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Research paper

Pediatric oral and dental manifestations of biliary atresia and Alagille syndrome: a comparative retrospective study

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ABSTRACT

Background: Case reports, small case series, and studies not specifically focused on a single type of cholestatic disorder suggest the presence of oral and dental manifestations in Alagille syndrome (AGS) and Biliary Atresia (BA). While some may be directly due to cholestasis, others may be phenotypic of these conditions.
Objectives: The aim of this study was to describe the oral characteristics of children with AGS and BA and to distinguish features specific to each condition from those attributable to cholestasis.
Methods and setting: Oral characteristics where retrospectively compared between children with cholestasis, including patients with AGS ("AGS group") and BA ("BA group"), and control children matched for age, sex and dentition, who had consulted in the Pediatric Dentistry and Rare Diseases Unit at Timone University Hospital (Marseille, France) between September 2021 and December 2023.
Results: Congenital cholestasis patients (10 with AGS and 16 with BA) were more likely to have tooth shape anomalies (14 vs 6 patients, $p = 0.01$), tooth number anomalies (10 vs 2 patients, $p = 0.02$), tooth structure anomalies (13 vs 7 patients, $p = 0.09$), tooth discoloration (18 vs 0 patients, $p < 0.001$), and poor oral hygiene (19 vs 13 patients, $p = 0.09$) than matched controls, but not malocclusion (20 vs 17 patients, $p = 0.36$) or periodontal disease (15 vs 11 patients, $p = 0.27$). Carious lesions were more common in control patients (20 vs 14 patients, $p = 0.08$). Malocclusion was more frequent among AGS patients (10/10) than among BA patients (10/16, $p = 0.053$).
Conclusion: In this group of pediatric dental patients, congenital cholestasis was associated with a higher rate of dental abnormalities, particularly discoloration, tooth shape, and number anomalies. Our results provide a more detailed description of these features. Multicenter studies are required to confirm these findings on larger samples.

1. Introduction

Congenital cholestatic diseases are a heterogeneous group of disorders characterized by reduced bile production or flow. Alagille Syndrome (AGS, ORPHAcode, 52; prevalence, 1/70,000) [1,2], caused by mutations in the *JAG1* or *NOTCH2* genes, is associated with a paucity of intrahepatic bile ducts. Biliary atresia (BA. ORPHAcode, 498345) [3], of unknown etiology, is defined as a progressive, obliterative cholangiopathy affecting the bile ducts, typically presenting in the perinatal period, and has a prevalence of 1/19,000 to 1/15,000 live births. Case reports, small case series [4], and studies not specifically focused on a single type of cholestatic disorder [5–8], suggest the existence of oral and dental manifestations in AGS and BA. Some of these symptoms are probably due to cholestasis, but others may be phenotypic of AGS or BA.

The aim of this study was to describe the oral characteristics of children with AGS and BA and to distinguish features specific to each condition from those due to cholestasis.

2. Material and methods

This was a retrospective, single-center, descriptive-comparative study conducted in accordance with the STROBE guidelines for observational studies [9]. The study was registered in the French Health Data Access Portal (registration number, PADS23-2), and informed consent for the use of patient/parent photographs was obtained. The study was approved by the ethics committee of the GFHGNP (*Groupe Francophone d'Hépatologie-Gastroentérologie et Nutrition Pédiatriques*; reference number, 2023-47).

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2.1. Participants

The "cholestasis group" consisted of patients currently or previously followed up for AGS or BA in the multidisciplinary pediatric department of Timone University Hospital (Marseille, France) who had consulted in the pediatric dentistry and rare diseases unit of Timone University Hospital (Marseille, France) between September 2021 and December 2023. These dental consultations were conducted as part of standard care by two clinicians specialized in oral health problems associated with cholestatic diseases. The cholestasis group was divided into AGS and BA subgroups. Data on liver transplant status and immunosuppression regimen were collected.

The control group consisted of patients with an unremarkable medical history who underwent a comprehensive dental examination as part of initial check-up visits for scheduled care in the same unit between September 2021 and December 2023. Control patients were matched for age, sex, and dentition with patients in the AGS and BA groups and selected at random in cases where multiple control patients matched the same AGS or BA patient (Table 1).

