacyclovir would be expected to cross the barrier better than acyclovir. Our patients may have demonstrated more benefit compared to those in previous reports since the each presented very soon after their symptoms and began treatment within 1–14 days. In addition, our patients were not treated with steroids.

There is one reported case of AZOOR with CNS inflammation,²⁴ but none of our patients had any neurological signs or symptoms. There are also cases of acute retinal necrosis associated with herpetic encephalitis.^{25–28} Our findings suggest that some cases of AZOOR may be due to an occult viral retinitis, or behave as a “*subacute*” ARN, which also develops in immunocompetent patients analogous to other CNS infections.^{29–32} The concept of an occult viral infection with subacute or even asymptomatic disease in an immunocompetent host has been confirmed by laboratory testing with increased sensitivity.³³ Where antibody titers fail to confirm infection or reactivation of virus, DNA polymerase chain reaction (PCR) and RNA in situ hybridization have identified viral particles in the CSF of immunocompetent patients with subacute encephalitis.^{29, 34} Thus, a much greater diversity of phenotypes may exist for viral disease than was previously appreciated due to more sensitive laboratory detection methods.^{34–36}

A future, prospective study with additional patients, control subjects, complete diagnostic testing that includes ERGs and spectral domain OCT of the macula and disc will be required to confirm these findings.^{4, 37} Future studies might also perform PCR testing for herpes-family virus in the vitreous of these patients.³⁸ In our practice, we attempt a trial of valacyclovir in patients with an AZOOR-like illness in what is otherwise an untreatable condition often with significant visual loss.

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Figure 1. Case-1. The subject showed clinical features of AZOOR that improved following valacyclovir treatment

A, Normal fundus image of the right eye. **B**, Normal fundus image of the left eye. **C**, Goldmann visual field of the left eye shows new field constriction and scotoma. **D**, Goldmann visual field of the right eye shows constriction of all isopters. **E, F**, Goldmann visual fields showed improvement after 1-week following valacyclovir treatment. **G, H**, Goldmann visual field of the left eye showed normalization after 1-month of valacyclovir treatment and significant expansion in the right eye. **I**, ERG shows diminished b-wave in the

right eye compared to the left eye. **J**, A photograph of the left peripheral fundus shows a subtle patchy retinal pigment epithelial atrophy in the area corresponding to visual field loss.

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Figure 2. Case 2. Valacyclovir treatment reversed visual changes in the second eye of an AZOOR subject

A, Right fundus image shows old pigmentary changes, waxy disc pallor, and vascular attenuation. **B**, Normal fundus appearance in the newly symptomatic left eye. **C**, Goldmann visual field of the left eye shows new central scotomas. **D**, Goldmann visual field of the right eye demonstrates a stable, severe peripheral constriction and ring scotoma present 30 months prior to the development of symptoms in the left eye. **E**, Goldmann visual field of the left eye showed normalization after 1- week treatment with valacyclovir. **F**, Goldmann

visual fields of the left eye also showed mild expansion. **G**, The central scotomas in the left eye disappeared completely after 1-month of valacyclovir. **H**, There was retinal thinning with loss of the photoreceptor layer in the right eye (upper panel). This was not observed with treatment of the newly symptomatic left eye (lower panel).

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Figure 3. Case-3. New onset visual features of AZOOR rapidly improved after treatment with valacyclovir

A, Normal fundus image of the symptomatic right eye. **B**, Normal fundus image of the asymptomatic left eye. **C**, Multifocal ERG shows abnormal, depressed waveforms in the central macula of the right eye (left panel) compared to the left eye (right panel). **D**, Normal Goldmann visual field of the left eye. **E**, Goldmann and Humphrey visual field (inset) of the right eye shows central scotomas and an enlarged blind spot. **F**, There is increased

reflectivity in the outer nuclear layer (left arrow) corresponding to the area of visual field loss. **G**, Humphrey visual field of the left eye shows normalization after valacyclovir.

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