



# Alagille syndrome: an orphan disease in Colombia and summary of recent advances in treatment and survival – a case report

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**Introduction:** Alagille syndrome has been described as a multisystemic clinical spectrum caused by an autosomal dominant genetic disorder. Although it is estimated that there is 1 case per 100 000 live births, the prognosis for survival and quality of life for these patients is varied but tends to be negative. In Colombia, this condition is considered an orphan disease with difficult management due to the lack of specialized centers that have all the medical specialties and subspecialties. Some reports state that no more than 30 cases have been published in this country.

**Materials and methods:** The authors report a case of a male baby who, at 8 days old, he was taken to the general practitioner's outpatient clinic for persistent jaundice. At 3 months of age, he was reviewed by the pediatric gastroenterology department, which requested liver and biliary tract scintigraphy, showing atresia of the biliary tract, hepatomegaly, and the absence of a gallbladder.

**Results:** Liver transplantation is the definitive solution. However, in low- and middle-income countries, where there are no well-established organ transplantation programs, the prognosis for these patients is presumed to be worse.

**Conclusion:** Alagille syndrome is a rare disease that requires an accurate and early diagnosis and timely multidisciplinary management to reduce the impact of multisystemic complications. It is necessary to advance in transplant programs in low- and middle-income countries, to provide a solution to cases where there are no other therapeutic alternatives, and to contribute to the quality of life of the affected patient.

**Keywords:** bile duct diseases, cholestasis, Colombia, inborn genetic diseases, rare diseases

## Introduction

Alagille syndrome has been described as a multisystemic clinical spectrum caused by an autosomal dominant genetic disorder<sup>[1]</sup>. The main characteristic is the alteration of normal development in some hepatic cell lines at the expense of mutations in genes *JAG1* (Jagged Canonical Notch Ligand 1) or *NOTCH2* (Neurogenic Locus Notch Homolog Protein 2), causing a shortage of bile ducts, producing cholestasis, and severe hepatic complications

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## HIGHLIGHTS

- In low- to middle-income countries without well-established transplantations programs prognosis is presumed to be worse compared to high-income countries.
- Alagille syndrome is an orphan disease in low- to middle-income countries with the lack of resources for diagnosis and treatment.
- Late diagnosis in under resource areas lead to poor quality of life even under survival settings.

throughout life<sup>[1–3]</sup>. Among the most affected organ systems are cardiovascular (pulmonary artery involvement and heart failure), ophthalmic (development of the posterior embryotoxon and macular atrophy), musculoskeletal (development of butterfly vertebrae and altered bone growth), neurological (cerebrovascular anomalies, craniosynostosis, dolichoectasia), and pathological fascia, among others<sup>[1–6]</sup>.

Although it is estimated that there is 1 case per 100 000 live births, as a result of such alterations, the prognosis for survival and quality of life (QoL) for these patients is varied but tends to be negative<sup>[1,3]</sup>. During the first decade of life, children present with portal hypertension, protein synthesis dysfunction, severe pruritus, dyslipidemia, and pathologic bone fractures, which may subsequently culminate in hepatocellular carcinoma<sup>[2,3]</sup>. For this reason, it has been considered a powerful line of research in the last decades, advancing diagnostic and therapeutic techniques based on genetics and clinical biochemistry<sup>[4,5]</sup>. At present, there are few existing treatments, and liver transplantation is the only available solution<sup>[5]</sup>.

In low- and middle-income countries, where there are no well-established organ transplantation programs<sup>[7]</sup>, the prognosis for these patients is presumed to be worse. Even more when rare diseases are forgotten due to their low prevalence. In Colombia, this condition is considered an orphan disease with difficult management due to the lack of specialized centers that have all the medical specialties and subspecialties. Some reports state that no more than 30 cases have been published in this country<sup>[8]</sup>. Based on the above, the aim of this manuscript was to report a case of exceptional presentation in the country of origin and to discuss aspects related to the progress in research on the therapeutics of Alagille syndrome that contribute to improving the survival of these patients. Informed consent was obtained for the publication of patient information and images.

### Presentation of case

This case report followed the CARE guidelines for its realization<sup>[9]</sup>. Informed consent was obtained for this case report.

A male baby consisting of the second gestation of a 24-year-old mother with normal prenatal controls, full-term birth at 38 weeks, vaginal delivery without complications, an Apgar of eight points at the first minute and 10 points at 5 min, birth weight of 2875 g, height of 50 cm, head circumference 33 cm, mother's hemoclassification O +, and neonate's hemoclassification of A +. In the previous ultrasound scans, no abnormal findings were ever evidenced.