2.2. Study variables

Patients were assessed and analyzed based on the eight binary categorical variables described in Table 2.

2.3. Statistical method

Binary categorical variables were compared between groups using Fisher's exact tests. Results were considered statistically significant at $p \leq 0.05$.

Variables with $p \leq 0.1$ in comparisons between the cholestasis and control groups were further investigated in separate comparisons between the AGS group and the control group, and between the BA group and the control group.

3. Results

Twenty-six patients (16 girls (61,5 %) and 10 boys (38,5 %) with congenital cholestasis were included, 10 (6 girls (60 %) and 4 boys (40 %)) with AGS, and 16 (10 girls (62,5 %) and 6 boys (37,5 %)) with BA. Patient age ranged from 1 to 23 years. Patient characteristics are summarized in Table 3 for AGS patients, Table 4 for BA patients, and in Table 5 for control patients.

3.1. Oral manifestations of congenital cholestasis

Fig. 1 compares the number of oral and dental anomalies observed in the cholestasis and control groups.

Patients in the cholestasis group had borderline higher dental plaque scores ($p = 0.09$). They had various forms of periodontal involvement (Fig. 2), while the only periodontal symptom in the control group was gingivitis (Fig. 2). Gingivitis was more frequent in the cholestasis group (14/26, 54 %) than in the control group (11/26, 42 %) (Fig. 2) and more frequent in liver-transplant patients (12/16, 75 %) than in those who had not undergone transplantation (2/10, 20 %). All three patients receiving cyclosporine and a majority of those receiving tacrolimus (9/13) had signs of periodontal inflammation. Gingival hyperplasia was observed only in liver-transplanted patients (in 2/3 patients receiving cyclosporine and 1/13 receiving tacrolimus).

Carious experiences were less common in the cholestasis group (14 patients) than in the control group (20 patients), at borderline significance ($p = 0.08$); however, severe early childhood caries (Fig. 3)

Table 1
Classification of patients by age, sex and dentition.

Age	Type of Dentition	Sex	AGS group ID	BA group ID	Control group ID
0–3 years	Primary dentition formation	Female	AGS1	BA1, BA10, BA11	T1, T2, T3, T4
		Male		BA14	T17
3–6 years	Stable primary dentition	Female	AGS2	BA2	T5, T6
		Male		BA15	T18
6–9 years	Mixed dentition formation	Female	AGS3	BA3, BA13	T7, T8, T9
		Male		BA16	T19
9 –12 years	Stable mixed dentition and onset of adolescent dentition	Female	AGS4	BA4, BA12	T10, T11, T12
		Male	AG7	BA7	T20, T21
>12 years	Establishment of permanent dentition	Female	AGS5, AGS6	BA5, BA6	T13, T14, T15, T16
		Male	AGS8, AGS9, AGS10	BA8, BA9	T22, T23, T24, T25, T26

AGS: Alagille syndrome; BA: Biliary atresia.

Table 2
Variables used for the clinical characterization of oral health in study participants.

Variable	Dichotomization criteria	
	Level 0	Level 1
Oral hygiene (Silness and Löe Plaque Index)	Clinically healthy periodontium	Plaque Index > 1 (dental plaque accumulation visible to the naked eye or at the marginal gingiva).
Periodontal status (Chicago Classification, 2017)	Clinically healthy periodontium	Clinically detectable inflammation (e.g., gingivitis, gingival hyperplasia) or reduced periodontium
Dental caries (ICDAS Classification):	No carious lesions	ICDAS score ≥ 2 (distinct visual change in enamel without air drying), presence of a restored lesion, or tooth missing due to caries
Malocclusion (Peer Assessment Rating Index)	No current malocclusion or history thereof	History of malocclusion, based on retrieved and analyzed diagnostic records qualifying the initial occlusal condition.
Tooth Color Anomaly	No visible tooth color abnormality	Presence of a tooth color abnormality
Tooth Shape Anomaly	No visible morphological abnormality	Coronal and/or radicular morphological abnormality
Tooth Structure Anomaly	No visible structural abnormality	Abnormality of the enamel and/or dentin.
Tooth Number Anomaly	None.	Hypodontia or hyperdontia (discrepancy between dental and chronological age, assessed clinically and radiographically where applicable). Numerical abnormalities were not considered when dental age was consistent with chronological age.

