

Hyperreflective Outer Nuclear Layer as a Biomarker of Early Stargardt Disease. A Case Report

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SUMMARY

Stargardt disease (STGD1) is among the most prevalent inherited macular dystrophies, characterized by typical flavimaculatus flecks and varying degrees of macular atrophy. This case report highlights the importance of optical coherence tomography (OCT) to detect subtle OCT changes in an 8-year-old girl without any detectable fundus abnormalities.

Key words: ABCA4 gene, flavimaculatus flecks, optical coherence tomography, Stargardt disease

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INTRODUCTION

Stargardt disease (OMIM#248200) represents one of the most prevalent autosomal recessive macular dystrophies. This disorder is caused by biallelic mutations within the ATP-binding cassette subfamily A member 4 (ABCA4) gene, leading to impaired function of the ABCA4 protein [1,2]. STGD1 is usually manifested within the first two decades of life, with patients experiencing a progressive and persistent decline in central and color vision, in addition to delayed dark adaptation [3]. Pathognomonic clinical features of STGD1 include yellow or white fish-shaped flecks and atrophy of photoreceptors, the retinal pigment epithelium (RPE), and the choriocapillaris [3].

While the classic manifestations of the disease have been well known, the data are scarce about the early-stage disease including the optical coherence tomography (OCT) signs [4]. Hence, we present the multimodal imaging features of an 8-year-old girl with the very early disease, with a genetically proven ABCA4 gene mutation.

CASE REPORT

An 8-year-old girl was examined by us for a routine eye evaluation. The patient did not report any complaints, and her past medical and family histories were unremarkable. There was no consanguinity between her parents. Upon ocular examination, eye movements were normal with full motility. Best-corrected visual acuity was 6/10 in both eyes. Slit-lamp examination was unremarkable. There were no noticeable changes with fundoscopy (Figure 1A, B). However, fundus autofluorescence (FAF) images showed a perifoveal ring of hyper-autofluorescence in both eyes (Figure 1C, D). Spectral domain (SD) raster OCT examination revealed a hyperreflective band in the outer nuclear layer (ONL) in both foveas (Figure 2A, B). Enface OCT findings looked unremarkable (Figure 3A–H). Genetic examination was positive for a missense variant heterozygote in the ABCA4 gene (NM_000350.3: c.3322C>T, p.(Arg1108Cys) rs61750120).

