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Superotemporal predisposition to traumatic subretinal fibrosis in Stargardt disease: A case report

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ABSTRACT

Purpose: Subretinal fibrosis has been reported as a presumed late sequela of orbital trauma in those with Stargardt disease (STGD). This case report highlights the sequential pathologic changes in response to trauma utilizing multimodal imaging.

Observations: An asymptomatic 19-year-old female with no significant ocular history presented for possible drusen. Initial imaging noted yellow-white pisciform perifoveal flecks in both eyes with corresponding hyper-and hypo-fluorescent lesions on fundus autofluorescence and hyperreflective deposits on near-infrared and spectral-domain optical coherence tomography (SD-OCT). A few months later, the patient presented with a new onset "black shadow" in the right eye after a traumatic periorbital injury, with multi-modal imaging revealing sequelae of commotio retinae superotemporally. Follow-up imaging three months later revealed a large patch of hyper-pigmented chorioretinal scar corresponding to the region of commotio. SD-OCT delineated findings consistent with subretinal fibrosis. Given the constellation of findings and subsequent genetic testing, the patient was diagnosed with STGD.

Conclusions and importance: Multimodal imaging allows for the detection of traumatic transformation of STGD and monitoring for early signs of massive lipofuscin release within the immediate post-traumatic period. Given the impact of minor orbital trauma on prognosis, caution should be taken to minimize and prevent orbital trauma in patients with STGD.

1. Introduction

Stargardt disease (STGD) is the most common inherited macular dystrophy, affecting approximately 1 in 10,000 individuals.[1–3] STGD typically presents in childhood or early adolescence, with an earlier age of onset suggesting a worse prognosis.[2,3] The best corrected visual acuity (BCVA) at initial presentation can range from 20/20 to 20/400, with symptoms including blurred vision, central scotoma, delayed dark adaptation, photopsia, photosensitivity, and abnormal color vision.[2,4–6] Classically, it is characterized as a bilateral, symmetrical, and progressive macular dystrophy, though it can present with a wide spectrum of disease.

Autosomal recessive inheritance of mutations in the *ABCA4* gene, which encodes for a rim protein involved in vitamin A metabolism in the outer segments of retinal rod and cone photoreceptors, results in Stargardt disease-1 (STGD1).[2,3,7] However, genetic heterogeneity exists with other allelic variants described as Stargardt-like diseases, notably Stargardt disease-3 and Stargardt disease-4, leading to macular dystrophy.[8] In the case of STGD1, the absence of rim proteins results in the build-up of a toxic byproduct, N-retinylidene-N-retinyl-ethanolamine, which causes enzyme-resistant lipofuscin accumulation and eventual photoreceptor and retinal pigment epithelium (RPE) cell death.[2,3,7] Phenotypic severity is determined by residual *ABCA4* function with STGD type 1 (STGD1) as the mildest of *ABCA4* phenotypes.[3,9]

Multimodal imaging aids in diagnosing and monitoring the progression of STGD1. Color fundus photography is typically normal in early disease, but fundus flecks, RPE hyperplasia, macular atrophy, and a "bronze-beaten metal" macula may be visualized with disease progression.[1,3] Some of the earliest disease features can be detected on short-wave fundus autofluorescence (SW-FAF), where lipofuscin

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accumulation results in hyper-auto fluorescence (AF) and RPE atrophy results in hypo-AF.[3] The hallmark finding on fundus fluorescein angiography is a "dark choroid," where retinal blood vessels appear highlighted against a hyperfluorescent choroid due to blockage of early choroidal fluorescence by lipofuscin deposition.[3,4,10] Spectral-domain optical coherence tomography (SD-OCT) can reveal the disruption or complete loss of inner and outer photoreceptor segment layers.[3,4] The clinical triad associated with STGD1 includes macular flecks, central macular atrophy, and peripapillary sparing.[4,11]

Atypical fundus findings like subretinal fibrosis have been reported as a presumed late sequela of orbital trauma in those with STGD. Traumatic transformation of STGD may result in a more severe visual decline due to scotoma formation and choroidal neovascularization.[12,13] Here, we present a case report of a 19-year-old girl with STGD1 featuring progressive subretinal fibrosis within the superotemporal retina. We highlight the sequential pathologic changes in response to trauma and the significance of the superotemporal localization utilizing multimodal imaging.

