Original Article

Clinical, Laboratory, Radiological, and Genetic Characteristics of Pediatric Patients with Alagille Syndrome

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Abstract

Background: Alagille syndrome (ALGS) is an autosomal dominant disease caused by *JAG1* or *NOTCH2* mutation. It is diagnosed by the presence of three out of five features: characteristic facies, posterior embryotoxon, peripheral pulmonary stenosis, vertebral defects, and interlobular bile duct paucity. This study aimed to review the prevalence, clinical presentations, diagnosis, treatment, and outcome of patients with ALGS.

Materials and Methods: This is a retrospective review of patients with ALGS at the Pediatric Department, Salmaniya Medical Complex, Bahrain, between August 1994 and October 2022. The diagnosis was based on clinical, laboratory, radiological, histopathological, and genetic findings.

Results: Five patients were found to have ALGS. The prevalence of ALGS in Bahrain was 1.04 patients per 100,000 (0.001%). Four were Bahraini and three were females. Median birth weight was 2.3 (2.3–2.5) kg. All patients presented at the time of birth with low birth weight, cholestatic jaundice, clay-colored stool, heart murmur, and dysmorphic facial features. All had congenital heart diseases, two had butterfly vertebrae, and one had posterior embryotoxon. All had elevated liver enzymes and normal abdominal ultrasound. Three had positive hepatobiliary iminodiacetic acid scan and one had bile duct paucity in liver biopsy. Three had intraoperative cholangiogram. Four were positive for *JAG1* mutation. All received ursodeoxycholic acid and fat-soluble vitamins. Two required liver transplantation.

Conclusion: ALGS is a rare disorder in Bahrain. Diagnosis is challenging as the disease can be associated with or misdiagnosed as biliary atresia. Patients with ALGS are at high risk of morbidity either by unnecessary intraoperative cholangiogram or unavoidable liver transplantation.

Keywords: Alagille syndrome, Bahrain, intrahepatic cholestasis, *JAG1*, jaundice

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Introduction

Alagille syndrome (ALGS) is a rare genetic disease that is inherited as autosomal dominant and was described by Daniel Alagille in 1969.[1] It can involve the liver, heart, eyes, skeletal system, and face.[2] It is caused most commonly by *JAG1* gene mutation (20p12.2) or less commonly by gene mutation in the components of Notch signaling pathway called *NOTCH2* gene mutation.[3]

AGLS is estimated to have a prevalence of 1 in 70,000–100,000 live births.[4] It usually manifests with five major features which are characteristic facies (broad forehead, deep-set eyes, bulbous nose, and pointed chin), posterior embryotoxon, peripheral pulmonary stenosis, vertebral defects, and paucity of interlobular bile ducts.[2,3] It can be diagnosed clinically if the patient had three or more of the major features.[4]

The genetic testing is considered as the confirmatory diagnosis test, even though 4% of patients with ALGS may not show gene mutation.[3] Most common causes of mortality are vascular accidents, cardiac disease, and/or liver disease, which is estimated by 10%.[5]

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On reviewing the literature, very few studies about AGLS were published from the Middle East. The aim of this study was to review the prevalence, clinical presentations, diagnosis, treatment, and outcome of patients with ALGS in Bahrain.

Materials and Methods

In this retrospective cross-sectional study, any infant admitted to the Pediatric Department, Salmaniya Medical Complex (SMC), Kingdom of Bahrain, between August 1994 and October 2022 who was diagnosed with ALGS has been included. All electronic and paper-based medical records were reviewed. SMC is the main tertiary hospital in Bahrain and all children with cholestatic jaundice are referred to it for diagnosis and management. The diagnosis of ALGS was based on the combinations of clinical presentations, liver function tests (LFTs) [serum total protein, albumin, globulin, total, direct and indirect bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT)], coagulation and lipid profiles, spine X-ray, abdominal ultrasound, echocardiography, hepatobiliary iminodiacetic acid scan (HIDA), liver biopsy, and genetic study.