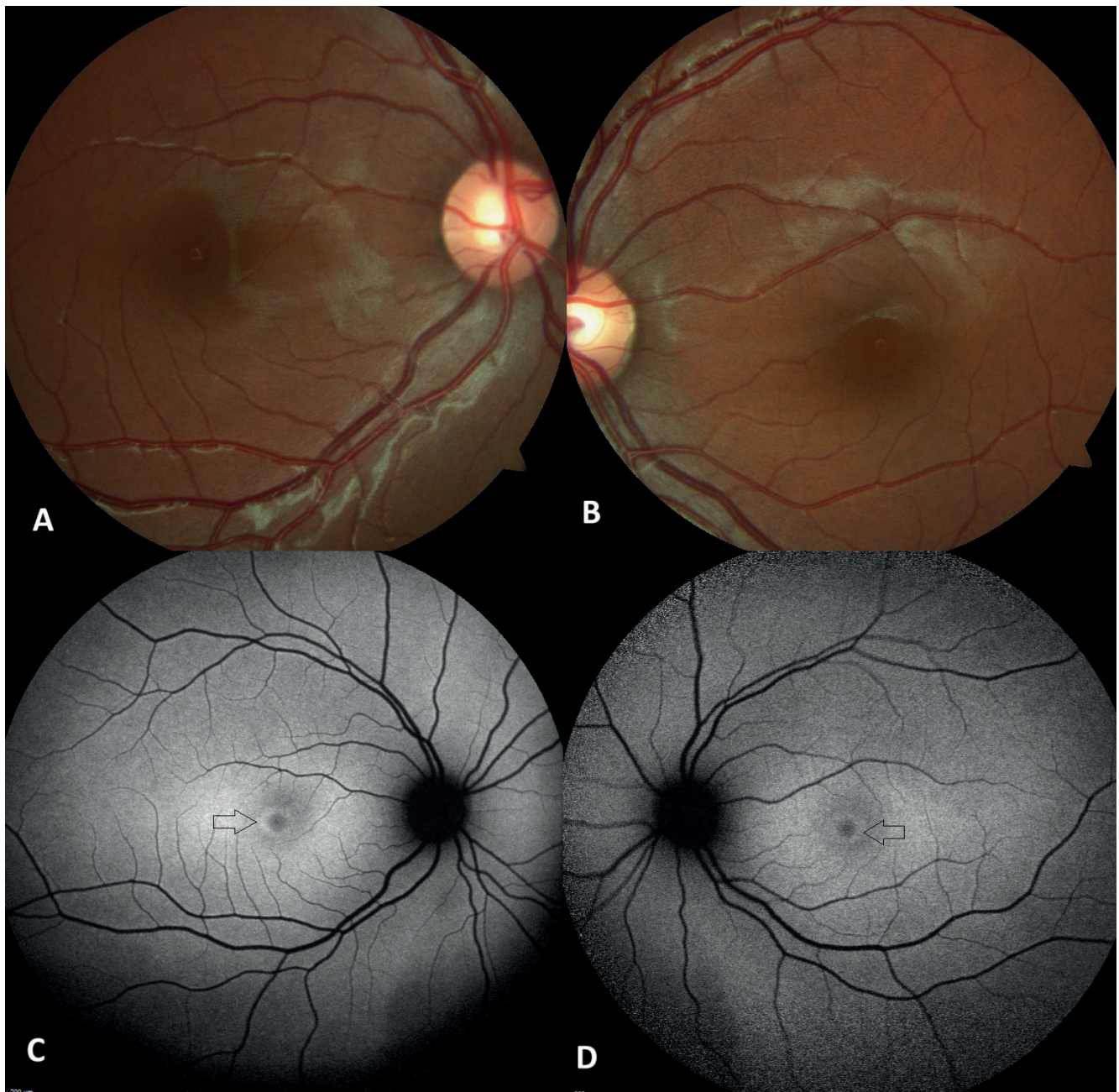


Figure 1. Color fundus images of the right (A) and left (B) eyes were normal. Fundus autofluorescence images showed a perifoveal ring of hyper-autofluorescence (black arrow) in the right (C) and left (D) eyes

DISCUSSION

A wide range of phenotypic variation and disease severity has been documented in ABCA4-associated retinopathy, such as fundus flavimaculatus, macular atrophy without flecks, bull's-eye maculopathy, retinitis pigmentosa, cone-rod dystrophy, and a foveal sparing phenotype. In addition, there is a considerable degree of allelic diversity, with over 700 variants of the ABCA4 gene having been identified thus far [5–7].

STGD1 presents in three forms: childhood-onset, adult-onset, and late-onset [2]. In childhood-onset, STGD1-type fundus findings are even more variable and

children can be asymptomatic and/or fundus abnormalities can even be absent in some cases. Fujinami et al. [5], observed a normal fundus architecture only in a single case among 42 STGD1 cases under the age of 17 years, while the remaining cases exhibited varying degrees of retinal flecks and macular atrophy during the baseline examination. In all 21 patients with available images, SD-OCT revealed disruption of the ONL at the fovea. Similarly, in a study by Lambertus et al. [8] that included 51 STGD1 patients with an onset age of ≤ 10 years, fundus anomalies could not be detected in approximately 1 out of 4 cases. In this study, SD-OCT was used to obtain cross-sectional images from 30 patients. The findings

