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Wagner syndrome: Novel *VCAN* variant and prophylactic management with encircling band and retinopexy

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ABSTRACT

Purpose: Wagner syndrome is an autosomal genetic vitreoretinopathy characterized by chorioretinal atrophy, avascular vitreous veils, reduced visual acuity and early retinal detachment in advanced cases. Management of Wagner syndrome usually results in observation then management of occurring complications.

Observations: We report the case of a 9-year-old girl presenting with supposed Wagner syndrome that we managed with prophylactic encircling band and retinopexy in both eyes. The genetic testing revealed a new variant in the intron 7 non canonical splice acceptor site, c.4004-12_4004-6delins17, that was also present in her father.

Conclusions and Importance: The *VCAN* variant found in this proband and her father has not been described yet but shows high predictions of pathogenicity. The previous reported variants in *VCAN* intron 7 and the associated phenotype for both cases allowed us to attribute this variant to Wagner syndrome. In Wagner syndrome, management is usually curative. After prophylactic surgery in our case, the zones of retinal delamination were well supported by the scleral buckle, releasing the vitreoretinal tractions, and the additional laser focalized on the temporal zones of dehiscence secured the retina. An encircling band may be a good way to prevent RD in patients with Wagner syndrome at risk.

1. Introduction

Wagner syndrome is an autosomal genetic vitreoretinopathy related to *VCAN/ CSPG2* gene (Versican protein).[1,2] It usually displays mild to severe myopia, avascular vitreous veils, cataract, progressive chorioretinal atrophy, reduced visual acuity (VA) and retinal detachment (RD) occurring in the late stages of the disease. This RD can occur in the childhood or in teenage.[3]

Management usually requires laser on retinal breaks and surgery for confirmed RD cases.

2. Observations

We report here the prophylactic management of a genetically confirmed Wagner syndrome case in a 9-year-old girl, with a novel heterozygote variant in *VCAN* gene, located in intron 7 non canonical splice acceptor site, c.4004-12_4004-6delins17, also present in her father.

She was followed for myopia from the age of 3. Her family history was marked by her father who underwent a spontaneous bilateral retinal detachment at the age of 15, without clear diagnosis made at that time; he had a relapse of the RD of the RE at the age of 30 and cataract surgery on both eyes at that time also. He had a prolapsus of mitral valve, albeit Wagner syndrome does not usually give systemic symptoms.[2] The father's family history reported only a case of a retinal tear treated with laser in his maternal grandmother but no other case of visual impairment.

She was referred to our tertiary center for peripheral retinal lesions and suspicion of RD in the left eye (LE). At examination, VA was 20/25 and IOP was normal in both eyes. Slit lamp examination was unremarkable. Her refraction was −3.50 (−2.75 at 180°) in the right eye (RE) et −2.25 (−2.50 at 6°) in the LE.

Fundus examination (Fig. 1A–B) showed papillary dysversion, normal posterior pole and diffuse peripheral pigmentary changes in both eyes. RE presented with white without pressure and circular snail track degeneration equatorial and posterior to the equator, whereas LE had temporal posterior lattice degeneration and atrophic holes with a schisis aspect. Autofluorescence (Fig. 1, C-D) showed a relatively normal

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posterior pole and a peripheral ring of nummular hypofluorescent spots corresponding to the chorioretinal atrophy.

Optical coherence tomography (OCT, Fig. 1, E-F) showed slightly disorganized retinal layers and epiretinal membrane.

Because of the posterior location of the lesions, we decided to perform first prophylactic encircling band with silicone Morin band (3.5 × 0.6mm). The surgery was performed for each eye, one month apart. Complementary temporal laser was then done in both eyes 1.5 month after the second procedure.