Table 3
Alagille syndrome (AGS group) patient characteristics IS, immunosuppressant; LT, liver transplantation; NR, not recorded; TC, tacrolimus.

ID	Age (years)	Neonatal jaundice	Surgery (age)	Dis-coloration	Structural defect	Shape defect	Number defect	Carious lesions	Periodontal tissue	Oral hygiene	Mal-occlusion	IS	Gene
AGS1	3	yes	-	-	Hypoplasia	-	-	-	Gingivitis	-	yes	-	*JAG1*
AGS2	2	yes	-	Yellow greenish	-	-	-	-	-	-	yes	-	*JAG1*
AGS3	6	yes	-	Greenish	-	-	Agenesis 52/12	-	-	Plaque, calculus	yes	-	*JAG1*
AGS4	12	NR	-	-	-	Peg-shaped 12/22	-	-	-	Plaque	yes	-	*JAG1*
AGS5	13	no	-	-	-	Microdontia, angulated roots	-	Active	-	Plaque	yes	-	*JAG1*
AGS6	13	NR	LT (10 y)	Yellow greenish	-	Globular crowns (central incisors, premolars), angulated roots	Agenesis 3rd molars, mesiodens	-	Gingivitis	Plaque, calculus	yes	TC	*JAG1*
AGS7	10	NR	-	-	Hypoplasia	-	Agenesis 23 & 3rd molars	Treated and active	Gingivitis	Plaque	yes	-	*JAG1*
AGS8	16	NR	LT (5 y)	Greenish, less on 2nd molars	Hypoplasia	Globular premolars	Agenesis 12/22/48	-	Hyperplasia gingivitis	Plaque	yes	TC	*JAG1*
AGS9	22	yes	-	-	Hypoplasia	-	-	Active	Gingival recession	-	yes	-	*JAG1*
AGS 10	19	NR	LT (5 y)	Greenish	Hypoplasia	Angulated roots	Agenesis 18/28	Active and treated	Gingivitis, hyperplasia	Plaque	yes	TC	*JAG1*
Column totals			3/10	5/10	5/10	5/10	5/10	4/10	6/10	7/10	10/10		*JAG1*

were more common in the cholestasis group (four children vs. two in the control group).

Vertical, sagittal, and transverse malocclusions were observed in a similar number of patients in both groups (20 in the cholestasis group, 17 in the control group, $p = 0.36$), but were more severe, especially in the vertical dimension, in the cholestasis group.

Tooth discoloration was common in the cholestasis group (18/26 patients) but absent in the control group ($p < 0.001$). The discoloration observed in patients with cholestasis ranged from yellowish to greenish and involved either the entire dentition or specific groups of teeth, with premolars and/or second permanent molars often unaffected. Discoloration was observed over the whole tooth or just the crown, with sharply demarcated borders.

Tooth shape anomalies were more frequently observed in the cholestasis group (in 14 patients vs. 6 in the control group, $p = 0.01$) and included crown shape anomalies (bulbous or rice-shaped incisors and/or premolars) and root anomalies (bifid or sharply angled second premolar roots). In the control group, one patient had short roots and five had crown shape anomalies (non-specific atypical shapes and peg-shaped lateral incisors). Structural abnormalities, hypoplasia or hypomineralization, were also more common in the cholestasis group (12 vs 7 patients, $p = 0.09$). One patient in the cholestasis group had a hypomineralized second primary molar. Tooth number anomalies were significantly more frequent in the cholestasis group (10 vs 2 patients; $p = 0.02$), including 10 instances of agenesis (canines, incisors, premolars, and/or third molars), one supernumerary deciduous incisor, and one mesiodens. The only tooth number anomalies in the control group were two cases of third molar agenesis.

3.2. Oral phenotypes in Alagille syndrome and biliary atresia

3.2.1. Alagille syndrome

The types of oral and dental abnormalities observed in AGS patients and matched controls are compared in Fig. 4.