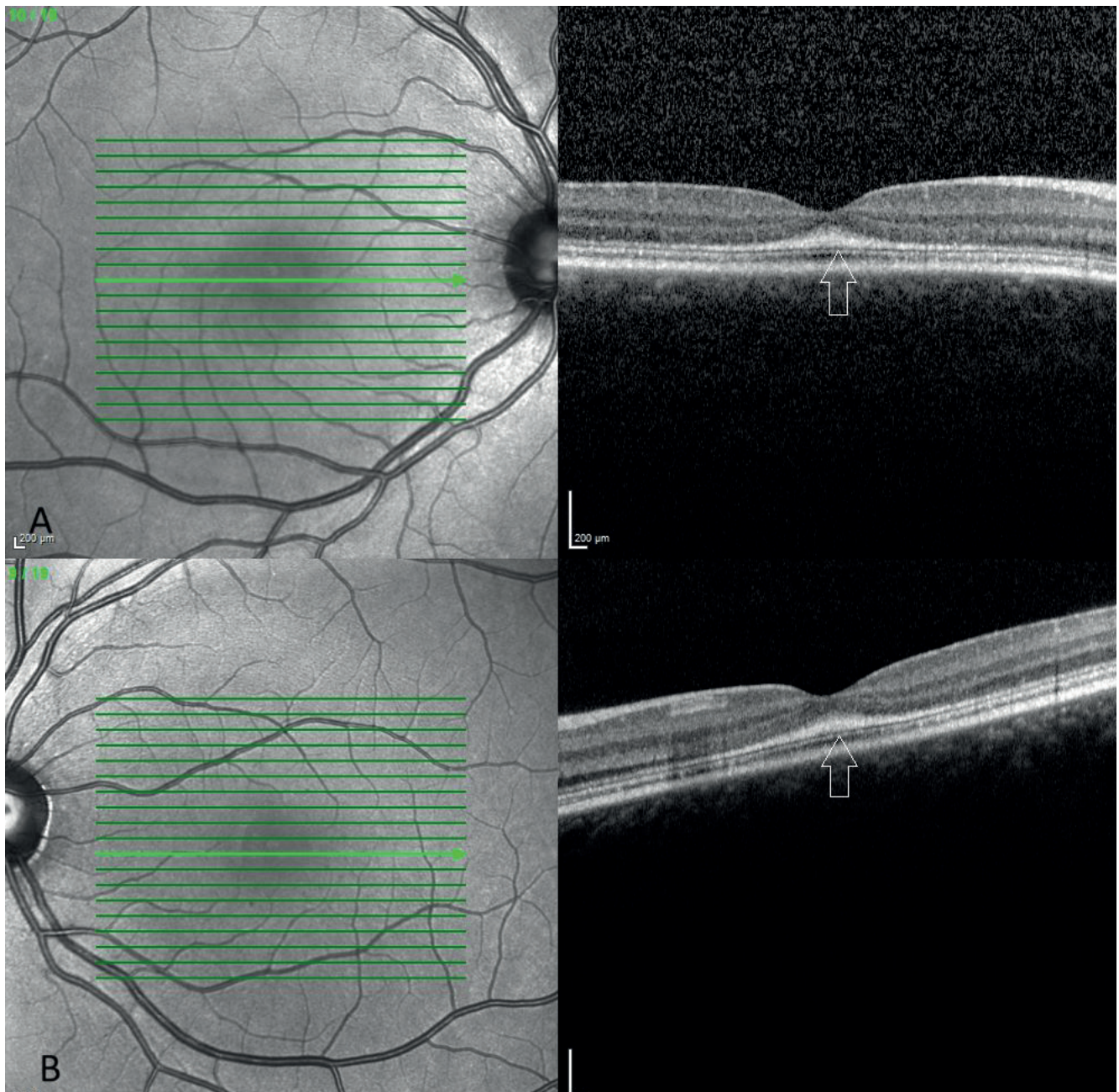


Figure 2. Spectral domain optical coherence tomography (OCT) revealed hyperreflectivity in the outer nuclear layer (white arrow) in the right (A) and left (B) eyes

suggested an apparent thickening of the external limiting membrane (ELM). Over time, SD-OCT demonstrated a thinning of the ONL and a loss of the ellipsoid zone (EZ), preceding the degradation of the RPE/Bruch's membrane complex. In addition, hyperreflective abnormalities were detected in the outer retina. Disease progression was characterized by a progressive loss of the ONL, EZ, RPE, and choriocapillaris. Furthermore, hyperreflective deposits were identified within the inner layers of the fovea, exhibiting a correlation with the intraretinal pigmentations observed in the fundus image. Khan et al. [4]. described early signs of macular degeneration in ABCA4-associated retinopathy without macular atrophy in a cohort of 8 chil-

