Alagille Syndrome and Ocular Findings: Report of Two Pediatric Cases

Síndrome de Alagille e Alterações Oculares: Descrição de Dois Casos Pediátricos

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ABSTRACT

Alagille syndrome (ALGS) is a rare multisystemic disorder, with an estimated prevalence of 1 in 30 000–70 000 live births, caused by pathogenic variants in *JAG1* or *NOTCH2*. It is characterized by variable expression of hepatic, cardiac, skeletal, facial, and ocular abnormalities.

We present two pediatric cases of confirmed ALGS, emphasizing the diagnostic value of ophthalmological findings. Comprehensive ophthalmological evaluation and multimodal imaging was performed at the Ophthalmology Department, Unidade Local de Saúde de Matosinhos, Portugal. Patients' anonymity was preserved in accordance with the Declaration of Helsinki.

Both patients presented systemic features typical of ALGS and distinct ocular changes, namely subtle anterior segment anomalies, optic disc elevation and pallor, and diffuse fundus hypopigmentation.

Ocular manifestations are key diagnostic clues in ALGS and support early identification and multidisciplinary management. Early ophthalmic evaluation facilitates genetic confirmation and can guide timely diagnosis and improve outcomes in affected children.

KEYWORDS: Alagille Syndrome/diagnosis; Alagille Syndrome/genetics; Child; Eye Abnormalities.

RESUMO

A síndrome de Alagille (ALGS) é uma doença multissistémica rara causada por variantes patogénicas nos genes *JAG1* ou *NOTCH2*, com prevalência estimada de 1:30 000–70 000 nascimentos. Apresenta expressão clínica variável, incluindo alterações hepáticas, cardíacas, esqueléticas, faciais e oculares.

Descrevem-se dois casos pediátricos com ALGS geneticamente confirmada, salientando-se o contributo dos achados oftalmológicos para o diagnóstico. Realizou-se avaliação oftalmológica completa e estudo imagiológico no Serviço de Oftalmologia da Unidade Local de Saúde de Matosinhos, garantindo-se o anonimato conforme a Declaração de Helsínquia.

Ambos os doentes evidenciaram manifestações sistémicas típicas, associadas a alterações oculares características, incluindo anomalias subtis do segmento anterior, alterações do nervo

ótico e hipopigmentação difusa do fundo ocular.

Os achados oculares podem constituir um marcador precoce de ALGS, sendo fundamentais para o reconhecimento clínico e encaminhamento para estudo genético. A sua identificação facilita o diagnóstico precoce e o seguimento multidisciplinar.

PALAVRAS-CHAVE: Anomalias Congénitas do Olho; Criança; Síndrome de Alagille/diagnóstico; Síndrome de Alagille/genética.

INTRODUCTION

Alagille syndrome (ALGS) is a rare multisystemic disorder characterized by five major clinical abnormalities: cholestatic liver disease due to paucity of intrahepatic bile ducts, congenital heart defects, distinctive facial features, musculoskeletal anomalies, and ocular manifestations.[1,2] The estimated incidence ranges between 1 in 30 000 and 70 000 live births.[3]

It follows an autosomal dominant inheritance with variable expressivity and low penetrance.[1,2] Pathogenic variants in *JAG1* (20p12) account for 90%–96% of cases, while *NOTCH2* mutations represent a small fraction (<1%) and are more often associated with renal malformations.[1,2,4,5] Both genes encode transmembrane proteins of the NOTCH signaling pathway, essential for embryonic development.[4,6] Approximately 60% of cases arise from *de novo* mutations, with a relatively high rate of germline mosaicism.[5]

Diagnosis can be challenging due to genetic and phenotypic variability, even within families. Some carriers remain asymptomatic or present incomplete features, making genetic testing a key diagnostic tool, especially in atypical cases.[3,4]

CASE REPORTS

This report illustrates systemic and ophthalmological findings of ALGS in two pediatric patients, emphasizing early recognition of ocular signs for timely management. Both underwent full ophthalmologic evaluation at the Ophthalmology Department, Unidade Local de Saúde de Matosinhos, Pedro Hispano Hospital, Portugal. Optical coherence tomography (OCT) of the anterior and posterior segments, facial phenotype photography, B-scan ultrasound, fundus photography were attempted, though limited by poor cooperation due to young age. Data collection followed ethical standards and patient anonymity per the Declaration of Helsinki.

CASE 1

A 6-year-old boy, diagnosed with ALGS, presented with bilateral decreased vision. His mother and brother also had ALGS. He was under follow-up in cardiology for atrial septal defect and bilateral pulmonary artery stenosis, and in gastroenterology for chronic cholestasis, treated with ursodeoxycholic acid. He exhibited the typical triangular facial phenotype with broad forehead, hypertelorism, and small pointed chin (Fig. 1).