Poor oral hygiene was more common among AGS patients (7 vs 4; $p = 0.36$), whereas twice as many control patients had carious lesions (8 vs 4; $p = 0.16$). Carious lesions were only observed in adolescents during the formation of permanent teeth. All 10 AGS patients had malocclusion, compared with just six matched controls ($p = 0.02$). Half of the AGS patients had tooth discoloration, ranging from yellow to green in varying intensities, affecting either the entire dentition or individual teeth, and involving the entire crown with clear demarcation in all cases. None of the control patients had discoloration ($p = 0.03$). Shape anomalies, namely crown anomalies (microdontia, peg-shaped or bulbous crowns) and root anomalies (angled roots), were observed in five AGS patients. The only patient in the control group with tooth shape anomalies ($p = 0.14$) had a bulbous incisor crown. Structural anomalies were similarly common in both groups (5 and 3 patients, respectively; $p = 0.6$). Five patients in the AGS group had tooth number anomalies, compared with none in the control group ($p = 0.03$). All five of these patients had agenesis (of third molars in 4/5 cases, canines in 1/5 cases, and of temporary and permanent lateral incisors in 2/5 cases) and one had a supernumerary tooth (mesiodens).

3.2.2. Biliary atresia

Oral and dental abnormalities are compared between BA patients and matched controls in Fig. 5.

Poor oral hygiene and carious lesions were similarly frequent in the BA and control groups, but early childhood caries were more common among BA patients: of the six BA patients under 6 years old, four had severe early childhood caries. Tooth discoloration, which was not observed in any of the control patients, was observed in 13/20 BA patients ($p < 0.001$), and ranged from yellowish to greenish. In 10 of these cases, discoloration affected the entire dentition, uniformly across each tooth; in the remaining three patients, the

Table 4
Biliary atresia (BA group) patient characteristics.

ID	Age (years)	Neonatal jaundice	Surgery (age)	Dis-coloration	Structural defect	Shape defect	Number defect	Carious lesions	Periodontal tissue	Oral hygiene	Mal-occlusion	IS
BA1	3	yes	KPE (1 m)	-	-	-	-	-	-	-	-	-
BA2	3	yes	LT (2.5 y)	Greenish	-	-	-	Active	Gingivitis	Plaque	-	TC
BA3	7	yes	KPE (4 m) LT (2.5 y)	Greenish	-	Dysmorphic central incisor crown	Agenesis 3rd molars	Active	-	Plaque	yes	TC
BA4	12	yes	LT (2.5 y)	Greenish CIs, Cs and M1; healthy PMs	Hypoplasia, MIH	Bifid and bulbous PM	-	Treated	-	Plaque	yes	TC
BA5	13	yes	LT (1.5 y)	Greenish incisal edge of CIs, C tips and M1; healthy PMs and M2	Hypoplasia	Dysmorphic central incisor crown	-	-	Gingivitis	Plaque	yes	CsA
BA6	16	yes	LT (1.5 y)	Yellowish to greenish, greenish cervical areas on M2 and PMs	Hypoplasia	Dysmorphic central incisor crown	-	Active & treated	-	-	yes	TC
BA7	11	yes	KPE (failure) LT (14 m)	Greenish C tips, M1, incisal edge of CI/Cs; healthy PMs	Hypoplasia	Taurodontism bifid PM	-	-	Gingivitis	Plaque, calculus	yes	CsA
BA8	16	yes	KPE (failure) LT (5 y)	Yellowish to greenish	-	Bifid PM	Agenesis 38	Active	Gingivitis	Plaque	-	TC
BA9	23	yes	LT (10 m)	-	Hypoplasia	Dysmorphic central incisor crown	-	-	Gingivitis	Plaque	yes	TC
BA10	1	yes	-	Greenish	-	-	-	-	-	-	-	-
BA11	3	yes	KPE (22 d)	Yellowish	-	Rice-grain-shaped primary incisors	Extra 52	Active	-	Plaque	yes	-
BA12	8	yes	KPE (31 d) LT (1.5 y)	-	Turner's tooth (11)	-	Agenesis 3rd molars	-	Gingival hyperplasia, gingivitis	Plaque	yes	CsA
BA13	7	yes	LT (1.5 y)	Greenish with clear crown margin of maxillary CIs	Hypoplasia	-	-	Active	Gingivitis	Plaque	yes	TC
BA14	3	yes	LT (9 m)	Yellowish	-	-	-	Active	Gingivitis	-	-	TC
BA15	5	yes	LT (1 y)	Greenish	Hypoplasia	-	Agenesis 15/25	Active	-	Plaque	-	TC
BA16	8	yes	LT (4 y)	Greenish	-	Dysmorphic central incisor crown	-	Active	Gingivitis	Plaque	yes	TC
Column totals				13/16	8/16	9/16	5/16	10/16	9/16	12/16	10/16	

