International Journal of Research in Medical Sciences
Sharma AD et al. Int J Res Med Sci. 2023 Sep;11(9):3471-3474
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20232813

Case Report

Oral manifestations of Alagille-2 syndrome: a rare case report

Arun Dev Sharma*, Ajay Parihar, Prashanthi Reddy, Rashi Mandlik

Departments of Oral Medicine and Radiology, Government College of Dentistry, Indore, Madhya Pradesh, India

Received: 11 July 2023
Accepted: 10 August 2023

***Correspondence:**
Dr. Arun Dev Sharma,
E-mail: drarundev@gmail.com

ABSTRACT

Alagille-2 syndrome (AGLS-2) is a rare autosomal dominant illness that affects the Notch signalling pathway, with few studies reported in the literature related to dental science. It is recognized clinically, with anomalies of the liver, skeleton, kidneys, eyes, and face manifesting. The JAG1 gene accounts for about 97 percent of instances of Alagille syndrome variation, whereas mutations in NOTCH2 account for only 1 percent. When serum bilirubin levels in children are higher than 30 mg/dl, bilirubin builds up in dental tissue and results in varied greenish-brown dyschromia of the teeth. We discussed the dental findings of a patient diagnosed with NOTCH-2 who sought out dental treatment at the government college of dentistry in Indore, MP (India), complaining of pain and a stain in his teeth with typical features of facial dysmorphism.

Keywords: Alagille syndrome, NOTCH 2, Green tooth, Facial dysmorphism

INTRODUCTION

It is believed that the oral cavity is a reflection of general health, and patients can greatly benefit from an early diagnosis. When it comes to rarity, one may not be familiar with Alagille syndrome (ALGS). The French paediatric hepatologist Daniel Alagille (1925-2005) studied and identified the condition that bears his name, which is characterized by systemic affectation and intrahepatic cholestasis.[1] Alagille Syndrome was initially described by Daniel Alagille et al in 1969.[2] It is an autosomal dominant illness that affects the Notch signalling pathway. AGS is thought to affect between 1/100,000 and 1/70,000 newborns.[3] Even though the diagnosis of AGS has changed over time, it can still be challenging. These days, it is based on genetic testing and clinical criteria. Alagille syndrome was recognized using traditional criteria based on the manifestations of dysfunction in five key systems, i. e.; liver, skeleton, kidneys, eyes,and face.[4] According to the literature, haploinsufficiency of the JAG1 gene accounts for about 97 percent of instances of Alagille syndrome variation, whereas mutations in NOTCH2, which may cause more frequent renal issues, account for only 1% of cases.[5-7] In this case report,we are discussing a rare case of NOTCH-2-mutated heterozygous Alagille-2 syndrome with structural dental defects marked by greenish-brown staining and hypomineralization, along with other extraoral manifestations for clinical diagnosis. This case was validated by genetic testing.

CASE REPORT

Chief complaint

A 6-year-old boy from a nearby town reported to the department of oral medicine and radiology of the government college of dentistry in Indore, MP, with a chief complaint of pain in his lower jaw, right posterior side, for the last 10 days.

Medical history

After a complete anamnesis and report by the guardian, the patient's medical history showed that he was born with an atrial septal defect (ASD) and had undergone

surgery for it at the age of one. Later, at the age of four, he underwent surgery for hypospadias. The left kidney was not visualized on the DTPA renal scan. With a complaint of persistent pruritus and the presence of clinical indicators for Alagille syndrome, the patient was referred for genetic testing, and he was identified as having autosomal dominant heterozygous A2S with c.5342A>Gp. Asp1781Gly variant nomenclature in the NOTCH 2 gene. His blood profile was (Hb: 12.1 g/dl, total bile acid, serum: <3.2 Micromol/L, serum phosphorus: 7.1 U/L, ALP IFCC Gen 2: 165.06 U/L), and he was under Udcament Oral Suspension (Ursodeoxycholic Acid), Calcitriol Sachet (60000 IU Vitamin D3), and Capsule Aquasol (Vitamin A: 25000 IU).

