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Multimodal Imaging in Wagner Syndrome

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Abstract

Wagner syndrome is a rare vitreoretinopathy described in a limited number of families. Here the authors describe four cases of suspected Wagner syndrome. All four cases had depressed rod and cone function on electroretinography, outer retinal disruption on spectral-domain optical coherence tomography, and constricted central visual fields with smaller isopter testing. Fundus autofluorescence performed in one patient highlighted a perivascular pattern to chorioretinal atrophy. Two patients had a history of uveitis with active cystoid macular edema. The diagnosis of Wagner syndrome was supported in three cases with genetic testing for *VCAN* mutations, whereas the other case harbored a variation of unknown significance in *VCAN* that may have been nonpathogenic.

INTRODUCTION

Wagner syndrome (WS) (OMIM 143200) is a rare autosomal dominant, ocular-only syndrome initially described in 1938 in 13 members of a Swiss family. It is characterized by an optically empty vitreous cavity with avascular vitreous veils, moderate myopia, presenile cataracts, and chorioretinal atrophy.[1–3] Follow-up of 60 family members from this cohort in 1995 found additional clinical features such as depressed electroretinography (ERG) and tractional retinal detachment.[4] The disease was originally linked to a mutation in chromosome 5q13–145 and was subsequently isolated to the versican (*VCAN*) gene.[6] *VCAN* encodes a large chondroitin sulfate proteoglycan, which is a major component of the extracellular matrix of the vitreous gel. The central portion of *VCAN* is encoded by two exons — exons 7 and 8. At least nine different dominantly inherited mutations in the *VCAN* gene reported to date in families with WS that either affect the acceptor splice site of intron 7 or the donor splice site of intron 8.[6–13] These novel mutations have on occasion been linked to new phenotypic variants not identified in the original Swiss cohort. In this

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observational case series, we describe the clinical and multimodal imaging findings in four members of three families with suspected WS. Three of the reported cases harbored mutations in *VCAN* predicted to be pathogenic, whereas one patient harbored a variant of undetermined significance (VUS) in *VCAN*.

REPORT OF CASES

Case 1 (Family A)

A 33-year-old black woman was referred to the University of Michigan Kellogg Eye Institute for a possible diagnosis of retinitis pigmentosa (RP). She reported decreased visual acuity for approximately the past 3 years and difficulty with night vision. Cataracts were removed at the age of 33. Family history revealed that the proband's father was diagnosed with RP at the age of 35 and her full brother had been diagnosed with RP at the age of 32. The proband's paternal half-brother (age 31) reported night vision problems; however, he did not carry a definitive diagnosis. The proband had four daughters, of whom one reported difficulty with night vision. Visual acuity was 20/60 in both eyes (OU). Anterior segment examination identified trace flare in the right eye (OD). Fundus examination (Figure 1A) showed generalized retinal pigment epithelial (RPE) atrophy with peripheral pigmentary changes OU. Retinal vessels were attenuated and optic discs were full with mild pallor OU. A vitreous veil was noted on examination OU (arrows, Figure 1A). Goldmann visual field (GVF) testing (Figure 1B) showed a markedly constricted central visual field OU. Spectral-domain optical coherence tomography (SD-OCT) showed cystoid macular edema (CME) OD and outer retinal disruption OU (Figure 1C). Both the scotopic and photopic full-field ERG were markedly abnormal OU. Genetic testing revealed a mutation in *VCAN* (NM_004385.4), c.4004-1G>T, p.?, confirming the diagnosis of WS.

Case 2 (Family A)

This patient was the 10-year-old daughter (Figure 1D) of the patient presented in Case 1. The patient reported difficulty with night vision for the year prior and was subsequently referred for a possible diagnosis of RP. Her visual acuity was 20/125 OD and 20/160 in the left eye (OS). On fundus examination, her vessels were slightly attenuated and there was a generalized mottling of the RPE. A vitreous veil was noted OD (Figure 1E). GVF was markedly abnormal OU (Figure 1F). SD-OCT through the macula revealed outer retinal thinning OU (Figure 1G). Both rod and cone full-field ERGs were abnormal OU. Genetic testing identified a *VCAN* mutation, c.4004-1G>T, p.?, identical to that of her mother.