C, canine; CI, central incisor; CsA, cyclosporine; IS, immunosuppressant; KPE, Kasai portoenterostomy; LT, liver transplantation; M, molar; MIH, molar incisor hypomineralisation; PM, premolar; TC, tacrolimus.

Table 5
Control patient characteristics.

ID	Age (years)	Discoloration	Structural defect	Shape defect	Number defect	Carious lesions	Periodontal tissue	Oral hygiene	Mal-occlusion	IS
T1	1	-	-	-	-	-	-	-	-	-
T2	2	-	-	-	-	-	-	-	-	-
T3	3	-	-	-		-	-	-	-	-
T4	3	-	-		-	Active & treated	-	Plaque	-	-
T5	3	-	-		-	Active	-	-	-	-
T6	5	-	-			Active	-	-	yes	
T7	7	-	-	-		Active	Gingivitis	Plaque	-	-
T8	7	-	-			Active & treated	Gingivitis	Plaque	yes	
T9	8	-	-	-	-	Treated	Gingivitis	Plaque	yes	-
T10	9	-	-	Dysmorphic central incisor crown		Active & treated	Gingivitis,	Plaque	yes	-
T11	10	-	MIH		Agenesis 3rd molars	Active & treated	Gingivitis	Plaque, calculus	yes	–
T12	11	-	-	Peg-shaped lateral incisor		Active	Gingivitis	Plaque	yes	-
T13	13	-	Hypoplasia			Treated	-	-	yes	-
T14	14	-	-			-	-	-	yes	-
T15	16	-	-	Short central incisor roots		Active & treated	-	-	yes	-
T16	16	-	-			Active	Gingivitis	Plaque	yes	-
T17	2	-	-	Peg-shaped lateral incisor		Active	-	-	-	-
T18	5	–	-			Active	-	-	-	-
T19	7	-	Hypoplasia			Active	-	Plaque	yes	-
T20	10	-	Hypo-mineralization			Active & treated	Gingivitis	Plaque, calculus	yes	-
T21	9	-	Turner's tooth			Active & treated	Gingivitis	Plaque	-	-
T22	13	-	-	Dysmorphic central incisor crown	Agenesis 3rd molars	Active	Gingivitis	Plaque	yes	-
T23	15	-	Hypo-mineralization	Dysmorphic central incisor crown		Active & treated	Gingivitis	Plaque	yes	-
T24	16	-	-			-	-	-	yes	-
T25	22	-	-			-	-	-	yes	-
T26	25	-	Hypoplasia			Treated	-	-	yes	-
Column totals		0/26	7/26	6/26	2/26	20/26	11/26	13/26	17/26	0/26

IS, immunosuppressant; MIH, molar incisor hypomineralisation.

premolars and second permanent molars were unaffected. In three patients, a clear border between green-tinted incisal edges or cusps and non-discolored cervical areas was observed. Tooth shape anomalies were observed in 9/16 BA patients, compared with just 4/16 control patients (p = 0.15). The shape abnormalities observed in BA patients included peg-shaped lateral incisors, bulbous premolars, dysmorphic incisors, bifid maxillary second premolar or mandibular premolar roots in three patients, and one case of taurodontism (enlarged pulp chamber at the expense of root structure) [9]. The tooth shape anomalies observed in the matched controls were peg-shaped lateral incisors in two patients and atypical crown morphology in two other patients. Anomalies in enamel structure were more common among BA patients (p = 0.27). Tooth number anomalies were observed in five BA patients and none of the matched controls (p = 0.04). The number anomalies included third molar and premolar agenesis, and one case of supernumerary primary tooth.