dren with a median age of 8.5 years. All patients exhibited biallelic variants in ABCA4. Four children were found to be asymptomatic, while the other 4 reported a loss of visual acuity. At presentation, the macula appeared normal in 3 patients, exhibited a very mildly altered foveal reflex in 4 patients, and displayed fine yellow dots in 1 patient. FAF revealed the presence of hyperautofluorescent dots in the center of the macula in 3 patients, with 2 of them exhibiting a normal fundus appearance. At the initial presentation, a single patient exhibited a notable presence of hyperautofluorescent retinal flecks. OCT imaging revealed hyperreflectivity at the base of the ONL in all 8 patients. The observed hyperreflectivity at the base

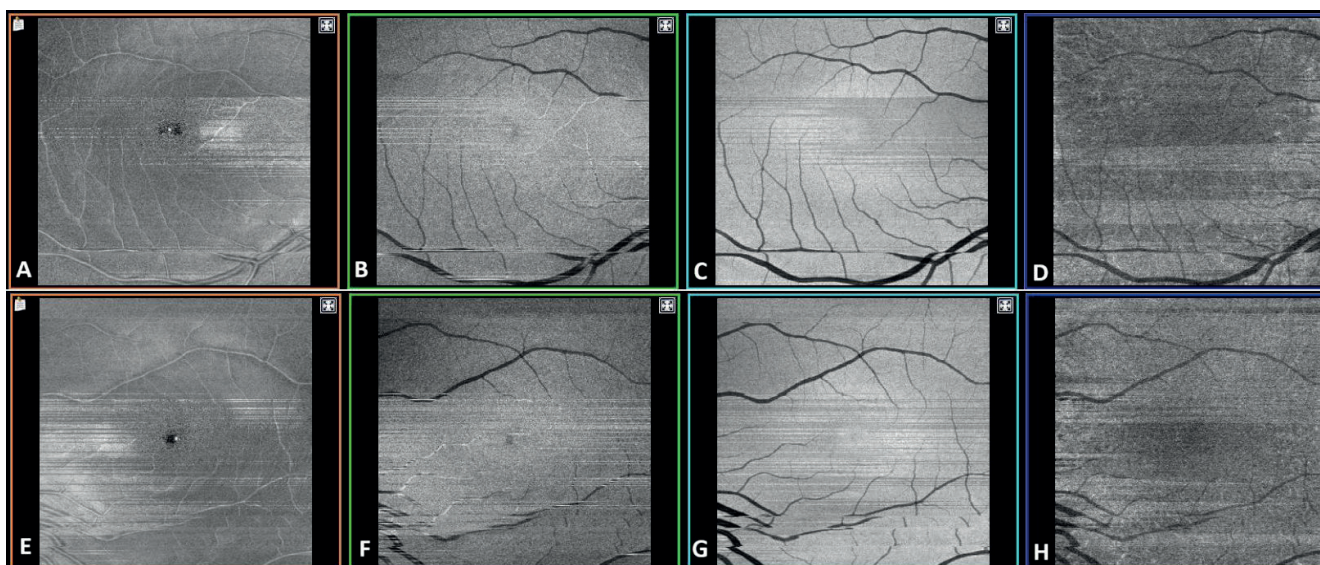


Figure 3. Enface Optical Coherence Tomography (OCT) images of the right (A to D) and left (E to H) eyes were normal on the superficial (A, E), deep (B, F), outer retina (C, G), and choriocapillaris (D, H) slabs

