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## Alagille Syndrome Associated with Xerophthalmia

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### Key Words

Alagille syndrome · Keratomalacia · Xerophthalmia · Vitamin A deficiency

### Abstract

**Purpose:** To report the occurrence of xerophthalmia and keratomalacia in a patient with Alagille syndrome. **Methods:** The patient's record and relevant literature were reviewed. **Results:** A 3-year-old boy with Alagille syndrome was examined at our institution due to severe bilateral ocular irritation. A corneal ulcer and keratomalacia were found in the right eye and severe dryness with corneal opacification was found in the left eye. He was treated with topical fortified antibiotics in the right eye, followed by amniotic membrane transplantation. Due to his systemic condition, characterized by severe cholestasis and intestinal malabsorption, a suspicion of vitamin A deficiency was raised and was later confirmed in serum analysis. **Conclusion:** This is the first report of xerophthalmia in a patient with Alagille syndrome. Vitamin A deficiency leading to xerophthalmia is common in developing countries; however, its occurrence in the West is rare, leading to a reduced awareness of this disorder amongst clinicians. Unusual eating habits, intestinal malabsorption and liver disease are possible causes for such a deficiency. The purpose of this case report is to raise awareness to the possibility of vitamin A deficiency in children with keratopathy, especially when associated with these disorders.

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### Introduction

Alagille syndrome (arteriohepatic dysplasia) is a rare autosomal dominant disorder, caused by mutations in the *JAG1* gene located on the short arm of chromosome 20 [1]. Classic features include intrahepatic bile-duct hypoplasia causing neonatal cholestatic jaundice,

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cardiovascular defects, skeletal abnormalities and a characteristic facial appearance [2]. Additional common findings include renal abnormalities, growth retardation and mental retardation [3]. Alagille syndrome is also associated with ocular abnormalities, most commonly with posterior embryotoxon, which is present in 95% of cases and is considered a major feature of this disorder [4]. Other ocular abnormalities include retinal pigmentary changes, optic disc abnormalities, lens opacities, iris abnormalities and a slightly reduced corneal diameter without significant refractive errors [4–6]. Patients with Alagille syndrome have a relatively good prognosis, and are typically managed with pruritus-relieving medication and nutritional supplementation of the fat-soluble vitamins (A, D, E and K) [2, 7, 8].

We report a patient with Alagille syndrome, with significant bilateral keratopathy secondary to reduced vitamin A levels that had occurred despite nutritional supplementation.

### Case Report

A 3-year-old boy was examined at our institution due to severe bilateral ocular-surface disease, more severe in the right eye. His medical history included neonatal cholestatic jaundice, which prompted us to make a thorough systemic evaluation. Liver biopsy revealed paucity of the intrahepatic bile ducts. Cardiac echography revealed a left-to-right shunt through an atrial septal defect and mild stenosis of the pulmonary arteries. Vertebral structure was normal on X-ray. The patient was first examined at our clinic at the age of 9 months, and a prominent posterior embryotoxon was noted bilaterally (fig. 1). The combination of typical facial characteristics including a prominent forehead, bulbous nose and pointed chin together with systemic and ocular findings led to a clinical diagnosis of Alagille syndrome. His parents were reluctant to have genetic testing performed. During infancy, the main complaint was his failure to thrive, and a percutaneous endoscopic gastrostomy tube was inserted for added caloric supplementation along with the fat-soluble vitamins. The patient suffered from a significant developmental delay (e.g. he started walking only at the age of 2.5 years) and severe growth retardation under full caloric and pancreatic-enzyme supplementation (at the age of 3.5 years, he weighed 7.2 kg, which is below the 3rd percentile). He received chronic daily treatment with ursodeoxycholic acid and supplementation with the fat-soluble vitamins (AquADEKs, 1 ml until the age of 1 year, and then 2 ml; 1 ml contains vitamin A as 87%  $\beta$ -carotene and 13% palmitate, 5,751 IU which is 383% of the daily value for infants).

Several months prior to examination at our clinic, he started complaining of severe bilateral ocular irritation. Because of constant eye-rubbing, it was assumed that he suffered from vernal keratoconjunctivitis, and he was treated with topical antihistamines. After failing to improve with this treatment, he was referred for our examination. At the initial evaluation, a central corneal ulcer was noted in the right eye, with marked opacity and central thinning of the cornea. The cornea in the left eye displayed mild opacities and diffuse superficial punctate keratitis. The fundus could not be seen in the right eye, but in the left eye, mild tilting and optic-disc pallor were noted as well as a few retinal pigmentary changes. A culture taken from the corneal ulcer in the right eye was positive for *Staphylococcus mitis*. The patient was treated with intensive topical cefamezine, garamycin and lubrication, and experienced a gradual improvement. Three weeks after his initial presentation to our clinic, the corneal infiltrate resolved, but a marked thinning remained. He underwent amniotic membrane transplantation with lower punctual occlusion (fig. 2). Due to the clinical findings and his systemic condition, a suspicion of vitamin A deficiency was raised. This was confirmed by serum analysis of vitamin A, which measured 2  $\mu\text{g}/\text{dl}$ ; this is significantly