3.2.3. *Comparison between Alagille syndrome and biliary atresia patients*

Tooth parameters are compared between AGS and BA patients in Table 6. Malocclusion, present in 10/16 BA patients and 10/10 AGS

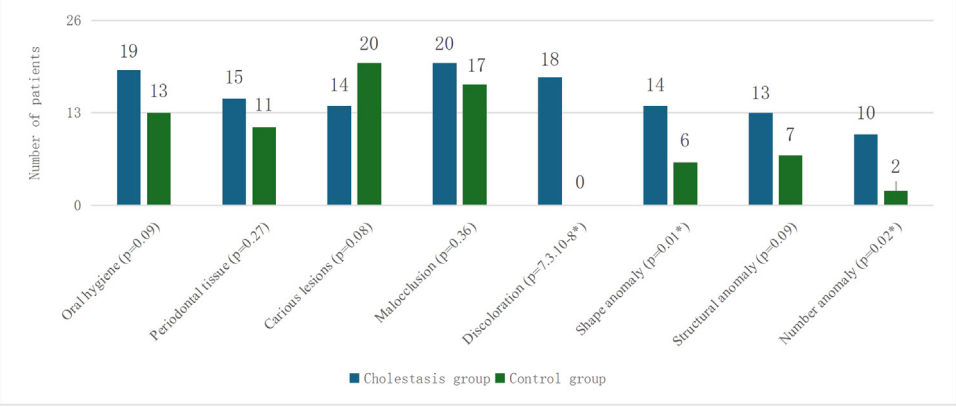

Fig. 1. Frequencies of oral and dental abnormalities compared between congenital cholestasis (Alagille syndrome and biliary atresia) and control patients.

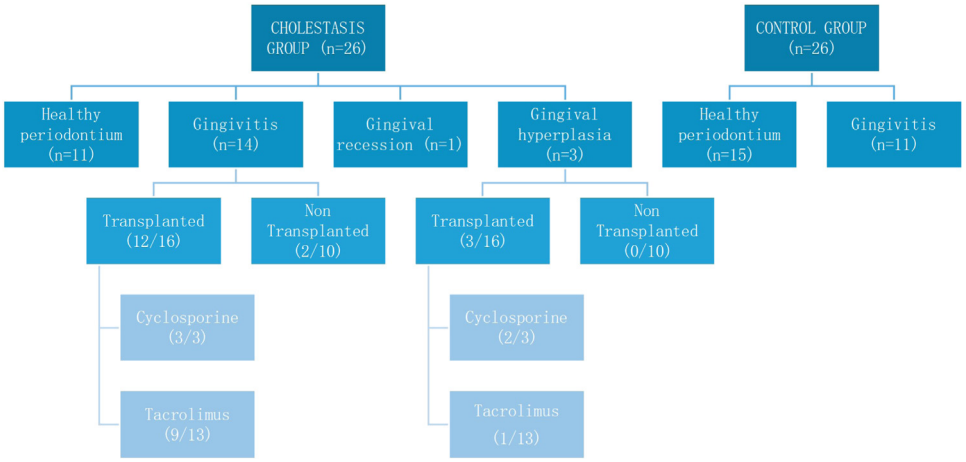

Fig. 2. Distribution of periodontal abnormalities in the cholestasis and control groups.

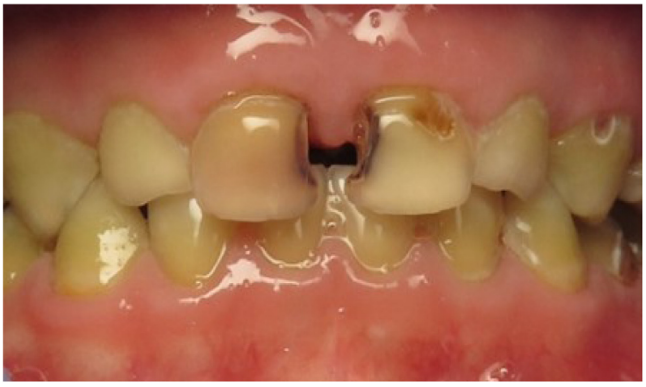

Fig. 3. Severe early childhood caries in the decidual teeth.