2. Case report

A 19-year-old female with a past medical history of asthma and no significant past ocular history was referred by her local optometrist for possible drusen of both eyes (OU) on a dilated fundus examination. The patient reported no acute visual changes. Her social history was unremarkable, and she had no family history of ocular disease. She denied the use of hydroxychloroquine, pentosan polysulfate, or other medications with associated ocular toxicity.

On initial ophthalmologic evaluation, the patient's best corrected visual acuity (BCVA) was 20/25 in the right eye (OD) and 20/25-1 in the left eye (OS). Her pupil exam, intraocular pressure, extra-ocular motility, and confrontational visual fields were all within normal limits. The anterior segment was unremarkable, but a dilated fundoscopic examination was notable for yellow-white pisciform perifoveal flecks OU (Fig. 1A and D). FAF demonstrated corresponding small irregular perifoveal lesions of both increased and decreased autofluorescence as well as additional foci of similar hyper-autofluorescent lesions nasal to the optic disc (Fig. 1B and E). Near-infrared imaging demonstrated hyperreflective flecks surrounded by a dark ring perifoveally. SD-OCT highlighted outer retinal layer thinning and ellipsoid zone (EZ) disruption nasal and temporal to the fovea, along with scattered intraretinal hyperreflective deposits (Fig. 1C and F). At the time, the patient was referred to the inherited retinal disorders service for further counseling and genetic testing.

A few months later, the patient presented for an emergency visit due to a new onset "black shadow" in the right eye. She reported being struck with a volleyball to the right face and right eye during a competitive match. She did not experience any loss of consciousness, though experienced a vision blackout in both eyes that lasted for a few seconds, presumptively an early concussive symptom.[14] The following day, she awoke with a dark shadow in the right eye that persisted until her visit. Her ocular review of symptoms was negative for any flashes or floaters, ocular pain, or photophobia. On examination, her BCVA was 20/20 OU with a normal pupillary exam. Multi-modal imaging revealed peripheral gray-white opacification of the superotemporal retina consistent with commotio retinae of the right eye (Fig. 2B). No vitreous hemorrhage, retinal tears or detachment was noted on the scleral depressed exam. Observation with close follow-up was recommended.

Three months later, follow-up imaging of the right eye revealed the development of a large patch of hyperpigmented chorioretinal scar corresponding to the previously noted region of commotio (Fig. 2C & F). SD-OCT with rasters through the peripheral region delineated irregular areas of RPE clumping consistent with subretinal fibrosis (Fig. 3).

Given the constellation of findings, including pisciform flecks, macular atrophy, and peripapillary sparing, the patient was presumed to have Stargardt disease. Her diagnosis was supported by marked post-traumatic changes, which have not been reported in pattern dystrophy or other inherited maculopathies. Genetic testing via a next-generation sequencing panel revealed two pathogenic variants in *ABCA4*:c.6079C > T, p.(Leu2027Phe) and c.4139C > T, p.(Pro1380Leu), consistent with a molecular diagnosis of STGD (Blueprint Genetics Inc, Marlborough, MA., USA CLIA-certified). The patient was recommended to wear safety glasses when playing volleyball and protective eyewear outdoors, and avoid vitamin A.