Patient's demographic data including age at the time of study, age of presentation, sex, nationality, and clinical presentations were collected. Laboratory findings, results of radiological imaging, liver biopsy histology, and genetic investigations were gathered. Medical and surgical therapies were reviewed. Follow-up period and patient's outcomes were assessed.

Statistical analysis

The patient's data were analyzed using Microsoft Excel 2016. The frequencies and percentages were calculated for categorical variables. Continuous variables were presented as median and range.

Results

During the study period, five patients were found to have ALGS. According to the latest Bahrain health statistics in 2020, the total population was 1,472,204. Population at risk, up to age of 18 years, was 481,819. So, the prevalence of ALGS in Bahrain is 1.04 patients per 100,000 (0.001%). Demographic data, clinical, laboratory, and radiological features are shown in Table 1. Four patients were Bahraini, and one was non-Bahraini. Three were females and two were males. All the patients presented at the time of birth with low birth weight, cholestatic jaundice, clay-colored stool, heart murmur, and dysmorphic facial features. All the patients were born at full term. Patients 1 and 5 were delivered via lower cesarean section delivery; patients 2 and 3 were delivered via normal vaginal delivery, while patient 4 was born via an emergency cesarean section due to fetal distress. All the patients had both breast- and bottle-feeding. The parents of the first four patients were unrelated, while the parents of patient 5 were consanguineous. All the patients had a negative family history of ALGS. As for the clinical features, all the patients had the classical dysmorphic features [Figure 1] and peripheral

Table 1: Clinical, laboratory, and radiological features of Alagille syndrome patients

Features/Investigations	Normal range	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	-	28	9	6	3	0.4
Sex	-	Female	Female	Male	Female	Male
Nationality	-	Bahraini	Indian	Bahraini	Bahraini	Bahraini
Birth weight (kg)	-	2.4	2.3	2.5	2.3	2.3
Hepatosplenomegaly	-	Yes	No	No	No	No
Xanthomas	-	Present	Present	None	None	None
Hemoglobin (g/dL)	12-14.5	11.5	11	11.5	14.4	11.7
Total protein (g/L)	64-82	69	69	71	57	55.8
Serum albumin (g/L)	38-54	39	37	41	37	39.7
Serum globulin (g/L)	15-30	30	32	23	20	16.1
Total bilirubin level (µmol/L)	<21	319	187	111	178	151
Direct bilirubin (µmol/L)	0-5	165	159	91	75	112
Indirect bilirubin (µmol/L)	<18	154	28	20	103	9
ALP* (U/L)	150-420	209	536	932	172	710
ALT‡ (U/L)	<41	177	141	294	26	181
GGT§ (U/L)	<18	256	102	1585	150	291
Cholesterol (mmol/L)	3.6-5.2	11.1	17.5	4.4	3.7	4.8
Triglyceride (g/L)	0.2-1.8	0.6	2.2	1.1	1.6	2.1
Spinal X-ray	-	Normal	Butterfly vertebrae	Normal	Normal	Butterfly vertebrae
Abdominal ultrasound	-	Normal	Normal	Normal	Normal	Normal
HIDA¶ scan	-	Absent excretion	Absent excretion	Not done	Not done	Absent excretion
Liver biopsy	-	Bile ducts paucity	Normal bile ducts	Not available	Not done	Normal bile ducts
Genetic study	-	No deletions	*JAG1* mutation	*JAG1* deletion	*JAG1* mutation	*JAG1* and *NOTCH2* mutations

*Alkaline phosphatase, ‡alanine aminotransferase, §gamma-glutamyl transferase, ¶hepatobiliary iminodiacetic acid

pulmonary stenosis while one had posterior embryotoxon. The mother of patient 1 had posterior embryotoxon and oval discs on fundoscopy, gestational diabetes mellitus (GDM), and urinary tract infection during her pregnancy while the mother of patient 2 had GDM and hypothyroidism for which she was receiving L-thyroxin therapy. The mother of patient 3 had sickle cell trait. The mother of patient 5 had GDM and asthma. Median birth weight was 2.4 kg (range: 2.3–2.5). Patient 1 had a hepatomegaly of 2 cm below costal margins at presentation.