Case 3 (Family B)

A 45-year-old white male was referred to Oregon Health & Science University, Casey Eye Institute, for a possible diagnosis of RP. The patient reported a 5-year history of reduced vision and difficulty with dark-adaptation. The patient had a history of treatment for intermediate uveitis with CME OU with a negative workup. He subsequently developed a cataract OS, which was extracted. He had also undergone vitrectomy OU in an attempt to relieve the macular edema. Family ocular history was unremarkable except for the proband's maternal grandmother having a history of an unspecified retinal degeneration and retinal detachment (Figure 1H). The patient had moderate myopia with a visual acuity of 20/60 OU.

Fundus examination revealed vascular attenuation with perivascular chorioretinal atrophy (Figures 2A and 2B) accentuated on fundus autofluorescence (Figures 2C and 2D), as well as perivascular pigment deposition. SD-OCT through the macula revealed segmental outer retinal disruption OU and nasal CME OS (Figures 2E and 2F). Kinetic perimetry (Figure 3A) was markedly abnormal OU. Full-field ERG (Figure 3B) showed severely depressed scotopic and photopic responses. Multifocal ERG (Figure 3C) showed subnormal amplitude of the macular cone responses. Genetic testing revealed an exon 8 change in *VCAN*, c. 4882G>A, p.Val1628ILe.

Case 4 (Family C)

A 32-year-old black woman was referred to the University of Michigan Kellogg Eye Institute for a diagnosis of WS versus pericentral RP. She reported a history of poor vision since the age of 18 and a history of night vision difficulties of unknown duration. Cataracts were removed at the age of 32. At the time of referral, she was only aware of a maternal uncle with decreased vision. Subsequently, her daughter was diagnosed with early RP at the age of 6.

Visual acuity was 20/100 OD and 20/80 OS. Scattered pigment deposits, retinal scarring, diffuse atrophy, and peripheral veils were present in both eyes (Figure 1). GVF showed a ring scotoma OU. Both the scotopic and photopic full-field ERG were markedly abnormal OU with reduced photopic and scotopic ERGs. Genetic testing revealed a mutation of *VCAN* (NM_004385.4), (c.4004-1G>T, p.?,) confirming the diagnosis of WS.

DISCUSSION

WS is a rare vitreoretinopathy which was historically diagnosed strictly based on clinical features and pedigree analysis. Among patients with WS, ERG shows progressive generalized rod and cone dysfunction, visual fields show ring scotomas with progressive loss of central vision, and fundus autofluorescence highlights progressive peripheral and perivascular chorioretinal atrophy. These features are typical findings in several other retinal dystrophies such as RP, thus making the diagnosis of WS challenging. Based on this phenotypic overlap, genetic analysis has emerged as a necessary ancillary for the definitive diagnosis of this condition. In all four cases presented in this report, changes in *VCAN* were uncovered through testing for a larger retinal dystrophy gene panel. No variants were found in other genes in this panel, and confirmatory Sanger sequencing for *VCAN* was performed in all four patients.