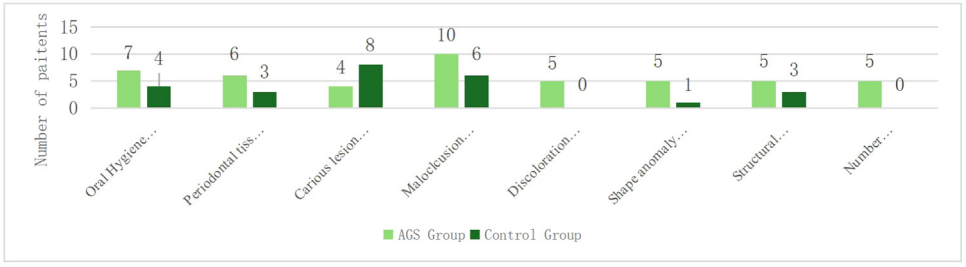

Fig. 4. Frequencies of oral and dental abnormalities compared between Alagille syndrome (AGS) patients and matched controls.

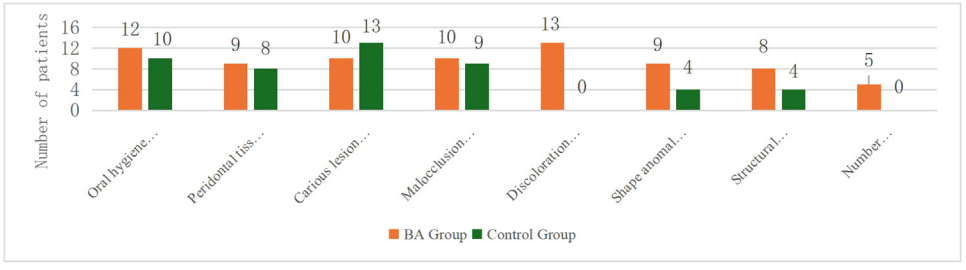

Fig. 5. Frequencies of oral and dental abnormalities compared between biliary atresia (BA) patients and matched controls.

Table 6
Frequency of dental anomalies in children with Alagille syndrome and biliary atresia.

Dental anomaly		Alagille syndrome (N = 10)	Biliary atresia (N = 16)	p-value
Discoloration	YES	5	13	0.23
	NO	5	3	
Tooth structure	YES	5	8	1
	NO	5	8	
Tooth shape	YES	5	9	0.75
	NO	5	7	
Number	YES	5	5	0.34
	NO	5	11	
Carious lesions	YES	4	10	0.42
	NO	6	6	
Periodontium	YES	6	9	1
	NO	4	7	
Oral hygiene	YES	7	12	1
	NO	3	4	
Malocclusion	YES	10	10	0.05
	NO	0	6	

patients (p = 0.05) was the only variable that differed significantly between the two groups.

3.3. Association between tooth discoloration and carious lesions or structural anomalies

For the cholestasis group, tooth discoloration was not significantly associated either with carious lesions (present in 11/18 patients with tooth discoloration vs 3/8 patients without discoloration; p = 0.40) or with enamel structure anomalies (observed in 8/13 patients with tooth discoloration vs 4/13 patients without discoloration; p = 0.24).

4. Discussion

Our study, the largest to date specifically among children with AGS and BA, provides a detailed description of the oral phenotypes of these conditions and distinguishes features that appear to be associated with cholestasis from those that seem to be specific to either AGS or BA. Note that although there were more female than male patients in our study group, there is no established link between sex and the prevalence of these diseases [8].

Children with cholestasis had a higher prevalence of malocclusion, periodontal disease, developmental anomalies, tooth discoloration, and poor oral hygiene, despite fewer having carious lesions than controls. To our knowledge, certain tooth-shape anomalies, such as bifid premolar roots and dysmorphic crowns, have never been reported in this population. Although taurodontism is frequently described in the literature [10,11], it was only observed in one patient in this study group.

