

Case report

Ultra-widefield and anterior-segment optical coherence tomography in Alagille syndrome

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ABSTRACT

Purpose: We describe the ocular findings in a patient with Alagille syndrome, included those obtained with ultra-widefield and anterior-segment optical coherence tomography (AS-OCT) imaging.

Observations: A previously asymptomatic 29-year-old woman with a heterozygous pathogenic variant in the *JAG1* gene was referred for an ophthalmic evaluation. The ocular abnormalities included bilateral posterior embryotoxon, iris atrophy, retinal pigmentary changes in the peripheral and peripapillary regions, and optic disc elevation. Ultra-widefield OCT showed bilateral retinal thinning with increased choroidal hyperreflectivity in the areas of peripheral retinopathy and optic disc elevation. AS-OCT confirmed bilateral iris atrophy.

Conclusions and Importance: The ocular abnormalities observed in the present case represent clinical features characteristic of Alagille syndrome. Both ultra-widefield and AS-OCT were useful for assessing the ocular abnormalities in Alagille syndrome.

1. Introduction

Alagille syndrome is defined by a paucity of intrahepatic bile ducts in association with five main clinical abnormalities: cholestasis, cardiac disease, skeletal and ocular abnormalities, and a characteristic facial phenotype.¹ The inheritance pattern of Alagille syndrome is autosomal dominant with low penetrance and variable expression.² Although pathogenic variants in the *JAG1* or *NOTCH2* gene have been identified, no genotype-phenotype correlations exist between the clinical manifestations of Alagille syndrome and the specific pathogenic variant types or the location of the variant within the gene.³ A wide variety of ophthalmic abnormalities are seen in Alagille syndrome that affect the cornea, iris, retina, and optic disc.^{2,4–7} We describe the ocular findings in a patient with Alagille syndrome, including evaluation with ultra-widefield and anterior-segment optical coherence tomography (AS-OCT).

2. Case report

A previously asymptomatic 29-year-old woman with a diagnosis of Alagille syndrome was referred for an ophthalmic evaluation. She had a

heterozygous pathogenic variant in the *JAG1* gene (c.1457dup p.[Asp487Argfs*4]), which denotes a frame shifting change with Aspartic Acid-487 as the first affected amino acid, changing into an Arginine, and the new reading frame ending in a stop at position 4. Based on our investigation with the gene variant databases including HGMD, LOVD, gnomAD, and HGVD (<https://www.hgvd.genome.med.kyoto-u.ac.jp/>), this variant has not been reported and is predicted to be pathogenic by resulting in premature truncation of the *JAG1* protein.

On presentation, the best-corrected visual acuity (BCVA) was 20/20 bilaterally with refractive errors of −0.5 diopter (spherical equivalent). The horizontal corneal diameters were 10.5 mm in the right eye and 10.0 mm in the left eye. The respective axial lengths were 21.1 and 21.0 mm and intraocular pressures 9 and 10 mmHg. Slit-lamp examination showed bilateral posterior embryotoxon and iris depigmentation (Fig. 1a). AS-OCT confirmed bilateral iris atrophy in the areas of iris depigmentation (Fig. 1b) when compared to normal control (Fig. 1c). Dilated ophthalmoscopic examination showed bilateral retinal pigmentary changes in the peripheral and peripapillary regions, which exhibited hypo-autofluorescence with fundus autofluorescence (Fig. 1d–g). OCT demonstrated a normal appearance in the macula and diffuse retinal thinning with loss of outer retinal structure in the areas of

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peripapillary retinopathy bilaterally (Fig. 2a and b). Ultra-widefield OCT confirmed bilateral retinal thinning with increased choroidal hyperreflectivity in the areas of peripheral retinopathy and optic disc elevation (Fig. 2c–f).

Goldmann perimetry showed moderate bilateral constriction, and Humphrey perimetry showed bilateral enlarged blind spots, with subnormal electroretinography (ERG) in both scotopic and photopic conditions (Fig. 3a–d). B-scan ultrasonography showed small localized areas of high reflectivity bilaterally within the optic nerve, which were suggestive of buried optic disc drusen (Fig. 3e).⁷

3. Discussion

Alagille syndrome comprises a broad spectrum of ocular anomalies involving the cornea, iris, retina, and optic disc. Hingorani et al. examined 22 patients with Alagille syndrome and reported that the most common ocular abnormalities were posterior embryotoxon (95%), iris

abnormalities (45%), diffuse fundus hypopigmentation (57%), and optic disc anomalies (76%).⁴ Brodsky and Cunniff studied six patients with Alagille syndrome and reported posterior embryotoxon (83%), microcornea (83%), iris stromal hypoplasia (100%), regional peripapillary retinal depigmentation (50%), and anomalous optic discs (83%).⁵ The ocular abnormalities in the present case represent clinical features characteristic of Alagille syndrome.