With identification of the causative gene mutation, diagnosis of WS has risen in the last decade. Alternative splicing of *VCAN* leads to four different isoforms (V0 – V3) of the translated protein based on the presence or absence of exon 7 and/or exon 8. This alternative splicing appears to cause phenotypic variations in WS. Three patients in this case series had a mutation (c.4004-1G>T) in the acceptor splice site on intron 7 of the *VCAN* gene. This mutation has been previously described[7,14] and is reported to result in upregulation of the V2 and V3 protein isoforms, which is predicted to be disease-causing.[14] The third patient in the case series had a missense mutation in *VCAN* (c.4882G>A); this variant has been reported in the Exome Aggregation Consortium (ExAC) database in 4/122,258 alleles all in

the heterozygous state for a frequency of 0.0033%. This relatively high frequency and lack of functional data makes this change a VUS. It is therefore possible that this variant is not pathogenic. However, it has been well-established in the original Wagner cohort that the disease is characterized by variable expressivity and ocular pleiotropy. It is thus unclear if other carriers of this allelic variant may have had subtle ocular pathology. Genetic testing for genes that cause RP did not reveal any mutations, although an alternative diagnosis of pigmented paravenous chorioretinopathy remains possible. More information as to significance of this change in *VCAN* in this patient will be needed before a conclusive diagnosis can be made.

In this series, we describe two adult patients who had prominent spontaneous uveitis as part of their clinical presentation. Three other families with WS have been reported to have uveitis with the first report of this association in 2007.[11–13] Although *VCAN* is known to play a pivotal role as an inflammatory mediator,[15] its role in uveitis in WS is poorly understood. However, with uveitis now having been described in five families with WS diagnosed at a molecular level, it is evident that the presence of uveitis may help separate this condition from other retinal and vitreoretinal degenerations.

With a limited dataset available worldwide to describe this condition, our knowledge of the phenotypic characteristics and variations of WS is likely incomplete. Judicious genetic testing in cases of atypical retinal and vitreoretinal degenerations could lead to improved diagnosis and understanding of this complex condition.

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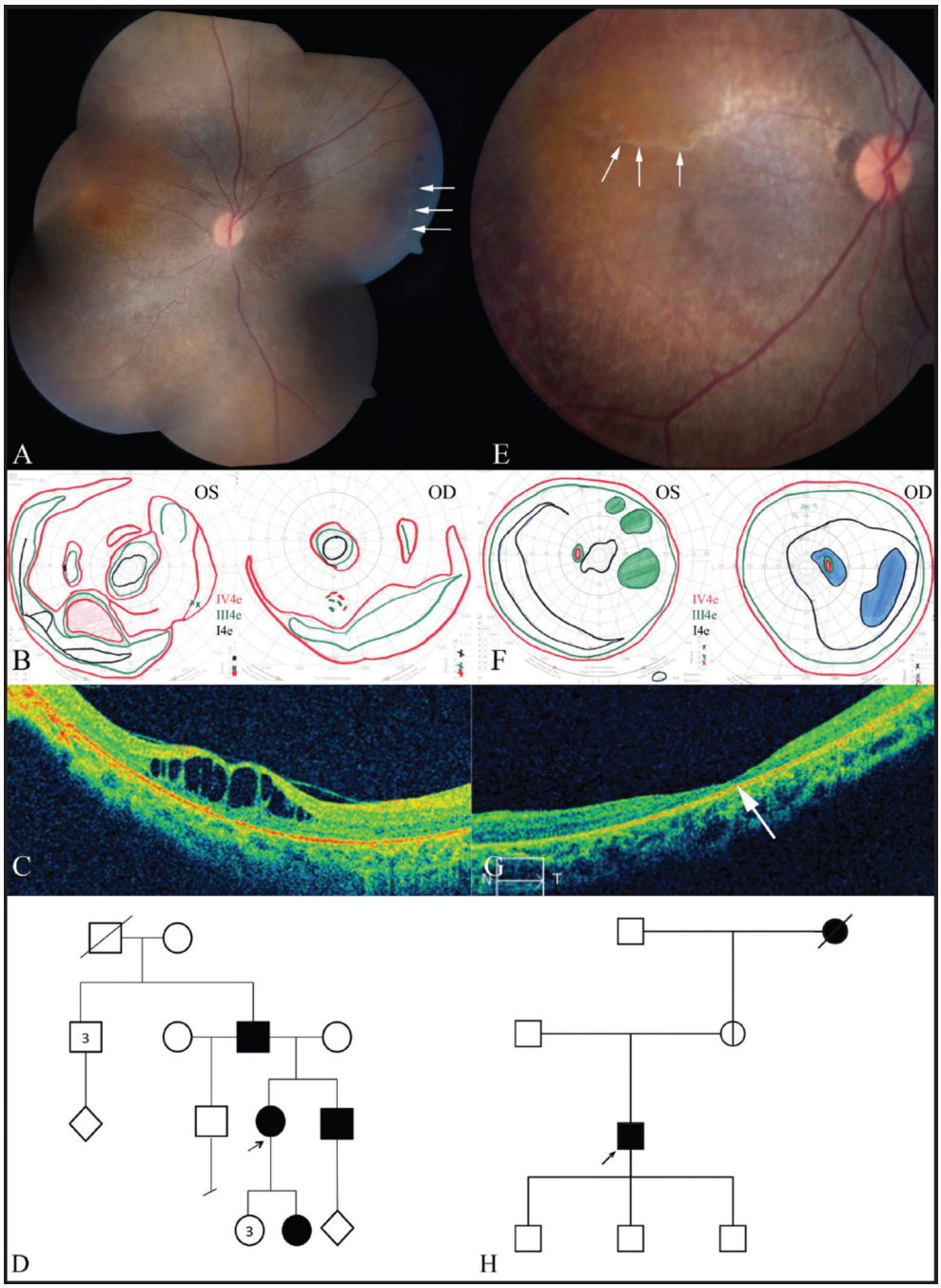