Extraoral examination

The general physical examination revealed that the patient was of short stature and low body weight, with chronic malnutrition based on a nutritional screening value of height 98.5 cm (-2.2 SD), weight 14.35 kg (-1.4 SD), and BMI 14.7 (-0.07 SD). Typical features of the facial dysmorphism associated with ALGS were seen as deeply and widely placed eyes (hypertelorism), a flat nasal bridge, a bulbous-tipped nose, a pointed chin, giving rise to a triangular facial appearance, large and prominent ears, a prominent forehead, a prognathic mandible, and an abnormally long tongue (Figures 1). The hands digits were fusiform in shape, and the terminal phalanges were somewhat hypoplastic (Figure 1E). The Prognathism mandible and prominent forehead were visible on the lateral cephalogram (Figure 3A), but the OPG (Figure 3B) did not indicate any structural abnormalities in the cortical, trabecular, hard lamina, or periodontal ligament spaces.

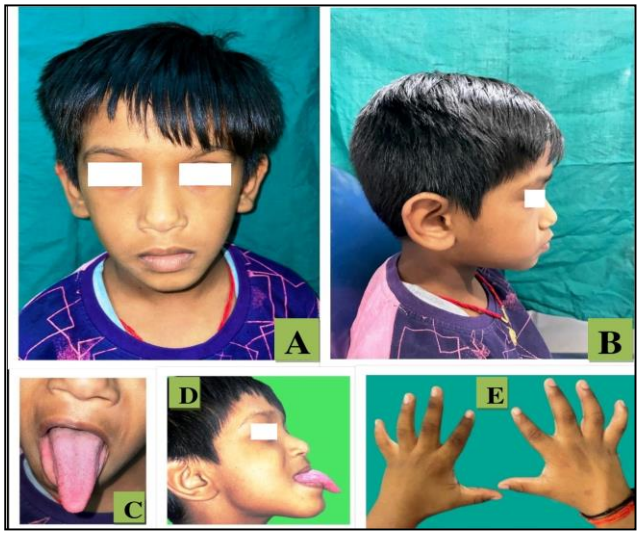

Figure 1 (A-E): Hypertelorism, a flat nasal bridge, a bulbous-tipped nose, and a pointed chin. Large and prominent ears, a prominent (Prognathism) mandible and prominent forehead. Abnormally long tongue. Fusiform digits with hypoplastic phalanges.

Intraoral examination

In the intraoral examination, the patient was in the early mixed dentition, and his dental development was normal for his chronological age. In the oral characteristics, several alterations were found that are also related to the syndrome: Right upper deciduous central incisor and deciduous canine showed a greenish/brownish discoloration band with focal areas of enamel hypoplasia (Figure 2 A and C), while lower erupted anteriors showed a greenish hue (Figure 2 B) over crown portion.

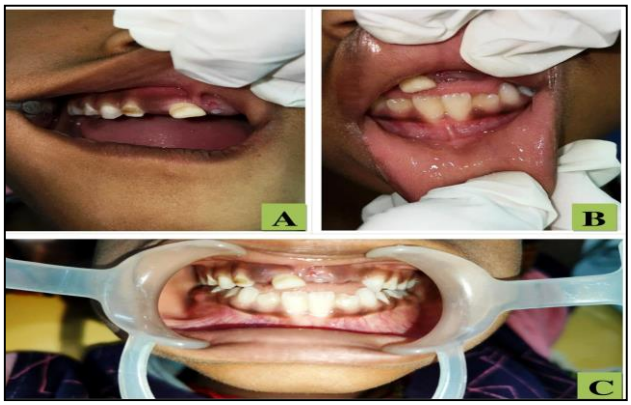

Figure 2 (A-C): Right upper primary CI and canine with a greenish/brownish discoloration band with focal areas of enamel hypoplasia. Greenish hui enamel of the lower anteriors, and hypomineralization areas over the crown portion.