LFTs at the time of presentation revealed elevated total, direct, and indirect bilirubin levels and high GGT in all patients, high ALT in four, and hypoalbuminemia and high ALP in three patients each. Coagulation profile was normal for all patients. Hypercholesterolemia was noted in patients 1 and 2 while hypertriglyceridemia was seen in patients 2 and 5. The median cholesterol level was 4.8 mmol/L (range: 3.7–17.5; normal range: 3.6–5.2), while that of triglyceride was 1.6 g/L (range: 0.6–2.2; normal range: 0.2–1.8).

Chest X-ray showed two butterfly vertebrae in both patient 2 [Figure 2] and patient 5 (T5–T8). Echocardiography revealed peripheral pulmonary stenosis in all the patients, and one had an associated tetralogy of fallot (TOF). Three patients (patients 1, 2, and 5) had HIDA scan performed which showed a good isotope uptake by the liver, but no intestinal activity seen in early or delayed images [Figure 3].

Liver biopsy was carried out in four patients (patients 1, 2, 3, and 5). For patient 1, the liver biopsy showed a lobular architecture of the hepatocytes with pseudoxanthomatous transformation, giant cells, and bile imbibition with a few bile thrombi in between. There was Kupffer cells prominence and a few foci of extramedullary hematopoiesis. The portal tracts showed a few proliferating bile ducts (reduced in number) with increase in the fibrous tissue. For patient 2, the biopsy showed intrahepatic and canalicular cholestasis, feathery degeneration of hepatocyte and mild infiltrate in portal triad with normal bile ducts, and no cirrhosis. The liver biopsy report of patient 3 was not available as it was done on Turkey, while patient 4 had no liver biopsy done. Patient 5 liver biopsy report showed subcapsular liver tissue with five portal tracts. The hepatocytes are arranged in one to two cells thick plated as confirmed by reticulin stain. Intracanalicular and intrahepatocyte cholestasis was noted along with mild iron deposition. The portal ducts showed mild ductular proliferation with neutrophils. There was no ductular paucity.

All the patients had a genetic testing done. Patient 1 had chromosomal study that showed a normal female karyotype with no apparent deletion on chromosome 20 short arms. Patients 2, 3, and 4 were positive for *JAG1* mutation. The next-generation sequence (NGS) was used to detect the gene mutation in patient 2 and c.703C>T (p.Arg235*) variant was detected in heterozygosity in the *JAG1* gene. For patient 3, a pathogenic heterozygous deletion encompassing the entire *JAG1* gene was detected by whole-exome study. For patient 4, the *JAG1* variant c.551G>A (p.Arg184His) was detected also by NGS. For patient 5, the *JAG1* pathogenic variant c.2106C>A (p.Cys702Ter) and *NOTCH2* gene variant

Figure 1: Dysmorphic features (triangular face, wide forehead, frontal bossing, prominent chin, and deep-set eyes) of patients with Alagille syndrome (patients 2, 3, 4, and 5)

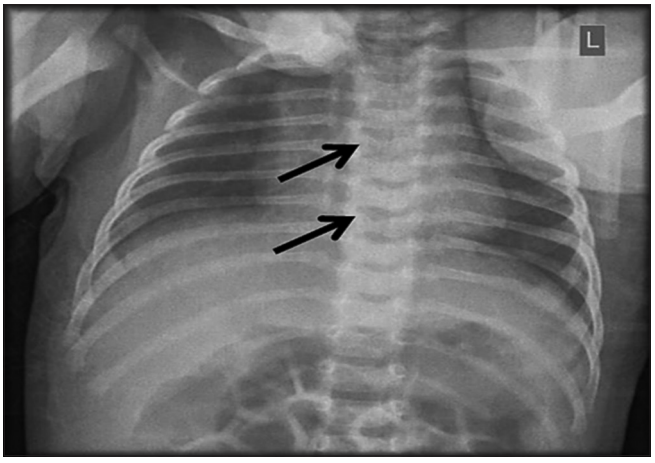

Figure 2: Chest X-ray of patient 2 showing butterfly vertebrae (arrows)