Figure 1.

Multimodal imaging of Wagner syndrome. Case 1 is represented in images A to C. Montage color fundus photo of the right eye (A) shows vascular attenuation, retinal pigment epithelium (RPE) atrophy, and a vitreous veil (arrows). Kinetic perimetry (B) shows a ring scotoma in the right eye, a partial ring scotoma in the left eye, and a constricted central visual field in both eyes. Spectral-domain optical coherence tomography (SD-OCT) of the right eye (C) shows cystoid macular edema. Pedigree analysis of family A (D) shows a dominant inheritance pattern. Case 2 is represented in images E to G. Color fundus photo of

the right eye (E) shows generalized RPE mottling and a vitreous veil (arrows). Kinetic perimetry (F) shows constricted central visual field and scattered scotomas in both eyes. SD-OCT of the left eye (G) shows foveal and parafoveal retinal thinning. (H) Pedigree analysis for family B.

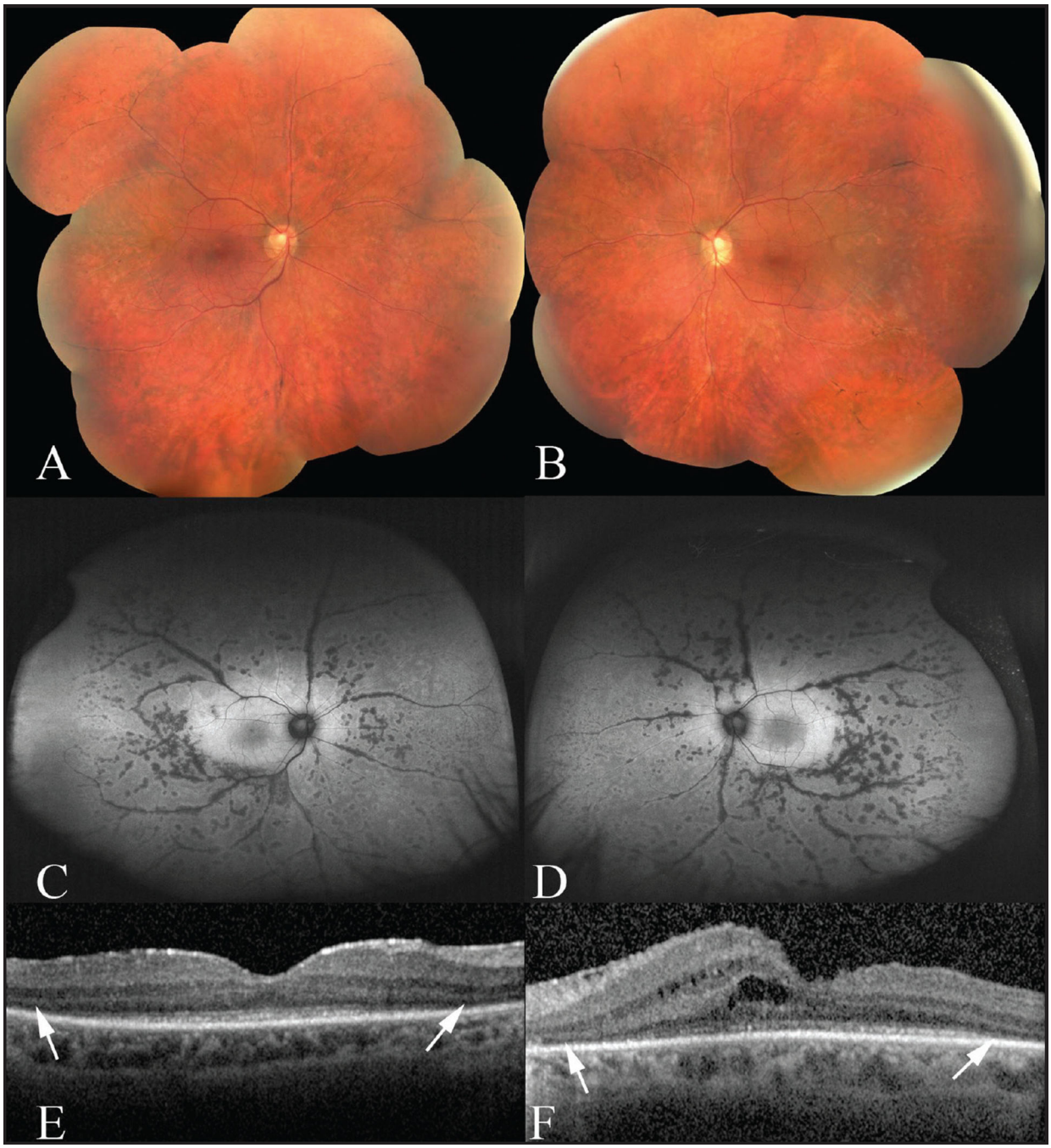

Figure 2.

Structural imaging of Case 3. Montage color fundus photos of the right (A) and left (B) eyes show vascular attenuation, perivascular and peripheral retinal pigment epithelium atrophy, and pigment clumping. Fundus autofluorescence of the right (C) and left eyes (D) show perivascular and peripheral hypoautofluorescence and peripapillary and macular hyperautofluorescence. Spectral-domain optical coherence tomography of the right (E) and left (F) eyes show segmental outer retinal disruption (arrows), with relative foveal sparing, epiretinal membranes in both eyes, and cystoid macular edema in the left eye.