2.5 years after the surgery, VA was 20/40 and IOP was 20 in both

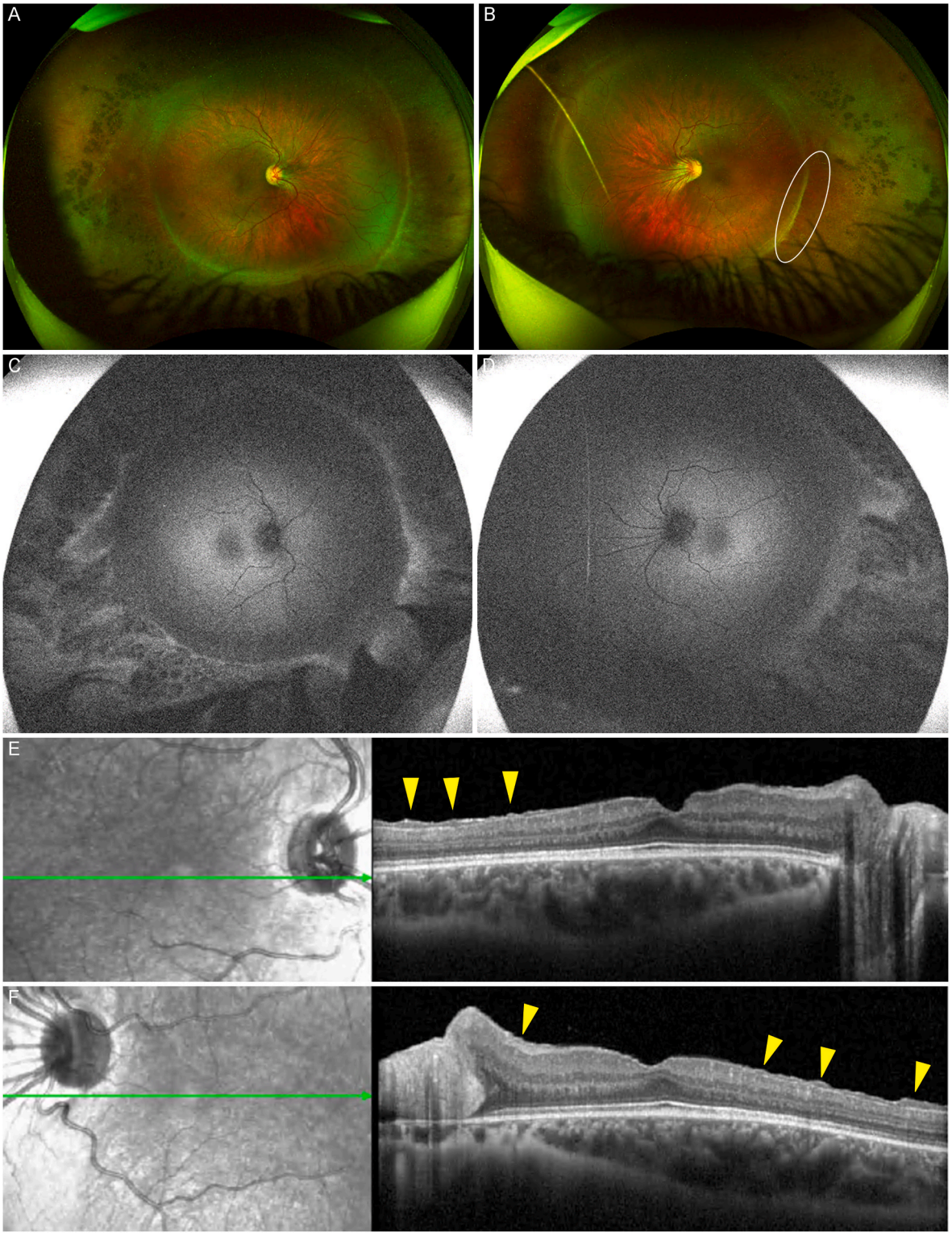

Fig. 1. Clinical aspect before surgery. (To note, panel C is after RE encircling band). A–B: Fundus aspect (pseudocolored, Optos). White ellipse shows the retinal lattice degenerations with retinal holes (schisis aspect) of the LE. C–D: Autofluorescence (Optos). E–F: OCT (Spectralis, Heidelberg engineering) showing slight disorganization of the retinal layers and epiretinal membrane at the vitreoretinal interface (yellow arrowheads). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

eyes. The retinal state is stable without RD or retinal tear. Refraction was −5.75 (−3.25 at 180°) for the RE and −4.25 (−3.50 at 180°). Slit lamp examination showed a beginning of cataract.

Fundus examination showed a protrusive encircling band. Retina is flat in both eyes with large temporal scars (Fig. 2A–B). The schisis zone of the LE is well protected by the laser (Fig. 2, B). Autofluorescence highlights the laser scars (hyperfluorescent) and the cerclage zone (slightly annular hyperfluorescence). (Fig. 2C–D). OCT did not show any changes (Fig. 2, E-F).