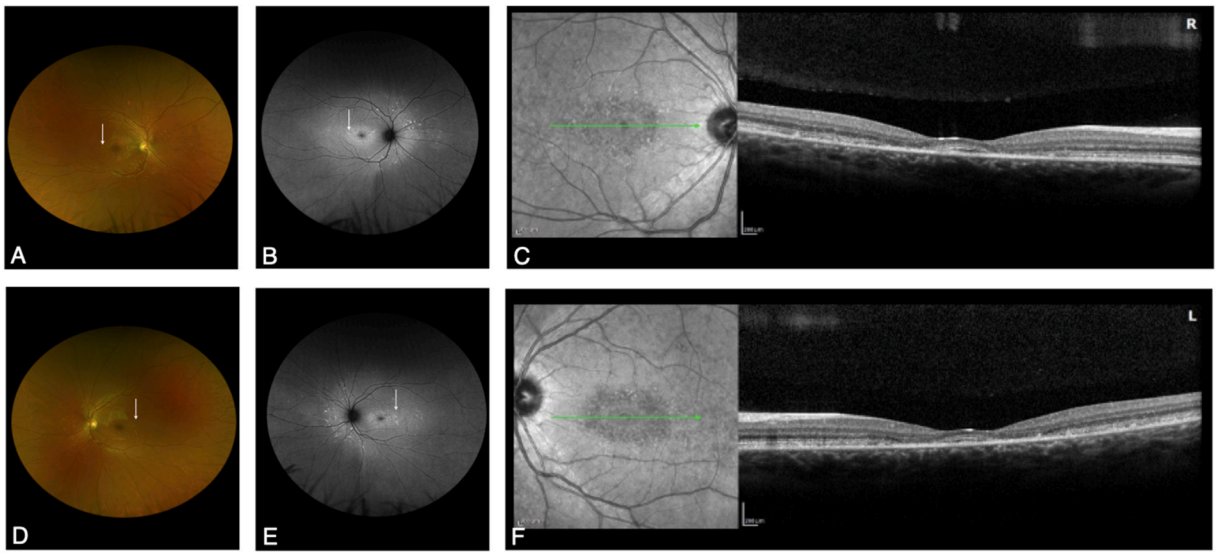

Fig. 1. Multimodal Imaging and Spectral-domain Optical Coherence Tomography (SD-OCT) at Initial Presentation
Ultra-widefield pseudocolor fundus photograph of the right (A) and left (D) eyes with macular yellow pisciform flecks (arrows). Fundus autofluorescence (FAF) of right (B) and left (E) eyes demonstrating scattered hyper-autofluorescence (arrows) corresponding to RPE disruption and lipofuscin accumulation/pisciform flecks seen in 1A and 1D. SD-OCT at the initial presentation of right (C) and left (F) eyes with horizontal raster. The scans reveal thinning of the outer retinal layers and disruption of the EZ; flecks appear as intraretinal hyperreflective deposits. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