lower than the normal range of 30–120 µg/dl. There were no Bitot's spots in either eye. It should be noted that, due to the patient's significant developmental delay, visual acuity could not be measured and he was unable to articulate any complaint regarding reduced vision or nyctalopia. The vitamin A supplementation was further increased and it resulted in a gradual improvement of the degree of ocular discomfort within the following months. The irritation had resolved, the patient was no longer rubbing his eyes, and the right cornea was adequately covered by conjunctival epithelium.

## Discussion

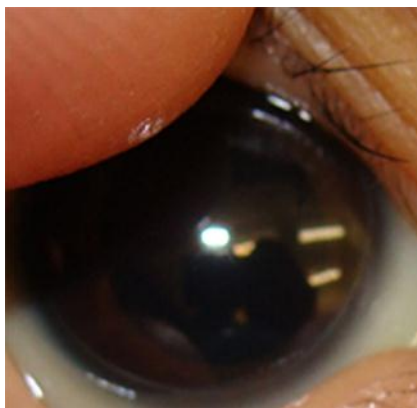
Vitamin A is an essential fat-soluble vitamin that has many systemic as well as ocular effects. In the eye, it is essential for the normal turnover of epithelial cells and mucin production and for the production of visual pigments in the photoreceptor cells [9]. Vitamin A deficiency is the leading cause of preventable childhood blindness worldwide [9]; however, this condition is rare in the Western world, where its occurrence is usually caused by lipid malabsorption, chronic liver disease or unusual dietary restrictions [10–13]. Ocular disease due to vitamin A deficiency is termed xerophthalmia, which typically develops in a sequential order [9]. Night blindness is usually the earliest manifestation, followed by ocular-surface changes which range from mild conjunctival and corneal drying (xerosis) to corneal ulceration and melting (keratomalacia) and eventually to pigmentary retinopathy [9]. An association between systemic vitamin A deficiency and increased intracranial pressure has also been described [14]. The World Health Organization (WHO) has published a classification of ocular changes secondary to vitamin A deficiency [15]. Our patient was compatible with the WHO classification class X<sub>3</sub>A in the right eye, presenting with corneal ulceration and keratomalacia involving one third or less of the cornea, and class X<sub>2</sub> in the left eye, which only had corneal xerosis. Although the child had previously been treated with vitamin A supplementation, the level of this vitamin in his body was markedly reduced. He also had significant growth retardation, and it is possible that the combination of his body's high demand for growth, chronic cholestasis and low storage capability due to his liver disease resulted in his vitamin A deficiency, despite dietary supplementation. Improvement occurred only when the vitamin A dosage was further increased.

The pigmentary retinopathy typical for Alagille syndrome has been presumed to relate to a deficiency of vitamins A and E [5, 16]; however, recent reports have identified normal serum levels of these vitamins in patients harboring retinal changes [3, 4]. None of the publications previously reporting on the ocular complications of Alagille syndrome have described keratomalacia from vitamin A deficiency.

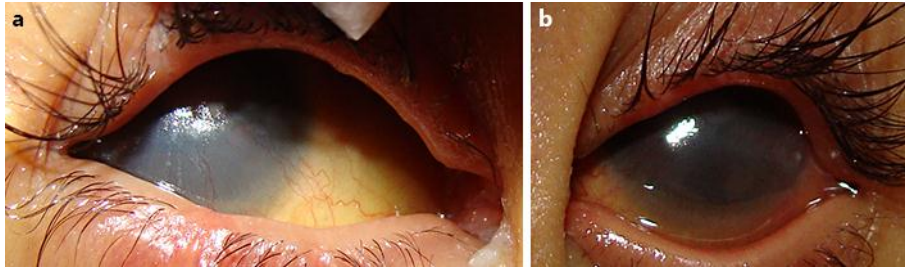
In conclusion, this case is unique since it is the first to describe xerophthalmia and keratomalacia in a patient with Alagille syndrome. It is also remarkable for the documented vitamin A deficiency and associated xerophthalmia despite dietary supplementation. This case also illustrates the potential hazards of vitamin A deficiency on the eyes, and should raise the awareness of corneal specialists and general ophthalmologists to this entity, which has become rare in the developed world.

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**Fig. 1.** At the age of 9 months, a prominent posterior embryotoxon was visible in the corneal periphery (shown in the right eye, present bilaterally).



**Fig. 2.** Bilateral manifestations of xerophthalmia. **a** Right eye – the cornea is opaque and covered by an amniotic membrane. **b** Left eye – conjunctival irritation and corneal opacification.