The *VCAN* variant was identified by Next Generation Sequencing of a large panel of 230 genes of inherited retinal dystrophies and validated by Sanger sequencing. The c.4004-12_4004-6delins17 is located in intron 7 of *VCAN* gene (NM_004385.5) and corresponds to the deletion of 7 nucleotides (TGTTTTT) replaced by the insertion of the sequence ATAACCTAAAAAAAACA. It was not reported in general population database (gnomAD V4, https://gnomad.broadinstitute.org/) nor in literature searches (HGMD, https://my.qiagendigitalinsights.com/bbp/view/hgmd/pro/all.php, or LOVD databases, https://databases.lovd.nl/shared/variants/VCAN/). The *in silico* predictions (SPIP score 98 %, SpliceAI Δ score Acceptor Loss: 0.96) supported the loss of the acceptor splice site leading to a splice defect. According to the ACMG-AMP guidelines,[4] this variant can be classified as likely pathogenic (class 4) with the following criteria (PM1, PM2, PP4, PP1, PP3). The segregation was confirmed by Sanger sequencing of both parents.

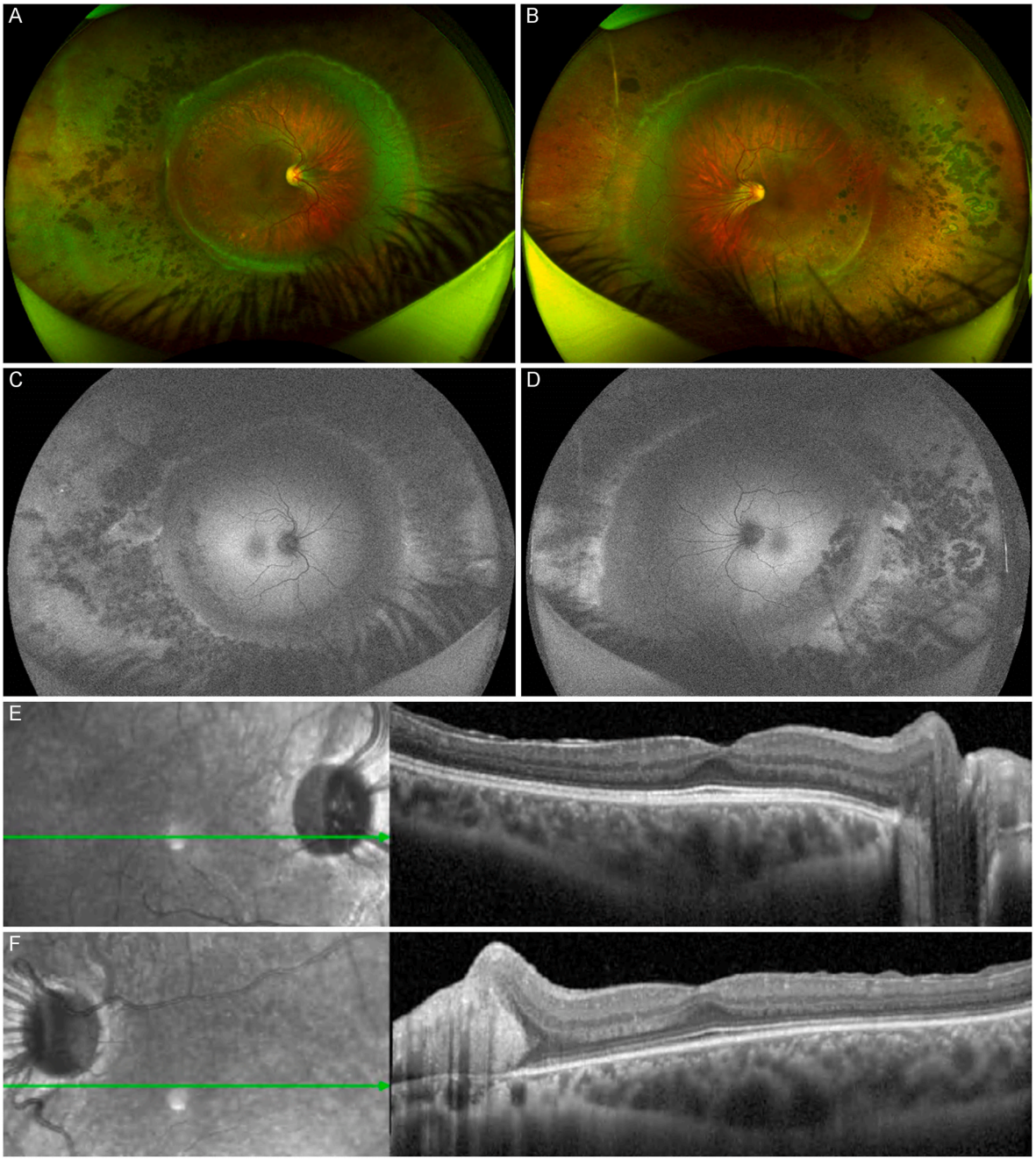

Fig. 2. Aspect 1 year after encircling band and laser of the 2 eyes. A–B: Fundus aspect (pseudocolored, Optos). Buckle is protrusive in both eyes and laser marks can be seen temporal posterior to the cerclage. Schisis zone of the LE is secured with posterior laser. C–D: Autofluorescence (Optos). E–F: OCT (Spectralis, Heidelberg engineering). A, C, E: RE. B, D, F: LE.