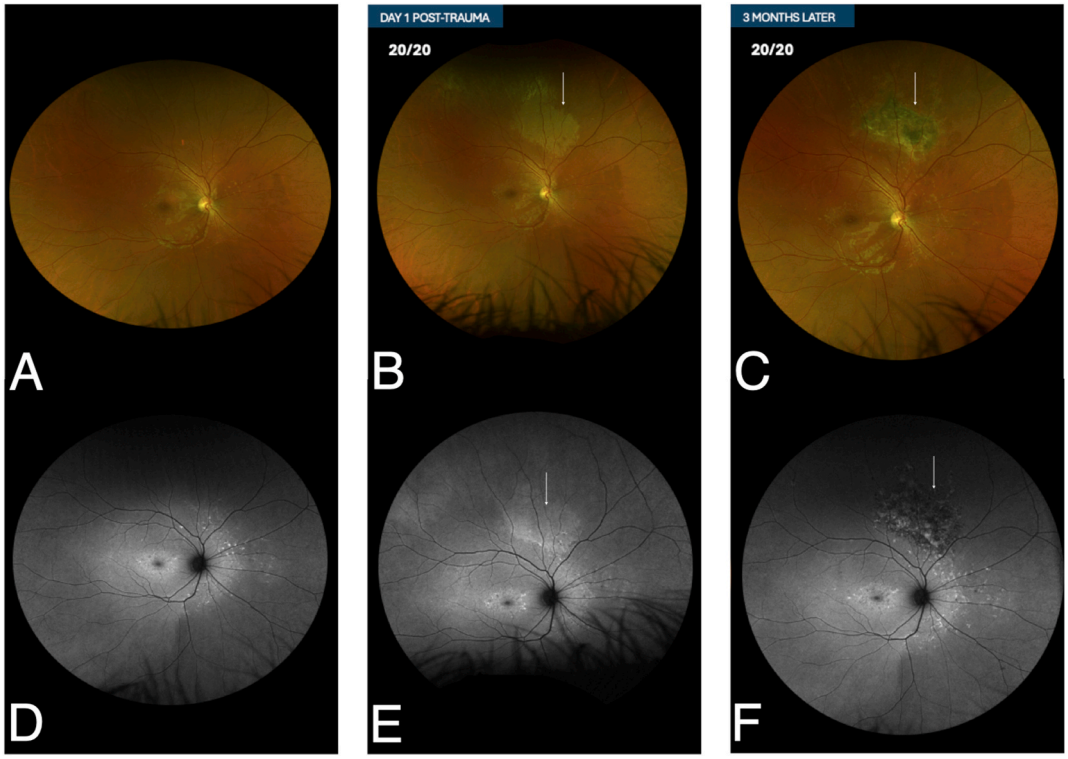

Fig. 2. Multimodal Imaging Post-Trauma
Fundus photograph and FAF of the OD at initial presentation (A, D) one day post-trauma (B, E) and three months post-trauma (C, F) highlighting an area of commotio retinae followed by subsequent dense pigmented chorioretinal scarring superiorly (arrows).

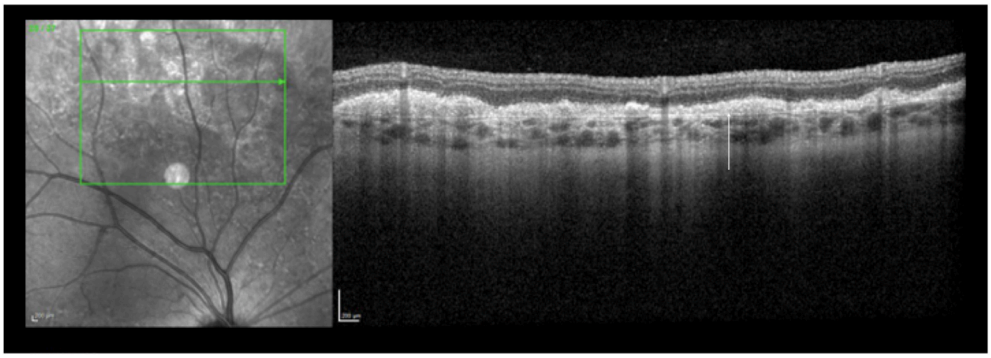

Fig. 3. SD-OCT Post-Trauma
SD-OCT OD at three months follow-up post-trauma with raster scan through peripheral chorioretinal scar superiorly. Dense irregular RPE clumping (arrow) consistent with subretinal fibrosis is observed.

3. Discussion

Our patient initially presented with classical clinical signs of STGD, including perifoveal flecks, but subsequently developed atypical features following orbital trauma, including massive subretinal fibrosis. These hypertrophic changes in the context of STGD were first suggested in the 1990s when case reports demonstrated susceptibility to fibrotic RPE dysplasia with mild antecedent ocular trauma in patients with Stargardt's and fundus flavimaculatus.[15,16] In a more recent case report, Rossi et al. reported on four patients with genetically confirmed STGD1 and subretinal fibrosis, all in the setting of mild ocular trauma or microtrauma.[17] Histological analysis revealed that ocular trauma leads to massive lipofuscin release, disrupting the RPE cells, with consecutive fibroglial or nonspecific inflammatory reactions propagating the final fibrotic stage. Diseased RPE cells that have lost normal *ABCA4* protein function are particularly vulnerable to posttraumatic reactions and lipofuscin release.