The BCVA is not affected significantly by the ocular abnormalities in most patients with Alagille syndrome. Hingorani et al. reported that 35 of 36 eyes with Alagille syndrome had a BCVA of 20/30 or better.⁴ Wells et al. also found that 13 of 16 eyes with Alagille syndrome had a BCVA of 20/30 or better.⁶ In the present case, the BCVA was 20/20 bilaterally; however, the results of visual field testing and ERG were subnormal. The bilateral constriction of the visual field and subnormal ERG responses seemed to be associated with peripheral retinopathy, and the enlarged blind spots seemed to be correlated with peripapillary retinopathy and/or elevated discs. Puklin et al. also reported a 31-year-old man with

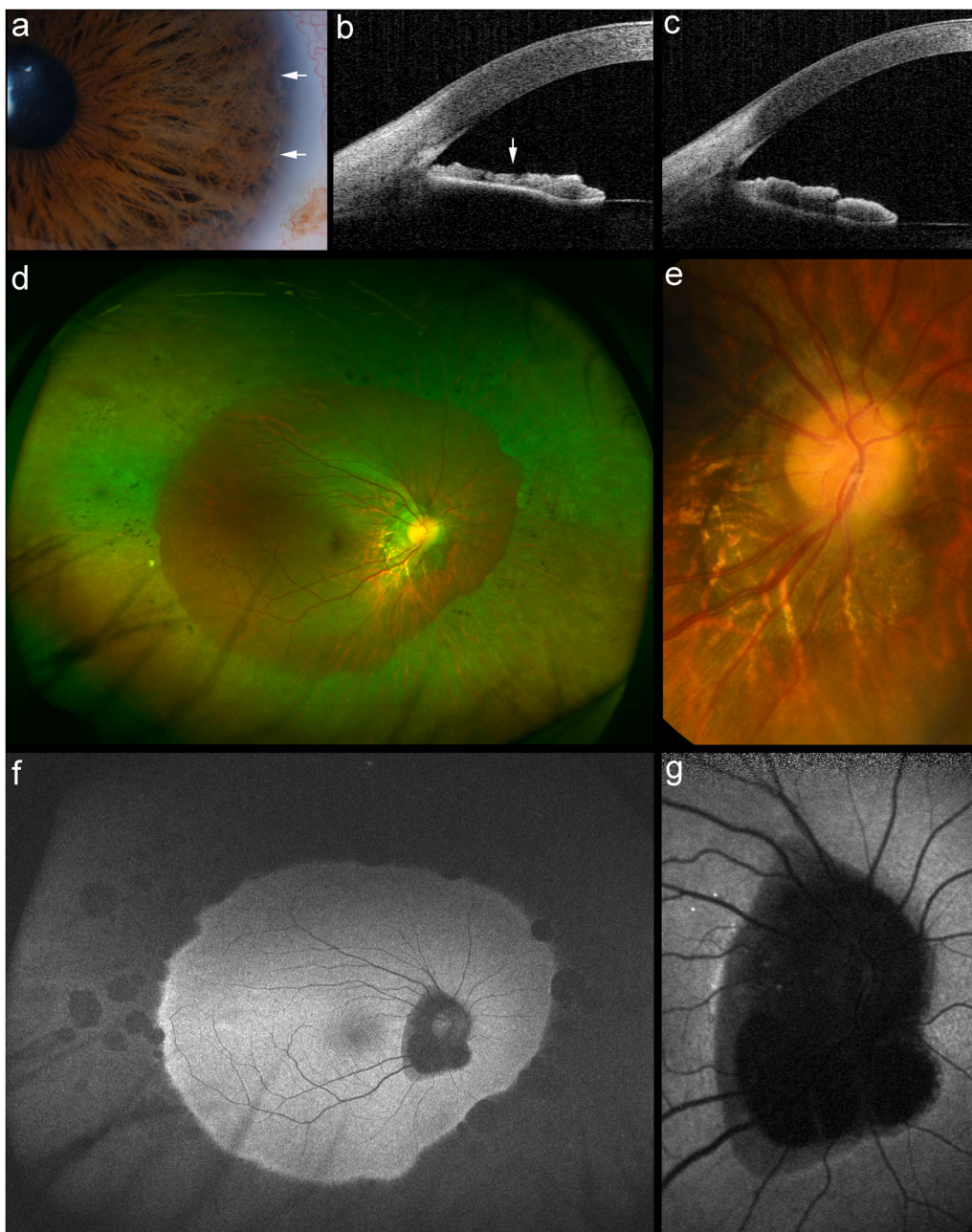


Fig. 1. Ocular findings in Alagille syndrome. (a) A slit-lamp photograph of the left eye shows posterior embryotoxon (arrows) and iris depigmentation. (b) An anterior-segment optical coherence tomography (AS-OCT) image of the left eye shows iris atrophy (arrow). (c) An AS-OCT image of the normal left eye (a 31-year-old woman with a spherical equivalent of 0 diopter). (d, e) Fundus photographs of the right eye show retinal pigmentary changes in the peripheral and peripapillary regions. (f, g) Fundus autofluorescence images of the right eye show hypo-autofluorescence in the peripheral and peripapillary regions.