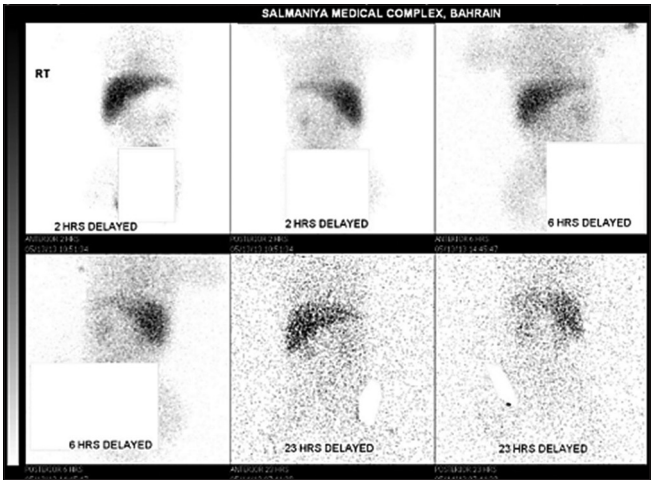

Figure 3: Hepatobiliary iminodiacetic acid scan (HIDA) of patient 2 which shows a good isotope uptake by the liver, but no intestinal activity seen in early or delayed images

c.5024G>A (p.Arg1675His) of uncertain significance were detected. All the patients received ursodeoxycholic acid and fat-soluble vitamins (vitamins A, D, E, and K). Patient 1 had laparotomy and an intraoperative cholangiogram at the age of one month which showed atresia of the proximal common bile duct, well-formed gallbladder, cystic duct, and distal common bile duct for which a Kasai porto-enterostomy was performed. She also developed bronchial asthma at childhood. Despite the medical and surgical therapies, she developed severe pruritus that was affecting her quality of life, hypercholesterolemia, and xanthomas. Accordingly, she underwent liver transplantation at the age of 5 years in the United Kingdom (her father was the donor). Now, she is 28 years old and using a single immunosuppressive medication.

Patient 2 also had an intraoperative cholangiogram performed in India which ruled out biliary atresia. She developed xanthomas in her feet [Figure 4] secondary to severe hypercholesterolemia for which she received lipid-lowering agent (Atorvastatin) which was successful in reducing the cholesterol to acceptable levels. Due to recurrent episodes of abdominal pain and distention, abdominal ultrasound and magnetic resonance imaging (MRI) were performed, and both showed hepatic cirrhosis. At the age of 9 years, MRI was repeated which showed cirrhotic liver with two well-defined mass lesions in the right and left lobes of the liver along with splenomegaly and minimal ascites. Liver biopsy was done, and malignancy was ruled out. The patient underwent liver transplantation in India. The mother was the donor. Postliver transplant, her LFTs and cholesterol levels were normalized. Lipid-lowering agent was stopped. Currently, she is on tacrolimus and multivitamin tablets.

Patient 3 had a left parietal intracerebral hemorrhage and subdural hematoma at age of 3 months that required admission to the intensive care unit, decompressive cranioectomy, and external drainage. At the age of 6 months, a skull reconstruction (cranioplasty) was performed. He also had a cardiac surgery for TOF at the age of 2 years. Currently, his age is 6 years old. Patient 4 is currently stable, and her age is 3 years. Patient 5 also had exploratory laparotomy and operative cholangiogram at the age of 2 months. He is currently 4 months old and stable on ursodeoxycholic acid, vitamin D, and fat-soluble vitamins.