Uncorrected visual acuity was 7/10 in the right eye (RE)

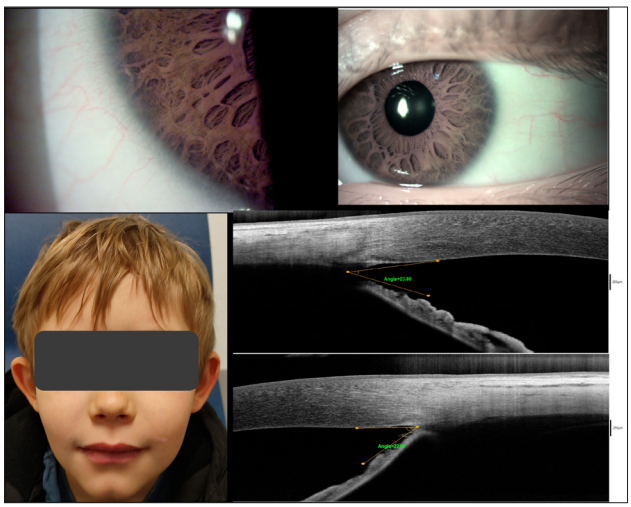

Figure 1. Anterior segment findings, facial phenotype photography and anterior segment optical coherence tomography (AS-OCT) of case 1.

and 8/10 in the left eye (LE) in the decimal scale. Pupils and ocular motility were normal. He was orthophoric and cycloplegic refraction revealed in RE +4.00+1.00×90º and in LE +4,25+0.75×110º. Slit-lamp exam showed peripheral iris processes touching the cornea but no posterior embryotoxon. Fundoscopy revealed bilateral optic disc elevation and vascular tortuosity, but normal fundus autofluorescence (Fig. 2). OCT confirmed thickening of the retinal nerve fiber layer (RNFL) consistent with pseudopapilledema (Fig. 3). Brain magnetic resonance imaging (MRI) showed Chiari type I malformation with clival hypoplasia, corpus callosum thinning, and mild optic nerve sheath enlargement, without globe flattening. Neuropediatric evaluation revealed no clinical signs of intracranial hypertension on neurologic evaluation.

Over one year of follow-up, vision improved (9/10 OU with correction), the optic disc appearance remained stable. Corneal tomography revealed in the RE, keratometry of K1 44,28D@20º, K2 46.26D@110º, with a corneal thickness of 623 µm and an anterior chamber of 2.97 mm. In the LE, keratometry of K1 44,27D@6º, K2 45,57D@96º, with a corneal thickness of 628 µm and an anterior chamber of 2.90 mm. Autofluorescence (AF) was unremarkable and ocular ultrasound was suggestive of buried optic disc drusen (Fig. 2).

CASE 2

A 10-year-old girl, born prematurely at 30+4 weeks, was first referred at age 1 for high ametropia in the LE.

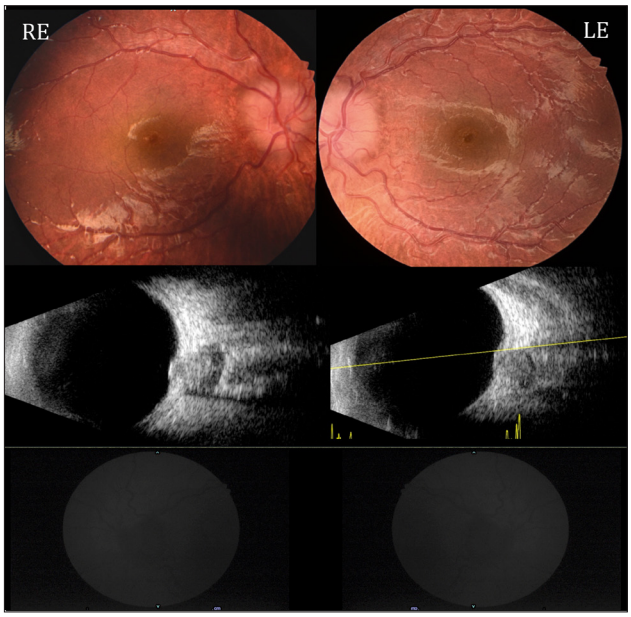

Figure 2. Fundus photos, B-scan ultrasonography and fundus autofluorescence of case 1 demonstrating bilateral optic disc elevation and vascular tortuosity with preserved autofluorescence.