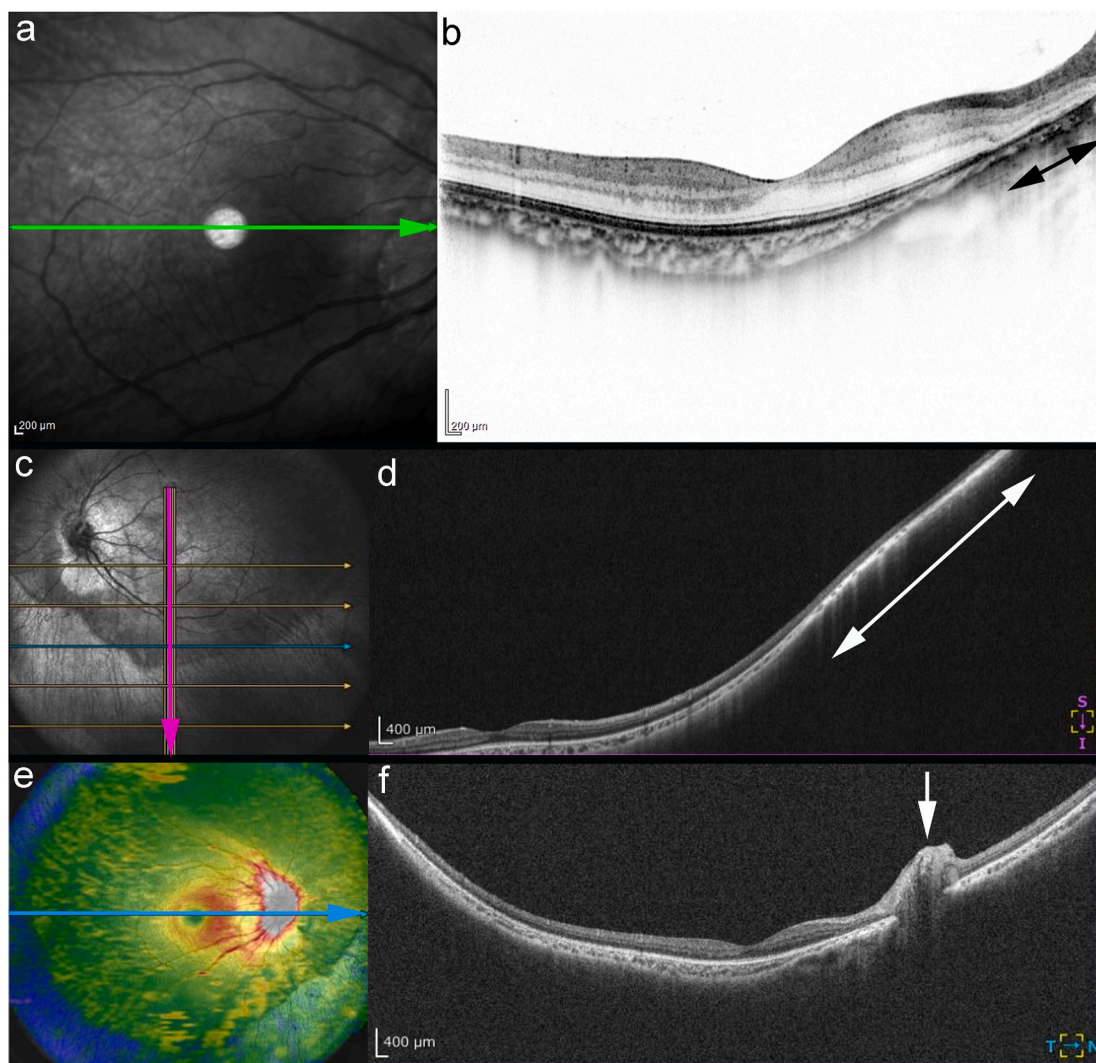


Fig. 2. Optical Coherence Tomography (OCT) in Alagille Syndrome.