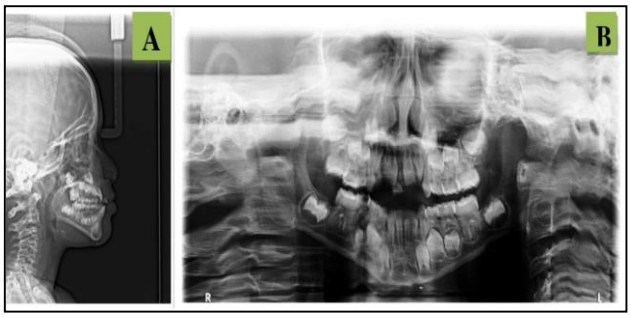

Figure 3 (A and B): Lateral cephalogram and OPG.

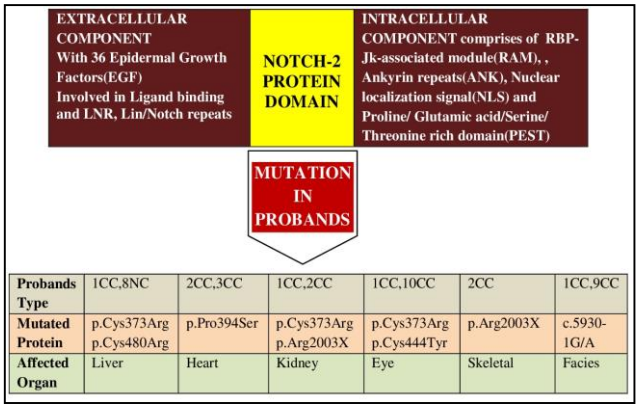

Figure 4: NOTCH-2 protein domain in human being.

Table 1: Tooth discoloration of developmental defects and systemic origin.

Condition	Features
Amelogenesis imperfect (AI)	Most of the time, it involves all teeth, a family history is present, and radiographs may reveal Taurodontism. The tooth is usually coloured at the time of eruption, with colours ranging from pale yellow to dark reddish orange. Hypoplastic variants of AI are mostly evident over buccal surfaces, while the incisal and occlusal portions are affected in hypomaturation entities.
Dentinogenesis imperfect (DI)	Hereditary or familial origins with an autosomal dominant pattern. In contrast to AI; dentinogenesis imperfecta affects all of the tooth surfaces. Both dentitions are affected. The colour ranges include bluish through amber brownish.
Molar-incisor hypomineralization	Molar incisor hypomineralization (MIH) is the name used to describe a condition that primarily affects the mineralization of permanent first molars and incisors.
Enamel hypoplasia	Enamel hypoplasia can be of hereditary or environmental origin. Lesions are mostly localized, usually at the centre of smooth surfaces, with brown discoloration. Turner's hypoplasia (incisors and Premolars), the Hutchinson incisor, and the Mulbury molar in syphilis are examples of enamel hypoplasia.
Dental fluorosis	Patient who has a history of consuming water with a high fluoride content. Affect teeth (Cuspid, bicuspids, second and third molars) that slowly calcify. Affected surfaces of enamel little bit more opaque than regular enamel; "paper white." Dental Fluorosis incredibly uncommon in deciduous teeth.
Tetracycline staining	Patient with past drug history of tetracycline in pregnant mother and up to the age of 8 years shows bright yellow to dark brown discoloration of all tooth surfaces. Both dentitions are involved.
Congenital erythropoietic porphyria	Generalized tooth involvement of both dentitions Enamel and dentin involvement in primary teeth while only dentin in permanent teeth. The patient has a medical history of an autosomal recessive metabolic disorder of porphyrin metabolism. The tooth colour is marked as red-brown.
Alkaptonuria	Generalized tooth involvement of both dentitions. The patient has a medical history of an autosomal recessive metabolic disorder. Tooth colour is mostly bluish-black.
Pulpal hemorrhage	Patient with a history of trauma, mostly upper anteriors. Pulp blood got clots, giving bluish-black discoloration to the traumatized tooth and hence localized.