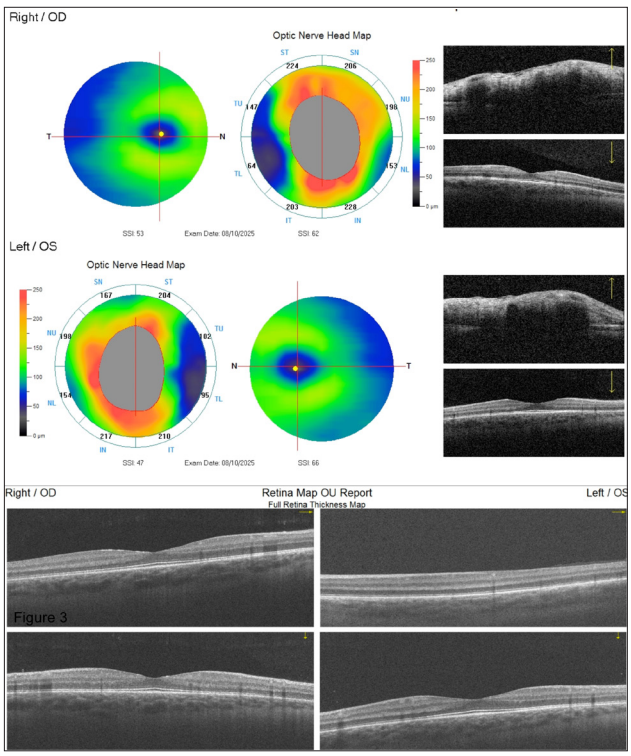

Figure 3. Optical coherence tomography (OCT) of the retina and optic nerve of case 1 showing thickening of the retinal nerve fiber layer consistent with pseudopapilledema.

She was previously diagnosed with ALGS and genetic testing revealed a pathogenic c.1059dup variant in exon 8 of *JAG1*, confirming the diagnosis. Family members, including the mother (with similar facial phenotype), were studied and revealed variants in *ACTN4*, *PLCE1* and *FAN1*, with no *JAG1* mutation, indicating no genetic correlation with the child's disease. Facial morphology resembled case 1. Cycloplegic refraction showed RE +4.50+1.50×70º, LE +2.00+1,25×110º. At age 10, she was orthophoric, with full ocular motility and persistent manifest-latent horizontal pendular nystagmus. She took maralixibat and K1 vitamin. BCVA was 6/10 RE (+2.00 +1.25 ×65º) and 8/10 LE (–0.50 +1.50 ×100º) in decimal scale. Cooperation was limited. Anterior segment exam showed shallow peripheral anterior chambers without posterior embryotoxon (Fig. 4).

Fundoscopy demonstrated optic disc pallor and diffuse retinal pigment epithelium (RPE) atrophy, although fundus imaging was limited by poor cooperation. OCT showed a shallow foveal pit suggesting a foveal hypoplasia (Fig. 4). Electrophysiological testing revealed normal P100 latency with inconclusive amplitudes on VEP; ERG could not be performed.

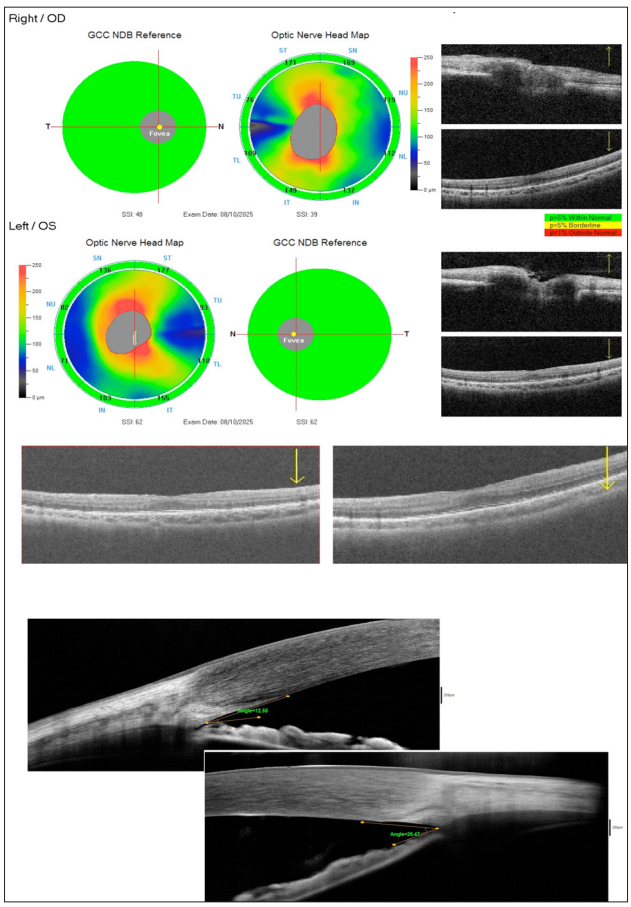

Figure 4. Anterior segment optical coherence tomography (AS-OCT) and optical coherence tomography (OCT) of case 2 demonstrating shallow peripheral chambers and a shallow foveal pit compatible with foveal hypoplasia.