(a, b) An OCT image of the right eye demonstrates a normal appearance in the macula and diffuse retinal thinning with loss of outer retinal structure in the areas of peripapillary retinopathy (between arrows). A green arrow in (a) shows the direction of OCT scan in (b). (c, d) An ultra-widefield OCT image of the left eye shows retinal thinning with increased choroidal hyperreflectivity in the areas of peripheral retinopathy (between arrows). A pink arrow in (c) shows the direction of ultra-widefield OCT scan in (d). (e, f) An ultra-widefield OCT image of the right eye shows optic disc elevation (arrow). A blue arrow in (e) shows the direction of ultra-widefield OCT scan in (f). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Alagille syndrome that had a pigmentary retinopathy in the peripapillary and equatorial regions, generalized constriction of Goldman visual fields, and subnormal ERG in both scotopic and photopic conditions.⁸

Small corneal diameters and decreased axial lengths are not associated with large refractive errors in patients with Alagille syndrome. Hingorani et al. reported that the mean corneal diameters were 10.28 mm in nine patients with a mean spherical equivalent of +0.85 diopter.⁴ Wells et al. found that the degree of hyperopia measured was less than expected considering the measured axial lengths.⁶ The current patient also had small corneal diameters and decreased axial lengths but small refractive errors. Wells et al. suggested that the relative lack of hyperopia is explained by the steep corneal curvatures that offset the effect of the decreased axial lengths.⁶

A previous case report described bilateral peripheral chorioretinal atrophy in a patient with Alagille syndrome; however, that was not observed with OCT.⁹ Xephilio OCT-S1 (Canon Lifecare Solutions, Tokyo, Japan) can capture ultra-widefield images up to 23 mm in one scan.¹⁰ In the present case, this ultra-widefield OCT clearly showed bilateral retinal thinning with increased choroidal hyperreflectivity in the areas of peripheral retinopathy. On OCT, areas of retinal pigment epithelial

atrophy appear as choroidal hyperreflectivity from loss of the overlying retinal pigment epithelium.¹¹ In addition, AS-OCT confirmed bilateral iris atrophy in the present case, which otherwise might be difficult to evaluate without histopathologic analysis.¹²

4. Conclusions

We report the ocular findings in a patient with Alagille syndrome. The ocular abnormalities observed in this case included bilateral posterior embryotoxon, iris atrophy, retinal pigmentary changes in the peripheral and peripapillary regions, optic disc elevation, and buried optic disc drusen. Both ultra-widefield and AS-OCT were useful for assessing these ocular abnormalities. However, further investigations are required to determine whether the retinopathies in the peripheral and peripapillary regions are progressive.

Patient consent

The patient provided written informed consent for the research and publication of this study and all accompanying images.

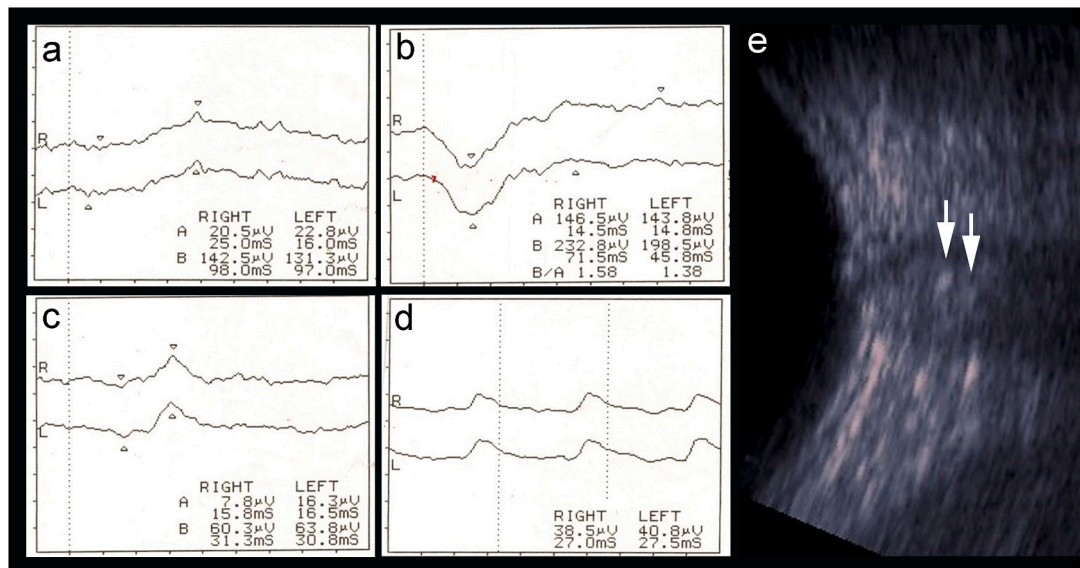


Fig. 3. Electoretinography (ERG) and B-scan ultrasonography in Alagille Syndrome.

(a) Scotopic ERG (rod responses). (b) Scotopic ERG (combined rod and cone responses). (c) Photopic ERG (cone responses). (d) Photopic ERG (flicker). (e) B-scan ultrasonography of the left eye shows small localized areas of high reflectivity within the optic nerve (arrows), which are suggestive of buried optic disc drusen.

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Authorship

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

Declaration of competing interest

The following authors have no financial disclosures related to this work: NK, MH, RT, YW, and SY.

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