3. Discussion

Autosomal dominant variations in *VCAN* gene causing specifically Wagner syndrome have been described occurring in the introns 7 (splice acceptor site)[5–7] and 8[8,9] and the exon 8,[10,11] leading to splicing defects such as exon skipping or aberrant transcripts. The *VCAN* variant found in this proband and her father has not been described yet but shows high predictions of pathogenicity. In modifying the acceptor splice site, this variant may affect the correct splicing of intron 7, which is a hot spot of splicing variants (15 publications reported in HGMD). We expect an exon skipping and the synthesis of a truncated protein or the absence of synthesis by activation of the Nonsense Mediated Decay. This prediction as well as previous reported variants in *VCAN* intron 7 and the associated phenotype for both cases allowed us to attribute this variant to Wagner syndrome.

Retinal prophylaxis is already reported to be efficient to prevent retinal detachment in Stickler syndrome, which is the most common inherited cause of pediatric retinal detachment, and comprise laser photocoagulation for the majority of patients, scleral buckling or cryotherapy.[12–15] Stickler and Wagner syndromes are both congenital vitreoretinopathies. Stickler syndrome is caused by a mutation in collagen and is characterized by systemic features and ocular findings with anomalies of the vitreous, lattices, retinal tears and rhegmatogenous detachment in more than 50 % of the cases and systemic features. Wagner disease is associated with ocular findings only, such as chorioretinal atrophy, tractional and rhegmatogenous detachment in various proportion (up to 75 % of the patients according to the series).[3,16]

In Wagner syndrome, management is usually curative[2] (laser in case of retinal tears, surgery in case of RD). As far as we know, there is no report of prophylactic management in literature. Here the silicone band allows to release the vitreous traction on the retina. After surgery, the zones of lattice degeneration, located equatorial are well supported by the buckle. However, traction is not the only mechanism of retinal detachment in Wagner disease, which is the reason why we performed additional laser focalized on the temporal zones of dehiscence to secured the retina and to avoid detachment without restricting visual field too much. Intense temporal laser should nevertheless be avoided in those patients as it may affect child's accommodation or lead to epiretinal membrane development, and could also generate weak points for forming new breaks on their fragile retina.

The visual loss measured in this patient may be related to the natural history of the disease and due to presenile cataract, progressive chorioretinal atrophy, depressed cone and rod function,[2,17] abnormalities in the superficial retinal capillary plexus[18] or thinning of the peripheral retina and abnormal persistence of 1 or more retinal layers in the central fovea.[19]

Scleral buckling surgery can have potential adverse effects, such as cataract, induced myopia and the surgery itself can induce family stress. A larger cohort and a longer follow-up could help determining whether the benefits of surgery outweigh the adverse effects.

Follow-up is maintained with fundus examination every 4 months.

4. Conclusion

An encircling band may be appropriate to prevent RD in patients at risk (personal or family history of RD, posterior lattice degeneration) with *VCAN* variant. Whether scleral buckling, laser or both treatments should be used needs to be determined on a larger cohort.

Patient consent

Ethical approval is not required for this study in accordance with national guidelines. This report does not contain any personal information that could lead to the identification of the patient.

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Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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CRediT authorship contribution statement

Ysé Borella: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing. **Claire-Marie Dhaenens:** Investigation, Methodology, Writing – original draft, Writing – review & editing. **Olivier Grunewald:** Project administration, Supervision. **Georges Caputo:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – review & editing, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Meredith SP, Richards AJ, Flanagan DW, Scott JD, Poulson AV, Snead MP. Clinical characterisation and molecular analysis of Wagner syndrome. *Br J Ophthalmol*. 2007; 91(5):655–659. https://doi.org/10.1136/bjo.2006.104406.
2. Kloeckener-Gruissem B, Amstutz C. VCAN-related vitreoretinopathy. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. *GeneReviews®*. University of Washington, Seattle; 1993. http://www.ncbi.nlm.nih.gov/books/NBK3821/. Accessed August 4, 2023.
3. Araújo JR, Tavares-Ferreira J, Estrela-Silva S, et al. WAGNER syndrome: anatomic, functional and genetic characterization of a Portuguese family. *Graefes Arch Clin Exp Ophthalmol*. 2018;256(1):163–171. https://doi.org/10.1007/s00417-017-3800-0.
4. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American college of medical genetics and genomics and the association for molecular pathology. *Genet Med*. 2015;17(5):405–424. https://doi.org/10.1038/gim.2015.30.
5. Miyamoto T, Inoue H, Sakamoto Y, et al. Identification of a novel splice site mutation of the CSPG2 gene in a Japanese family with Wagner syndrome. *Invest Ophthalmol Vis Sci*. 2005;46(8):2726–2735. https://doi.org/10.1167/iovs.05-0057.