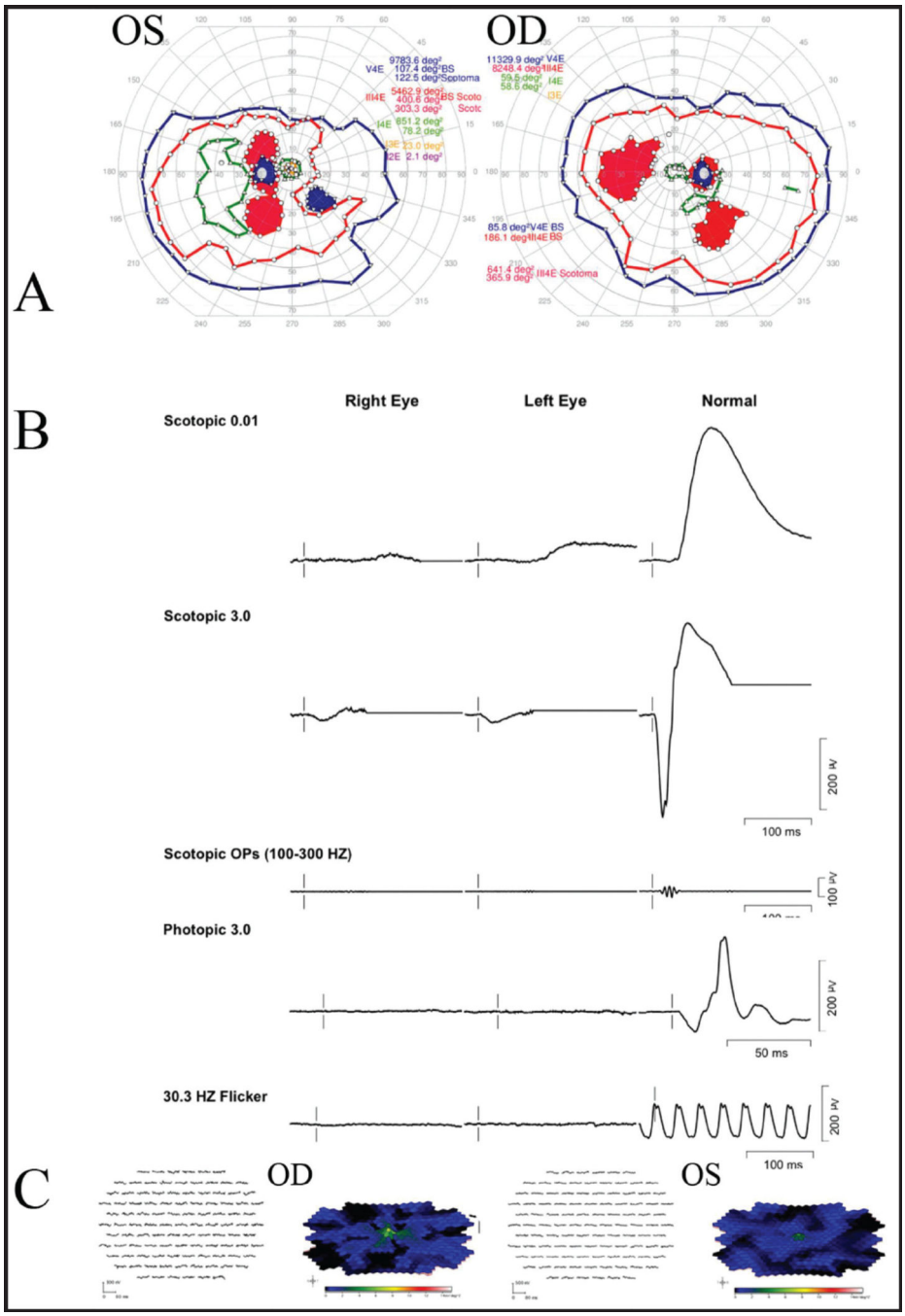

Figure 3.

Functional imaging of Case 3. Kinetic perimetry (A) reveals eccentric scotomas in both eyes to the V4e and III4 test targets. The smaller/dimmer test targets are constricted to a small central island in both eyes. Full-field electroretinography (ERG) (B) shows severely depressed scotopic and photopic responses in both eyes. Multifocal ERG (C) shows subnormal macular cone responses in both eyes.