of the ONL, formerly characterized as thickening of the ELM, probably denotes a structural modification at the level of the foveal cone nuclei. In a study conducted by Bax et al. [9], researchers investigated the medical records of 280 patients with childhood-onset STGD1, with a median age of 8 years (range: 1-18). They observed that 31 patients (11.1%) did not exhibit fundus anomalies during the initial examination. The initial SD-OCT was conducted 9 years post-disease onset in 23 out of 31 patients. The other 8 patients did not undergo any SD-OCT scans. All the obtained OCT scans demonstrated abnormalities, with the RPE appearing either disorganized or absent. Furthermore, a thickened ELM was detected in 2 patients at 0.5 and 1 year after the onset of the disease. The authors observed that the median interval between the initial onset of symptoms and the diagnosis was 3 years, with a range of 0 to 19 years. Throughout this duration, patients frequently received misdiagnoses, including amblyopia, myopia, optic disc pathology, mental health

issues, and uveitis. Notably, FAF revealed subtle abnormalities like lipofuscin accumulation earlier in the disease course compared to ophthalmoscopy. In addition, OCT revealed distinctive features such as a thickened ELM. In our case, parallel to the case series mentioned above, there was a prominent hyperreflective band in the ONL on OCT and a perifoveal ring of hyper-autofluorescence on FAF without any evident changes on fundoscopy.

CONCLUSIONS

STGD1 can manifest in the early stages with characteristic OCT findings before fundus abnormalities emerge. It is crucial for clinicians to be aware of these early STGD1 manifestations. Familiarity with these findings can assist in the early diagnosis of asymptomatic patients. In symptomatic patients, it can help prevent unnecessary investigations for other causes of visual impairment.

REFERENCES

1. Heath Jeffery RC, Chen FK. Stargardt disease: Multimodal imaging: A review. *Clin Exp Ophthalmol*. 2021 Jul;49(5):498-515. Epub 2021 Jun 1. doi: 10.1111/ceo.13947.
2. Fujinami K, Waheed N, Laich Y, et al. Stargardt macular dystrophy and therapeutic approaches. *Br J Ophthalmol*. 2024 Mar 20;108(4):495-505. doi: 10.1136/bjo-2022-323071
3. Cicinelli MV, Battista M, Starace V, Battaglia Parodi M, Bandello F. Monitoring and Management of the Patient with Stargardt Disease. *Clin Optom (Auckl)*. 2019 Nov 28;11:151-165. doi: 10.2147/OPTO.S226595
4. Khan KN, Kasilian M, Mahroo OAR, et al. Early Patterns of Macular Degeneration in ABCA4-Associated Retinopathy. *Ophthalmology*. 2018 May;125(5):735-746. Epub 2018 Jan 6. doi: 10.1016/j.ophtha.2017.11.020
5. Fujinami K, Zernant J, Chana RK, et al. T. Clinical and molecular characteristics of childhood-onset Stargardt disease. *Ophthalmology*. 2015 Feb;122(2):326-334. Epub 2018 Jan 6. doi: 10.1016/j.ophtha.2014.08.012
6. Burke TR, Tsang SH. Allelic and phenotypic heterogeneity in ABCA4 mutations. *Ophthalmic Genet*. 2011 Sep;32(3):165-174. Epub 2011 Apr 21. doi: 10.3109/13816810.2011.565397
7. Westeneng-van Haaften SC, Boon CJ, Cremers FP, Hoefsloot LH, den Hollander AI, Hoyng CB. Clinical and genetic characteristics of late-onset Stargardt's disease. *Ophthalmology*. 2012 Jun;119(6):1199-1210. Epub 2012 Mar 24. doi: 10.1016/j.ophtha.2012.01.005
8. Lambertus S, van Huet RA, Bax NM, et al. Early-onset stargardt disease: phenotypic and genotypic characteristics. *Ophthalmology*. 2015 Feb;122(2):335-344. Epub 2014 Oct 17 doi: 10.1016/j.ophtha.2014.08.032
9. Bax NM, Lambertus S, Cremers FPM, Klevering BJ, Hoyng CB. The absence of fundus abnormalities in Stargardt disease. *Graefes Arch Clin Exp Ophthalmol*. 2019 Jun;257(6):1147-1157. Epub 2019 Mar 22. doi: 10.1007/s00417-019-04280-8