6. Mukhopadhyay A, Nikopoulos K, Maugeri A, et al. Erosive vitreoretinopathy and wagner disease are caused by intronic mutations in CSPG2/Versican that result in an imbalance of splice variants. *Invest Ophthalmol Vis Sci*. 2006;47(8):3565–3572. https://doi.org/10.1167/iovs.06-0141.
7. Brézin AP, Nedelec B, Barjol A, Rothschild PR, Delpech M, Valleix S. A new VCAN/versican splice acceptor site mutation in a French Wagner family associated with vascular and inflammatory ocular features. *Mol Vis*. 2011;17:1669–1678.
8. Ronan SM, Tran-Viet KN, Burner EL, Metlapally R, Toth CA, Young TL. Mutational hot spot potential of a novel base pair mutation of the CSPG2 gene in a family with Wagner syndrome. *Arch Ophthalmol*. 2009;127(11):1511–1519. https://doi.org/10.1001/archophthalmol.2009.273.
9. Rothschild PR, Audo I, Nedelec B, et al. De novo splice mutation in the versican gene in a family with wagner syndrome. *JAMA Ophthalmol*. 2013;131(6):805–807. https://doi.org/10.1001/jamaophthalmol.2013.681.
10. Ankala A, Jain N, Hubbard B, Alexander JJ, Shankar SP. Is exon 8 the most critical or the only dispensable exon of the VCAN gene? Insights into VCAN variants and clinical spectrum of Wagner syndrome. *Am J Med Genet*. 2018;176(8):1778–1783. https://doi.org/10.1002/ajmg.a.38855.
11. Zhong J, Shi J, Zhang X, et al. A novel splicing variant of VCAN identified in a Chinese family initially diagnosed with familial exudative vitreoretinopathy. *Mol Genet Genomic Med*. 2023;11(2), e2083. https://doi.org/10.1002/mgg3.2083.
12. Av N, Pj B, Pa Q. Retinal detachment prophylaxis for patients with stickler syndrome: a survey of pediatric retinal specialist treatment preferences. *Ophthalmic Surgery, Lasers Imaging Retina*. 2023;54(2). https://doi.org/10.3928/23258160-20230119-01.
13. Alexander P, Fincham GS, Brown S, et al. Cambridge prophylactic protocol, retinal detachment, and stickler syndrome. *N Engl J Med*. 2023;388(14):1337–1339. https://doi.org/10.1056/NEJMc2211320.
14. Linton E, Jalil A, Sergouniotis P, et al. Laser prophylaxis in stickler syndrome: the manchester protocol. *Retina*. 2023;43(1):88–93. https://doi.org/10.1097/IAE.0000000000003634.
15. Monin C, Van Effenterre G, Andre-Sereys P, Haut J. [Prevention of retinal detachment in Wagner-Stickler disease. Comparative study of different methods. Apropos of 22 cases]. *J Fr Ophtalmol*. 1994;17(3):167–174.
16. Edwards AO. Clinical features of the congenital vitreoretinopathies. *Eye*. 2008;22(10):1233–1242. https://doi.org/10.1038/eye.2008.38.
17. Thomas AS, Branham K, Van Gelder RN, et al. Multimodal imaging in wagner syndrome. *Ophthalmic Surg Lasers Imaging Retina*. 2016;47(6):574–579. https://doi.org/10.3928/23258160-20160601-10.
18. Bleicher ID, Garg I, Hoyek S, Place E, Miller JB, Patel NA. Widefield swept-source optical coherence tomography angiography findings in wagner syndrome. *Retin Cases Brief Rep*. 2022. https://doi.org/10.1097/ICB.0000000000001307. Published online August 11.
19. Rothschild PR, Burin-des-Roziers C, Audo I, Nedelec B, Valleix S, Brézin AP. Spectral-domain optical coherence tomography in wagner syndrome: characterization of vitreoretinal interface and foveal changes. *Am J Ophthalmol*. 2015;160(5):1065–1072.e1. https://doi.org/10.1016/j.ajo.2015.08.012.