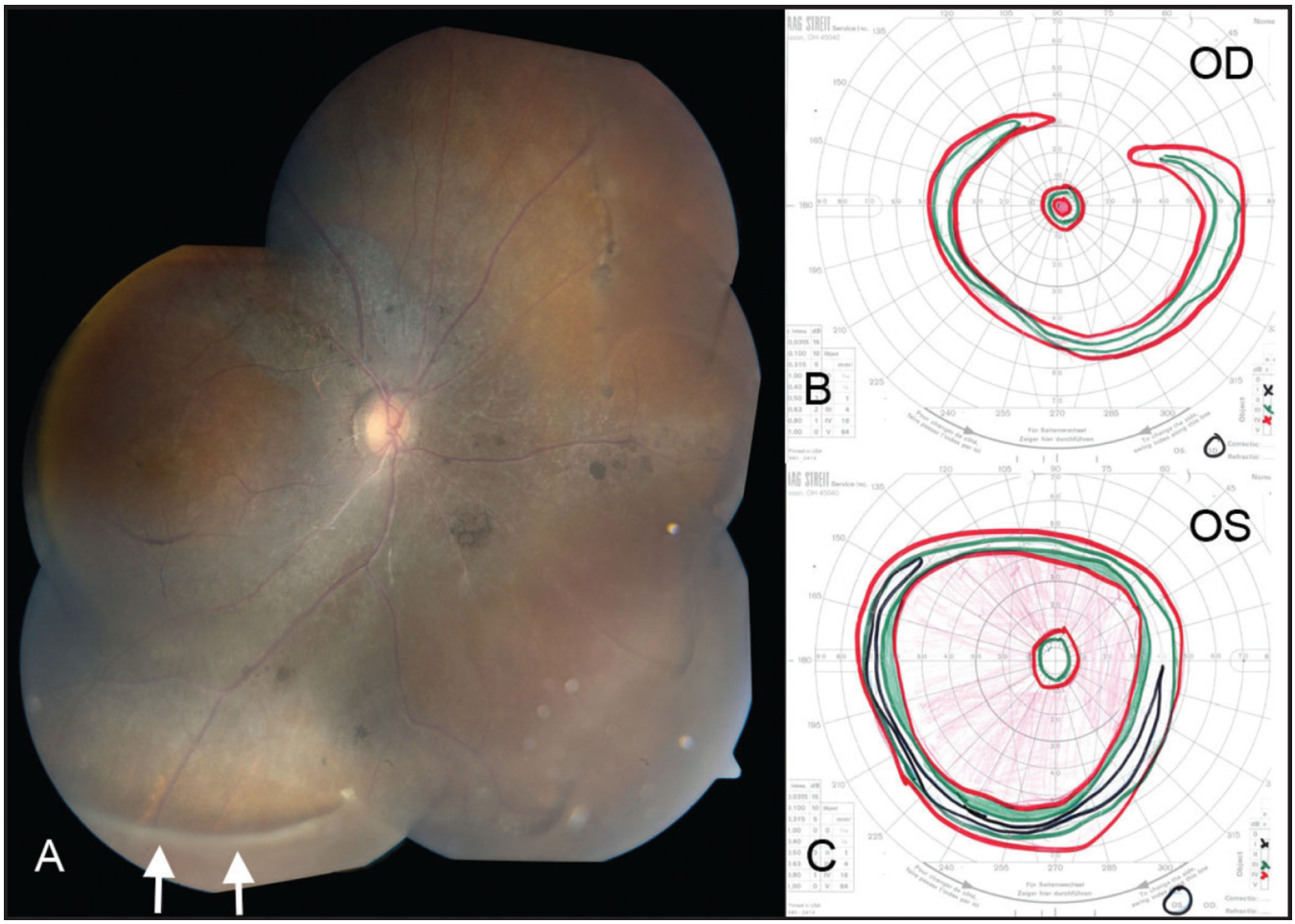

Figure 4.

Imaging in Patient 4. Montage of the right fundus (A) showing vascular attenuation, chorioretinal scarring, and pigment deposition. Peripheral vitreous veils are visible (arrows). Goldmann visual field of the right (B) and left (C) eye showing ring scotoma formation and constricted central isopters.