Our case highlights the progression of post-traumatic changes in STGD through multimodal imaging techniques. While several case reports have previously recognized subretinal fibrosis development in the setting of trauma, the timeline of the transformative post-traumatic changes remains poorly understood. In our case presentation, we demonstrate the sequential changes within a 3-month period following minor orbital injury: initial disruption of photoreceptor outer segments layers characteristic of commotio retinae was subsequently followed by RPE clumping and subretinal fibrosis. Wide-field multicolor images, short-wave FAF, and SD-OCT demonstrate these sequential fundoscopic changes from massive lipofuscin release to the traumatic transformation of lipofuscin deposition into subretinal fibrosis. A limitation of our study is the lack of early dedicated volume scans over the lesion of interest at the time of injury or OCT angiography at subsequent follow-up.

In the largest retrospective case series of subretinal fibrosis in STGD,

Jimenez-Rolando and colleagues reported on six cases with long-term follow-up, half of which included known preceding trauma.[13] Follow-up imaging and visual fields remained clinically stable over time without further progression. Among their cohort, subretinal fibrosis developed as early as 14 weeks after trauma.[13] Consistent with the timing of fibrosis development in our case presentation, these findings suggest that a therapeutic window may exist within the immediate post-trauma period to prevent lipofuscin discharge and possible fibrotic stage.[13]

While the phenomenon of traumatic fibrosis in STGD1 has been previously described, the observed predisposition for the superotemporal retinal localization remains unclear.[18] Among the case series of Jimenez-Rolando et al., all six patients demonstrated subretinal fibrosis involving the superotemporal midperipheral retina.[13] Similarly, our patient developed fibrotic changes in the same region. We postulate a two-fold explanation for this predilection. First, recent quantitative fundus autofluorescence (qFAF) studies assessing topographical lipofuscin distribution have demonstrated highest levels of lipofuscin superotemporally in healthy eyes.[19] Massive traumatic lipofuscin release has been implicated histologically in the propagation of the fibrotic stage.[20] Second, the tendon of the superior oblique muscle attaches in the posterosuperior lateral aspect of the globe.[21] This anatomical tethering combined with the upward deviation of the eye during forceful eyelid closure (Bell's phenomenon) may render the superotemporal retina more vulnerable to contrecoup and elastic injury during blunt trauma. Further supporting this hypothesis is evidence that the superotemporal retina is the second most common site of extramacular commotio retinae.[22]

The traumatic transformation described herein parallels that seen in pseudoxanthoma elasticum (PXE), a multisystem hereditary disease with ocular manifestations characterized by calcification of Bruch's membrane.[23] This calcification results in a brittle membrane prone to choroidal neovascularization (CNV) in the setting of trauma, subsequently leading to subretinal fibrosis.[23,24] With regard to STGD1, CNV is a recognized yet rare complication and typically develops after the fifth decade of life.[25] We unfortunately did not capture any fluorescein angiography or optical coherence tomography angiography to further assess for secondary CNV. However, we did not observe any retinal hemorrhages funduscopically or breaks in Bruch's membrane on OCT. Preceding case reports of traumatic subretinal fibrosis in STGD1 including fluorescein angiography similarly did not observe signs of secondary CNV.[17] In contrast to the CNV-driven traumatic transformation within PXE, the pathogenesis in STGD is related to the accumulation of toxic byproducts in the RPE and subsequent photoreceptor dysfunction.

Regarding post-trauma management and sports safety, a retrospective study utilizing a national database to assess pediatric sports- and recreational-related eye injuries found that volleyball had one of the lowest percentages of associated eye injuries.[26] Thus, given the low risk of significant orbital injury from volleyball, we counseled our patient that she could continue to play with the addition of safety glasses.