At 8 days old, he was taken to the general practitioner's outpatient clinic for persistent jaundice. Tests were performed and reported as follows: total bilirubin 22.7 mg/dl, indirect bilirubin 17.77 mg/dl, direct bilirubin 4.93 mg/dl, leukocytes  $17.4 \times 10^9/l$ , neutrophils 51.7%, lymphocytes 36.2, hemoglobin 19.3 g/dl, hematocrit 59.4%, and platelets  $423 \times 10^9/l$ . Considering the findings, he was referred to the emergency department with suspected neonatal sepsis, possibly due to ABO incompatibility or TORCH syndrome (infection by toxoplasmosis, other agents, rubella, cytomegalovirus, or herpes simplex). However, in the emergency department, the physical examination showed no specific signs of sepsis, and he was hemodynamically stable. Based on these findings, hepatic alteration was suspected, so liver and biliary tract ultrasounds were performed, which showed no abnormal findings. However, the *Toxoplasma gondii* test was positive (immunoglobulin M 0.212–immunoglobulin G 445.1). Phototherapy was performed due to ABO incompatibility. After observing a significant improvement hours later, it was decided to discharge the patient.

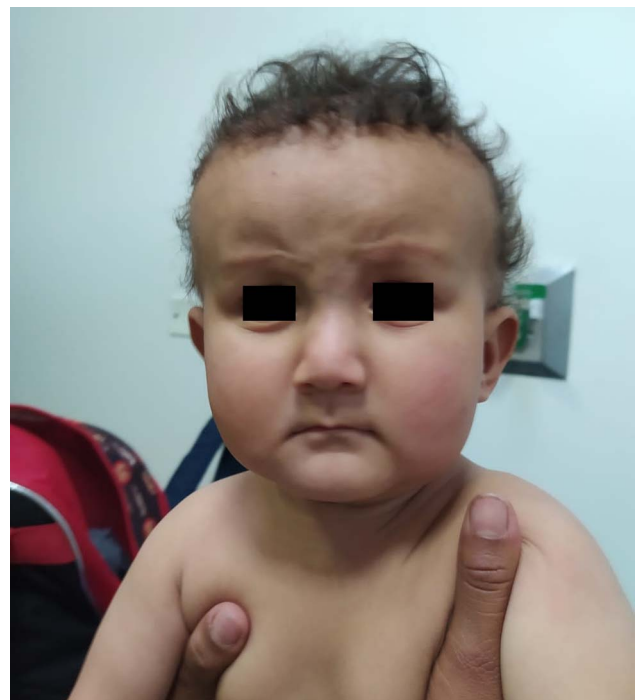
At 3 months of age, he was reviewed by the Pediatric Gastroenterology Department, which requested liver and biliary tract scintigraphy, showing atresia of the biliary tract, hepatomegaly, and the absence of a gallbladder. At this date, the infant remained slightly jaundiced, with pale stools and dark urine. In this consultation, a heart murmur was found on physical examination, so echocardiography was also requested to evaluate cardiac integrity, which showed levocardia, persistent foramen ovale, and a patent ductus arteriosus of 2.2 mm. A few days later, he was evaluated by the ophthalmology service, which found posterior embryotoxon in both eyes. The patient had low weight for height (– 1 SD), and high height and weight for age (+ 2 SD in both items) (weight 5.1 kg, height 58.2 cm, BMI  $15 \text{ kg/m}^2$ ).

Treatment was started to replace the required macronutrients and micronutrients (liposoluble vitamins, calcium carbonate, and ursodeoxycholic acid). At 4 months, a control ultrasound of the total abdomen was performed, and right renal hypoplasia was found, which was confirmed by a renogram. Pediatric nephrology established a diagnosis of chronic kidney disease secondary to renal dysplasia. The patient was later evaluated by clinical genetics, which detected an alteration in the *JAG1* gene (short arm of chromosome 20). A percutaneous liver biopsy revealed the absence of intrahepatic bile ducts. Based on the above, accompanied by characteristic abnormal facies (hypertelorism, broad forehead, sunken eyes) (Figs 1–2), a diagnosis of Alagille syndrome was established.

Finally, the patient was evaluated by psychiatry, psychology, and social work to review the emotional and family dynamics of the patient and his family and was found suitable for possible transplantation. During the last weeks of follow-up, the patient showed a favorable weight gain and improvement in his clinical picture. Strict follow-up by pediatrics and waiting for evaluation by the transplant surgery department while a donor is found.

### Discussion

One of the greatest interests in basic science, translational, clinical, and outcome research in rare diseases is to gain a deeper understanding of the etiopathogenesis and pathophysiology of these diseases in order to develop diagnostic tools and interventions that are effective, efficient, and safe<sup>[3–5]</sup>. Although it has been described that the genotype–phenotype correlation is determinant in Alagille syndrome, published case reports and case series show similar characteristics, which vary in intensity and timing of presentation according to timely multidisciplinary management<sup>[4–6,8,10]</sup>. Thus,



**Figure 1.** Photograph showing prominent forehead, deep set eyes, and pointed chin.



**Figure 2.** Photograph showing xanthoma in the left dorsal region.

in some cases where there are organized programs for diagnosis and follow-up of neonatal diseases, early diagnosis can be established and treatment can be initiated to reduce the impact of multisystemic complications and improve survival<sup>[10,11]</sup>.