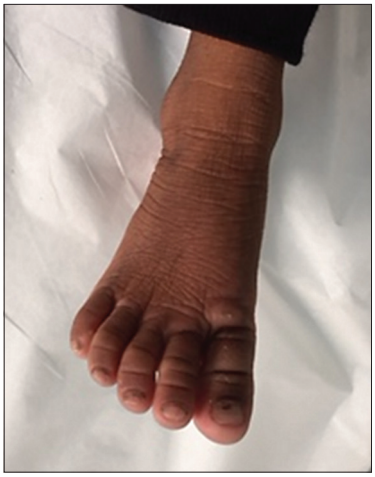

Figure 4: Xanthomas on right foot below her big toe (patient 2)

Discussion

Alagille syndrome is a very rare disease as only 500 cases were reported to have this syndrome around the world.[2] It is a complex multisystem disease that is caused by variations in *JAGGED 1* mutation.[5] According to the national organization of rare diseases, there are no gender predications regarding ALGS disturbance. In this study, three out of the five patients were females. Many reports described female patients.[1,5-10] However, others showed male patients.[2-4,11-13] Nevertheless, all of these were case reports and there were no case series that suggest the sex pattern of this disease.

Some of the diseases may show consanguinity related to the disease, especially in congenital diseases. In our study, one of the patients had related parents. This is similar to Sousa and Resende report which also showed related parents.[12] However, other reports published by Micaglio *et al*., Pati *et al*., Fischetto *et al*., Hannoush *et al*., and Reyes-de la Rosa *et al*. showed no consanguinity.[1-4,11]

In this study, two patients were products of normal vaginal delivery similar to a study published by Fischetto *et al*.[3] Three of our patients were products of Cesarean section, a type of delivery that was also reported by Reyes-de la Rosa *et al*. and Sousa and Resende case reports.[11,12]

Similar to our patients where all had low birth weight, which was ranging between 2.3 and 2.5 kg, two studies by Micaglio *et al*. and Fischetto *et al*. mentioned a birth weight of 2.49 and 2.50 kg, respectively.[1,3] However, two studies done by Pati *et al*. and Reyes-de la Rosa *et al*. reported a lower birth weight of 2.100 and 2.200 kg.[2,11]

Although three patients' mothers had GDM, one mother had hypothyroidism, and one had sickle cell trait during pregnancy; after extensive research, no link was found between these diseases and ALGS. Moreover, no link was found between any maternal hepatic illnesses and ALGS. Similarly, two studies reported by Pati *et al*. and Fischetto *et al*. excluded hepatic illnesses in their patients' family.[2,3]

In our study, jaundice was the first presentation in all patients since birth. This is similar to several studies in which their patients also presented with jaundice since birth.[1,2,4-6,10-13]

All the patients in the current study had facial dysmorphic features like board forehead, deep-set eyes, saddle nose, and narrow pointed chin. Other studies have also reported the same particular faces.[1-7,9-12]

Guo *et al*. reported 8 of 11 patients with ALGS who had an associated congenital heart disease.[14] In our study, all the patients were found to have an associated congenital heart disease at the time of presentation. Four patients had

peripheral pulmonary stenosis alone and one had TOF along with the pulmonary stenosis. Most of the previous studies also reported ALGS patients with an associated cardiac defect and the majority reported peripheral pulmonary stenosis.[1,4,7,9-11] Other congenital heart diseases such as atrial septic defect, right hypoplastic heart, and ventricular septal defect were also reported.[1,5,7,12] Fiorda-Diaz *et al*. reported a patient with unpaired TOF.[8] The results of our study were similar to the results of previous studies.