DISCUSSION

Alagille syndrome has two variants. Type 1 ALGS (related to JAG1) and type 2 ALGS (associated with NOTCH2) JAG1 (20p12) mutations account for about 90% of cases. JAG1-related deletions account for an additional 5-7% of the total, and NOTCH2 (1p13) mutations account for roughly 1% of all cases.[5-7] That is why our case is one of the rarest. Similar to JAG1, NOTCH2 has 34 exons and is a big gene that produces the NOTCH2 transmembrane protein. Sequencing of the NOTCH2 gene was done in cases of ALGS that were devoid of mutations in JAG1 due to the fact that mice with compound heterozygotes for JAG1 and NOTCH 2 mutations display a phenotype that is similar to ALGS in humans.[7] The majority of "green teeth" cases that have been documented in the literature are linked to infant cholestasis. Only primary teeth and newly erupted permanent teeth (incisors and first molars) in patients with biliary atresia (which accounts for 50% of newborn cholestasis cases) are affected.[8] The Notch signalling pathway participates in tooth regeneration as well as the development of several organs, including the skeleton and face.[9] In NOTCH2-related ALGS and JAG1-related cohort probands, the prevalence of clinical signs was compared, according to Kamath BM et al. Compared to JAG1 probands, ALGS patients with NOTCH2 mutations (Figure 4) displayed less penetration of recognisable facial features and skeletal involvement.[10] Cholestasis during odontogenesis can lead to hypomineralization, hypoplasia, and opacification of the enamel in the teeth. When serum bilirubin levels in children are higher than 30 mg/dl, bilirubin builds up in dental tissue and results in varied greenish-brown dyschromia of the teeth. Both temporary and permanent dentition may be associated with oral symptoms.[11]

Differential diagnosis

For a better understanding of tooth discoloration from a Clinical diagnosis perspective, tooth discoloration in ALGS should be carefully differentiated from other conditions with tooth discoloration of developmental defect or systemic origin (Table 1).[12-14]

Medical management

Depending on the findings of each affected person, management requires a multidisciplinary approach. With liver disease, supportive care is the main course of treatment. Ursodeoxycholic acid, naltrexone, rifampin, colesevelam, and cholestyramine are medications that help with cholestasis and are used to treat severe pruritus and xanthomas. Additionally employed for this reason are

surgical partial internal biliary diversion and ileal exclusion, none of which stop the course of liver disease. With an 80% five-year survival rate, liver transplantation for end-stage liver disease improves liver function and enables catch-up growth.[15,16]

Dental management

All dental work must be done in consultation with the physician, who will recommend the right medication choices and the use of antibiotics as a prophylaxis or to control bleeding after extraction. Leucopenia, thrombocytopenia, or anaemia may develop from the suppression of bone marrow brought on by persistent immunosuppression following transplantation. Patients may be more susceptible to severe bleeding after dental surgery and opportunistic infections such as mycosis, herpes super infection, and leukoplakia development. Consuming cyclosporine is linked to drug-induced gingival hypertrophy, which can cause gingivitis and damage to periodontal tissues.[17-19]