4. Conclusion

The rapid development of subretinal fibrosis in the setting of trauma in patients with STGD is a rarely reported yet important phenomenon. The use of multimodal imaging allows for the characterization of traumatic transformation of STGD and monitoring for early signs of massive lipofuscin release within the immediate post-traumatic period. As demonstrated previously, the superotemporal retina remains a vulnerable area to this phenomenon, potentially as a result of underlying histological and anatomical features. Given the impact of minor orbital trauma on prognosis in patients with STGD, particular caution should be taken to minimize and prevent orbital trauma. This case also highlights the need for further studies to better understand post-traumatic time-sensitive interventions to potentially prevent fibrotic development.

CRediT authorship contribution statement

Jamie A. Nassur: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Conceptualization. **Jose S. Pulido:** Writing – review & editing, Writing – original draft, Project administration, Funding acquisition, Conceptualization. **Rebecca Procopio:** Writing – review & editing, Writing – original draft, Conceptualization. **Alaa A. Ghoneim:** Writing – review & editing. **Anton Orlin:** Writing – review & editing, Writing – original draft. **Richard S. Kaiser:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Saif A. Hamdan:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Investigation, Formal analysis, Data curation, Conceptualization.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

Conflicts of interest

The following authors have no financial disclosures: JN, JP, RP, AO, RK, SH.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: N/A.

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References

1. Fishman GA. Fundus flavimaculatus. A clinical classification. *Arch Ophthalmol*. 1976; 94(12):2061–2067. https://doi.org/10.1001/ARCHOPHT.1976.03910040721003.
2. Altschwager P, Ambrosio L, Swanson EA, Moskowitz A, Fulton AB. Juvenile macular Degenerations. *Semin Pediatr Neurol*. 2017;24(2):104. https://doi.org/10.1016/J.SPEN.2017.05.005.
3. Kohli P, Tripathy K, Kaur K. Stargardt disease. https://www.ncbi.nlm.nih.gov/books/NBK587351/; 2024. Accessed June 23, 2024.
4. Tanna P, Strauss RW, Fujinami K, Michaelides M. Stargardt disease: clinical features, molecular genetics, animal models and therapeutic options. *Br J Ophthalmol*. 2017; 101(1):25–30. https://doi.org/10.1136/BJOPHTHALMOL-2016-308823.
5. Vandenbroucke T, Buyl R, De Zaeytijd J, et al. Colour vision in stargardt disease. *Ophthalmic Res*. 2015;54(4):181–194. https://doi.org/10.1159/000438906.
6. Bernstein A, Sunness JS, Applegate CA, Tegins EO. Mapping the dense scotoma and its ENLARGEMENT in STARGARDT disease. *Retina*. 2016;36(9):1741–1750. https://doi.org/10.1097/IAE.0000000000001003.
7. Sheffield VC, Stone EM. Genomics and the eye. *N Engl J Med*. 2011;364(20): 1932–1942. https://doi.org/10.1056/NEJMRA1012354.
8. Entry - #248200 - stargardt disease 1; STGD1 - OMIM. https://omim.org/entry/248200. Accessed November 17, 2024.
9. Glazer LC, Dryja TP. Understanding the etiology of Stargardt's disease. *Ophthalmol Clin North Am*. 2002;15(1):93–100. https://doi.org/10.1016/S0896-1549(01)00011-6.