Regarding tooth number anomalies, BA patients mainly lacked third molars and second premolars, the teeth most commonly missing in the general population (respectively, approximately 20 % and 3 % of individuals) [12–14], whereas AGS patients tended to lack teeth that are rarely absent in healthy individuals. Enamel structure anomalies, previously described exclusively in AGS patients [8], were here observed in both groups of cholestasis patients. These anomalies could be due to changes in the enamel organic matrix during development, deficiencies in key vitamins essential for tooth development and mineralization, osteopenia, and/or disturbances in calcium and phosphate metabolism associated with chronic liver disease [15,16].

Tooth discoloration is directly attributable to cholestasis, and the location and severity of discoloration appear to be determined by bilirubin levels and age at the time of liver transplantation. While staining disappears from soft tissues due to rapid cellular turnover [17], bilirubin pigments accumulate in developing mineralized tissues [18–20]. While previous results [4] have suggested that discoloration is systematic in BA, some BA patients in our study did not exhibit discoloration of permanent teeth. These patients had undergone successful Kasai portoenterostomy or liver transplantation before 18 months of age. Conversely, AGS patients had discoloration of both primary and permanent teeth, likely because they had not received liver transplantation or had undergone liver transplantation at a later age (around 4 years).

The fact that cholestasis patients had fewer caries despite poorer oral hygiene may be due to closer monitoring and restricted diets. However, while caries were rare in the AGS group, several BA patients had severe early childhood caries. This could be explained by poor nutrient absorption leading to frequent feeding, especially in early childhood and the peri-transplantation period [15,18,19,21]. Given the multifactorial nature of dental caries [20], regular dental follow-up visits are essential to provide effective dietary and hygiene education.

The fact that all 10 AGS patients had malocclusion suggests that this is a phenotypic trait of AGS, unrelated to cholestasis. *JAG1* variants are often associated with maxillofacial dysmorphia, whereas *NOTCH2* mutations are believed to have lower penetrance in this regard [22]. Note that neither talon cusp, often described as a phenotypic marker of AGS [23,24], nor macrodontic maxillary incisors, described in one case report [10], were observed in these AGS patients.

The significantly higher prevalence of missing teeth in AGS patients and their atypical agenesis patterns may also be linked to *JAG1* variants, which have been associated with isolated or syndromic oligodontia [12]. Several cases of multiple agenesis and oligodontia in AGS have already been reported [23,25], suggesting that tooth number anomalies could be considered phenotypic markers of AGS.

Liver-transplanted patients were particularly affected by periodontal inflammation, especially gingivitis, likely due to immunosuppressive therapy [26–28]. Cyclosporine, in particular, has been linked to periodontal issues in other transplant patients, including kidney transplant recipients [29]. Gingival hyperplasia does not appear to be associated with any particular immunosuppressive drug [5]. Rather, the combination of a weakened immune system and poor oral hygiene facilitates the proliferation of pathogenic bacteria, increasing the risk of gingivitis and periodontal disease.

The main limitations of our study include a large age range, small size, and the fact that the control patients were recruited among hospital dental clinic attendees and may therefore not be representative of the general population, with the prevalence of some dental anomalies, particularly oral hygiene, periodontal disease, and caries, likely overestimated. In keeping with radiation exposure guidelines, radiographs were obtained only when clinically indicated, which may have led to underdetection of tooth-shape and number anomalies. The small size of the study, due to the rarity of congenital cholestatic

diseases, should be borne in mind when extrapolating our results. Larger multicenter studies are required to confirm these findings and clarify the dental phenotypes of these conditions.

5. Conclusion

Our study confirms the broad spectrum of oral manifestations of congenital cholestasis and provides a more detailed description of these features. Multicenter studies are required to confirm these findings in larger samples. Early involvement of pediatric dentists is essential to address the specific oral health needs of these children and to manage infectious risks, particularly in the context of liver transplantation.

Disclosures

This work is an original research article. The manuscript has not been published and will not be submitted elsewhere for publication while being considered by the Journal. The authors have no conflict of interest with other people or organizations to declare. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The study was approved by the Ethics Committee of the of the GFHGNP (Groupe Francophone d'Hépatologie-Gastroentérologie et Nutrition Pédiatriques) and was conducted according to the principles of the Declaration of Helsinki and in compliance with ethical standards in France.

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