CONCLUSION

In dentistry, Alagille syndrome is a relatively uncommon and little-discussed syndrome. Discussion of such case reports is very important, as dentist familiarity with the syndrome will help to diagnose a rare systemic disease with oral and extraoral characteristics and make a timely referral if it is medically undiagnosed. In the case of a medically diagnosed case that comes for dental treatment, the dentist will be cautious with the peculiarities of this disease by modifying dental treatment. From a physician's point of view, oral and facial findings will give additional clues for making a sound diagnosis. In this way, it will be beneficial for the dental surgeon, the physician, and the patient itself.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Alagille D, Odièvre M, Gautier M, Dommergues JP. Hepatic ductular hypoplasia associated with characteristic facies, vertebral malformations, retarded physical, mental, and sexual development, and cardiac murmur. J Pediatr. 1975;86:63-71.
2. Alagille D, Habib EC, Thomassin N. L'atresie des voiesbiliairesintrahepa tiques avec voiesbiliaresextrahepatiquespermeables chez l'enfant. Editions Medicales Flammarion, Paris. 1969;301-18.
3. Mitchell E, Gilbert M, Loomes KM. Alagille syndrome. Clin Liver Dis. 2018;22:625-41.
4. Berniczei-Royko A, Chałas R, Mitura I, Nagy K, Prussak E. Medical and dental management of Alagille syndrome: a review. Med Sci Monit. 2014;20:476-80.
5. Li L, Krantz ID, Deng Y. Alagille syndrome is caused by mutations in human Jagged1, which encodes a ligand for Notch1. Nat Genet. 1997;16:243-51.
6. Oda T, Elkhound AG, Pike BL. Mutations in the human Jagged1 gene are responsible for Alagille syndrome. Nat Genet. 1997;16:235-42.
7. McDaniel R, Warthen DM, Sanchez-Lara PA, Pai A, Krantz ID, Piccoli DA, Spinner NB: NOTCH2 mutations cause Alagille syndrome, a heterogeneous disorder of the Notch signaling pathway. Am J Hum Genet. 2006;79:169-73.
8. Battineni S, Clarke P. Green teeth are a late complication of prolonged conjugated hyperbilirubinemia in extremely low birth weight infants. Pediatr Dent. 2012;34:103-6.
9. Mitsiadis TA, Feki A, Papaccio G. Dental pulp stem cells, niches, and Notch signaling in tooth injury. Adv Dent Res. 2011;23:275-9.
10. Kamath BM, Bauer RC, Loomes KM. Notch2 mutations in Alagille syndrome. J Med Genet. 2012;49:138-44.
11. Krantz ID, Piccoli DA, Spinner NB. Alagille syndrome. J Med Genet. 1997;34(2):1527.
12. Neville B, Damm DD, Allen C, Chi A. Oral and Maxillofacial Pathology. 1st South Asia edition New Delhi: Elsevier. 2015;49-105.
13. Shafer H. Levy: Textbook of Oral Pathology. 7th edition New Delhi: Elsevier. 2012;50-58.
14. Patidar D, Sogi S, Patidar. Enlightening Diagnosis and Differential Diagnosis of Dental Fluorosis-A Hidden Entity in a Crowd. Dental J Adv Studies. 2021;9.10.1055/s-0041-1725218.
15. D'Souza AM, Shah R, Gupta A, Towbin AJ, Alonso M, Nathan JD et al. Surgical management of children and adolescents with upfront completely resected hepatocellular carcinoma. Pediatr Blood Cancer. 2018:65(11):e27293.
16. Fujishiro J, Suzuki K, Watanabe M, Uotani C, Takezoe T, Takamoto et al. Outcomes of Alagille syndrome following the Kasai operation: a systematic review and meta-analysis. Pediatric Surg Intl. 2018;1.
17. Al-Mutawa S, Mathews B, Salako N. Oral findings in Alagille syndrome. A case report. Med Principles Pract. 2002;11(3):161-3.
18. Olczak-Kowalczyk D, Pawłowska J, Kowalczyk W: Oral health status in children with chronic liver disease. J Stoma. 2011;64(10):760-74.
19. Berniczei-Royko A. Medical and dental management of Alagille syndrome: A review © Med Sci Monit. 2014;20:476-80.

Cite this article as: Sharma AD, Parihar A, Reddy P, Mandlik R. Oral manifestations of Alagille-2 syndrome: a rare case report. Int J Res Med Sci 2023;11:3471-4.