DISCUSSION

ALGS was first described in 1956, with bile duct hypoplasia and persistent cholestasis as defining features.[7] Diagnostic criteria established in 1987 required interlobular

bile duct paucity plus at least three of five major findings: cholestasis, cardiac defects, vertebral anomalies, typical facies, or ocular abnormalities.[1,4,6,8]

Systemic manifestations are diverse. Cardiovascular anomalies occur in 83%, most frequently pulmonary artery stenosis (53%–67%), followed by tetralogy of Fallot (7%–16%) and septal defects.[4,5,9] Hepatobiliary involvement affects 61%, presenting with jaundice, hyperbilirubinemia, or cholestasis, sometimes requiring liver transplantation.[4,10] Butterfly vertebrae and skeletal anomalies occur in 60%, and the characteristic facies—broad forehead, straight nose, pointed chin, and prominent ears—are helpful diagnostic clues.[4,5,10]

Ocular findings, incorporated later into diagnostic criteria, occur in over 90% of patients.[6,11] Most have mild refractive errors, commonly hyperopia.[4,6,11] Anterior segment anomalies include posterior embryotoxon (70%–95%), microcornea (up to 83%), iris hypoplasia (45%), shallow anterior chamber, exotropia, band keratopathy, and cataracts.[2,4,5,11] Posterior findings include diffuse fundus hypopigmentation (50%–57%), pigmentary retinopathy, and optic disc changes (76%–83%) such as drusen, elevation, or small cups.[2,4,10] Retinal vascular tortuosity is frequent.[6] Disc elevation usually represents pseudopapilledema rather than raised intracranial pressure.[6,12] It often remains stable, attributed to glial proliferation or buried drusen.[6,10] Nevertheless, intracranial hypertension must always be excluded if disc changes progress or vision declines.[6]

Pigmentary retinopathy is variable—from diffuse hypopigmentation to geographic RPE loss—often sparing central vision. Visual field constriction or enlarged blind spots may occur.[2,10] Data on ERG and visual fields in ALGS remain limited.[2,4,6]

In case 1, bilateral optic disc elevation with stability over time and absence of neurological symptoms strongly suggest pseudopapilledema, caused by optic disc drusen, as suggested by ocular ultrasound, despite normal autofluorescence. The subtle peripheral iris–cornea adhesions is a possible ALGS feature, although gonioscopy was not feasible.

In case 2, RPE atrophy and disc pallor, though poorly documented, fit the ALGS pattern. The shallow foveal pit, however, is more likely attributable to prematurity-related developmental arrest rather than to ALGS, as foveal morphogenesis abnormalities are not a typical ocular feature of this condition. Persistent nystagmus in this patient also favors a prematurity-related etiology. Both cases highlight the difficulty of complete ophthalmic assessment in pediatric patients. Visual field testing may later aid functional–structural correlation.

ALGS requires a multidisciplinary approach that usually involves genetics, pediatrics, gastroenterology, cardiology, ophthalmology, and nephrology.[5] Hepatic assessment (with liver function tests, lipid profile, bile acids, coagulation studies, liver imaging and biopsy when indicated), detailed cardiac evaluation, spinal X-ray, ophthalmologic examination, and renal function tests are recommended.[5,9]

Treatment includes nutritional support, fat-soluble vitamin supplementation, and bile acid transporter inhibitors (maralixibat or odevixibat). Liver transplantation is reserved for end-stage disease.[9,10]

Despite improved care, morbidity and mortality remain high due to hepatic and cardiovascular complications.[10] Early ophthalmic detection may facilitate diagnosis and multidisciplinary care, improving outcomes.

CONCLUSION

ALGS is a rare multisystem disorder with highly variable expression. Its major manifestations include bile duct paucity with cholestasis, cardiac anomalies (mainly pulmonary artery stenosis), facial dysmorphism, skeletal and ocular changes. Other findings—renal defects, pigmentary retinopathy, and vascular anomalies—may also occur.[9] These cases demonstrate the wide ocular spectrum of ALGS, from subtle anterior findings to optic disc and retinal alterations. Comprehensive ophthalmologic evaluation is crucial, as ocular features can provide early diagnostic clues even in incomplete systemic disease. Despite advances in molecular testing and supportive therapy, ALGS remains associated with significant morbidity and variable prognosis.[4] Early recognition of ocular and systemic signs ensures appropriate genetic counseling, multidisciplinary follow-up, and timely management.[13]

Awareness of ophthalmologic findings can guide systemic assessment and improve patient quality of life.

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JSR: Data collection, manuscript writing an revision.
SJ: Data collection and review of the manuscript.
AM, IR, CF: Scientific review and final approval of the manuscript.
All the authors approved the final version to be published.

JSR: Recolha de dados, redação e revisão do manuscrito.
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AM, IR, CF: Revisão científica e aprovação final do manuscrito.
Todos os autores aprovaram a versão final a ser publicada.

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