Although it has been stated that the mortality rate is ~10%, it is necessary to emphasize that these statistics come from high-income countries, where the resources for personalized treatment and research are higher. This is how to quickly characterize cases such as that of Yang and Wang<sup>[10]</sup>, who in China found in-utero abnormal cardiovascular findings and shared a new frame shift variant in the *JAG1* gene through whole family exome sequencing<sup>[10]</sup>. Similarly, Paez-Escamilla *et al.*<sup>[12]</sup>, in the United States, followed a series of cases with this syndrome associated with the *JAG1* gene alteration for 8 years, analyzing ophthalmologic changes over time, showing a marked retinal and macular dysfunction through electrophysiological studies<sup>[12]</sup>. Nakajima *et al.*<sup>[4]</sup> also reported a case in Japan of an infant with severe dyslipidemia who had difficulties in the management of the condition until ~20 months of age, when his lipid profile was normalized<sup>[4]</sup>.

Therefore, it is not only necessary to think about the mortality rate, which is relatively low, but also about the impairment of the QoL and functional capacity of someone who has impaired visual field, renal, gastrointestinal, cardiovascular, and musculoskeletal function. If a compatible donor is not available, the prognosis for these patients is bleak due to the persistence of complications. One of the promising agents for managing this condition and improving survival is maralixibat, a sodium-dependent bile acid transport inhibitor that prevents enterohepatic recirculation of bile acids<sup>[13]</sup>. The results of the phase 2b clinical trial evaluating this drug (ICONIC study) were recently published<sup>[13]</sup>, which

included 29 participants in a withdrawal period group who had previously been exposed to the drug, finding that in the withdrawal period, there was an increase in serum bile acid levels (94  $\mu\text{mol/l}$ , 95% CI: 23–164) and frequency of pruritus (1.7 points, 95% CI: 1.2–2.2), compared to the control group. This drug was found to be well tolerated, and from its initiation until week 48, there was a maintained reduction in serum bile acid levels ( $-96 \mu\text{mol/l}$ , 95% CI:  $-162$  to  $-31$ )<sup>[13]</sup>.

Immediately after, the results of Shneider *et al.*<sup>[11]</sup> were published, who also evaluated the long-term outcomes of the use of maralixibat in children with cholestasis secondary to this syndrome. The authors found that at week 48, there was a significant improvement in the QoL score, as well as in the frequency and intensity of pruritus, platelet content, serum bile acids, and cholesterol. These changes remained stable until week 72 and at the end of treatment<sup>[11]</sup>. No deaths were reported. However, treatment was discontinued in nine participants due to adverse reactions, mainly due to increased total bilirubin and transaminase values<sup>[11]</sup>. However, it is necessary to mention that the study sample is still small (<100 patients), so caution is still needed in the interpretation of the results. But, evidently, the survival of these patients and their QoL will change substantially in a positive way.

Black *et al.*<sup>[14]</sup> conducted an interesting analysis of the US Transplant Scientific Registry, observing that those patients who received liver transplantation with an established diagnosis of Alagille syndrome have more frequently associated congenital cardiac disorders compared to those children with isolated biliary atresia not associated with the syndrome who also received transplantation (80.7 vs. 16.4%;  $P=0.001$ )<sup>[14]</sup>. Twenty-five percent of the children with the syndrome required cardiac surgery and had more severe renal injuries (higher creatinine levels). However, no significant difference was found in the survival of both groups, making this a reliable solution. That is, despite cardiac and renal comorbidities, the survival of those with Alagille syndrome was maintained<sup>[14]</sup>.

Another significant advance, but in the diagnostic field, is the use of molecular analysis by next-generation sequencing for targeted capture in cases of pediatric cholestasis. Although at present, it only performs the diagnosis in 30% of the cases, since there are cases where no molecular defects are identified<sup>[15]</sup>. Other work is currently focused on defining pathogenicity variants of *NOTCH2*, which are less frequent<sup>[16]</sup>; in identifying regulators of *JAG1* expression in portal mesenchymal cells<sup>[17]</sup>, and following up on the results obtained from different treatments<sup>[18]</sup>.

Health systems are responsible for guaranteeing access to health services, as well as promoting health education to reduce disease burden indicators and improve the QoL of the population. This case demonstrates the need to continue investing in research and a personalized and multidisciplinary approach to rare diseases in low- and middle-income countries. In this way, the catastrophic expense to the patient's family is reduced, the burden of disease caused, health costs are controlled, and the QoL of the affected person and his or her environment is promoted. The patient's parents were satisfied with the approach.

## Conclusion

Alagille syndrome is a rare disease that requires an accurate and early diagnosis and timely multidisciplinary management to

reduce the impact of multisystemic complications. It is necessary to advance transplant programs in low- and middle-income countries, to provide a solution to cases where there are no other therapeutic alternatives, and to contribute to the QoL of the affected patient. It is necessary to suspect this syndrome in any neonate or infant with persistent hepatic cholestasis, accompanied by abnormal cardiac, ocular, musculoskeletal, and renal findings.

### Ethical approval

I declare on my honor that the ethical approval has been exempted by my establishment.

### Consent

Informed consent was obtained for this case report.

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### Authors contribution

All authors equally contributed to the analysis and writing of the manuscript.

### Conflicts of interest disclosure

None.

### Research registration unique identifying number (UIN)

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### Guarantor

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