10. Lambertus S, Van Huet RAC, Bax NM, et al. Early-onset stargardt disease: phenotypic and genotypic characteristics. *Ophthalmology*. 2015;122(2):335–344. https://doi.org/10.1016/J.OPHTHA.2014.08.032.
11. Cremers FPM, Lee W, Collin RWJ, Allikmets R. Clinical spectrum, genetic complexity and therapeutic approaches for retinal disease caused by ABCA4 mutations. *Prog Retin Eye Res*. 2020;79. https://doi.org/10.1016/J.PRETEYERES.2020.100861.
12. Gass JDM, Hummer J. Focal retinal pigment epithelial dysplasia associated with fundus flavimaculatus. *Retina*. 1999;19(4):297. https://doi.org/10.1097/00006982-199907000-00005.
13. Jimenez-Rolando B, Garcia-Sandoval B, Del Pozo-Valero M, et al. Prevalence, multimodal imaging and genotype-phenotype assessment of trauma related subretinal fibrosis in stargardt disease. *Eur J Ophthalmol*. 2022;32(6):3201–3207. https://doi.org/10.1177/11206721221093986.
14. Master CL, Bacal D, Grady MF, et al. Vision and concussion: symptoms, signs, evaluation, and Treatment. *Pediatrics*. 2022;150(2). https://doi.org/10.1542/PEDS.2021-056047/188533.
15. Posttraumatic reaction in a case of fundus flavimaculatus with atrophic macular degeneration - PubMed. https://pubmed.ncbi.nlm.nih.gov/8338316/. Accessed June 22, 2024.
16. De Laey JJ, Verougstraete C. Hyperlipofuscinosis and subretinal fibrosis in Stargardt's disease. *Retina*. 1995;15(5):399–406. https://doi.org/10.1097/00006982-199515050-00005.
17. Rossi S, Testa F, Attanasio M, et al. Subretinal fibrosis in Stargardt's disease with fundus flavimaculatus and ABCA4 gene mutation. *Case Rep Ophthalmol*. 2012;3(3):410. https://doi.org/10.1159/000345415.
18. Parodi MB. Progressive subretinal fibrosis in fundus flavimaculatus. *Acta Ophthalmol*. 1994;72(2):260–264. https://doi.org/10.1111/J.1755-3768.1994.TB05027.X.
19. Sparrow JR, Duncker T, Schuerch K, Paavo M, de Carvalho JRL. Lessons learned from quantitative fundus autofluorescence. *Prog Retin Eye Res*. 2020;74. https://doi.org/10.1016/J.PRETEYERES.2019.100774.
20. Ko MK, Lee WR, McKechnie NM, Hall-Parker B. Post-traumatic hyperlipofuscinosis in the human retinal pigment epithelium. *Br J Ophthalmol*. 1991;75(1):54–60. https://doi.org/10.1136/BJO.75.1.54.
21. Remington LA. Extraocular muscles. *Clinical Anatomy and Physiology of the Visual System*. January 1, 2012:182–201. https://doi.org/10.1016/B978-1-4377-1926-0.10010-4. Published online.
22. Blanch RJ, Good PA, Shah P, Bishop JRB, Logan A, Scott RAH. Visual outcomes after blunt ocular trauma. *Ophthalmology*. 2013;120(8):1588–1591. https://doi.org/10.1016/J.OPHTHA.2013.01.009.
23. Pfau K, Lengyel I, Ossewaarde-van Norel J, et al. Pseudoxanthoma elasticum – genetics, pathophysiology, and clinical presentation. *Prog Retin Eye Res*. 2024;102,101274. https://doi.org/10.1016/J.PRETEYERES.2024.101274.
24. Ebran JM, Martin L, Leftheriotis, et al. Subretinal fibrosis is associated with fundus pulverulentus in pseudoxanthoma elasticum. *Graefe's Arch Clin Exp Ophthalmol*. 2018;256(4):699–707. https://doi.org/10.1007/S00417-018-3937-5/FIGURES/3.
25. Souied EH, Pawlak D, Algan M, Sayag D, Coscas G, Soubrane G. Photodynamic Therapy for choroidal neovascularization on late-onset fundus flavimaculatus. *Am J Ophthalmol*. 2005;140(2):312.e1–312.e4. https://doi.org/10.1016/J.AJO.2005.01.024.
26. Miller KN, Collins CL, Chounthirath T, Smith GA. Pediatric sports- and recreation-related eye injuries Treated in US emergency Departments. *Pediatrics*. 2018;141(2),20173083. https://doi.org/10.1542/PEDS.2017-3083/38093.