In the present study, patient 1 had posterior embryotoxon as an ophthalmological anomaly. Hannoush *et al*., Xie *et al*., and Guo *et al*. also reported posterior embryotoxon in their studies.[4,5,14]

In our study, patients 1 and 2 developed xanthomas in both hands and feet due to high cholesterol levels. Hannoush *et al*., Reyes-de la Rosa *et al*., and Sousa and Resende studies also reported similar finding on their patients.[4,11,12]

Patient 3 who had an associated TOF developed an intracerebral hemorrhage and subdural hematoma at the age of 3 months that was before the surgical repair of TOF. This is similar to a case study reported by Fiorda-Diaz *et al*. who also described a subarachnoid hemorrhage in a patient with unpaired TOF.[8]

All five patients were having abnormal LFTs at presentation. That is similar to the studies published by Hannoush *et al*. and Huang and Wang,[4,6] while elevated bilirubin was also detected in Micaglio *et al*. and Brennan and Kesavan studies.[1,7]

In patients 2 and 5, butterfly vertebrae appeared in the spinal X-ray; this finding was also found in studies reported by Hannoush *et al*., Xie *et al*., Huang and Wang, Ennaifer *et al*., and Reyes-de la Rosa *et al*.[4-6,10,11]

All our patients had abdominal ultrasound images in which the swelling of the liver and spleen were excluded. That is comparable to a Chinese study published by Xie *et al*. that was done on twin sisters with ALGS and showed no liver or spleen swelling on abdominal ultrasound.[5] On the other hand, a study published by Souda and Resende showed mild hepatomegaly on ultrasound.[12]

In this study, patient 1 had a liver biopsy which showed a reduced number of the bile duct in the portal triad while patients 2 and 5 had normal bile ducts. Liver biopsy results reported by Pati *et al*., Brennan and Kesavan, Ennaifer *et al*., and Shaul *et al*. also showed bile duct paucity.[2,7,10,13] This might be explained by the single small liver biopsy in our study that might not reflect the whole histological findings and might miss the presence of bile duct paucity. Patient 1 had a co-occurrence of extrahepatic biliary atresia that required Kasai procedure. Although rare, the co-occurrence of ALGS and biliary atresia has been reported before. In 1981, Kocoshis *et al*. reported the first case of this co-occurrence in a newborn who had pseudotruncus arteriosus, butterfly vertebrae, and was diagnosed to have extrahepatic biliary atresia in postmortem autopsies.[15] In 1991, Maurage *et al*. reported the second case on record of ALGS with well-documented extrahepatic biliary atresia who was the first to undergo a Kasai procedure.[16] In 2015, Dědič *et al*. also reported 5 of 72 patients with biliary atresia, who were diagnosed with ALGS based on a positive *JAG1* mutation, but they showed the major clinical features late at the age of 3 years.[17] Nonetheless, the association between ALGS and biliary atresia remains rare. These two conditions can mimic each other which make the differentiation between them in young infants challenging. Moreover, patients with ALGS are likely to be misdiagnosed as biliary atresia which might subject them to unnecessary surgical interventions. That was the case in two of our patients who underwent laparotomy and intraoperative cholangiograms. To prevent these morbidities, rapid testing for *JAG1* mutations in early infancy is necessary to improve patient outcomes.[17]

In this study, genetic testing data of four patients (patients 2, 3, 4, and 5) revealed *JAG1* mutations that confirmed ALGS diagnosis. This is similar to several studies which mostly reported *JAG1* mutations.[1,3-5,7,11,14,18]

Patient 2 had heterozygous gene variant of c.703C>T (p.Arg235*). This gene variant was reported by Krantz *et al*.[19] Patient 3 genetic study showed a pathogenic heterozygous deletion encompassing the entire *JAG1* gene and this was previously reported by Krantz *et al*. and Warthen *et al*.[20,21] As for patient 4, she was found to have *JAG1* variant c.551G>A (p.Arg184His) that was also reported by Krantz *et al*., Morrissette *et al*., and Tada *et al*.[19,22,23] For patient 5, the *JAG 1* variant c.2106C>A (p.Cys702Ter) was detected, along with a NOTCH2 gene variant c.5024G>A (p.Arg1675His) which was of uncertain significance. However, few studies such as Brennan and Kesavan, Shaul *et al*., and Sangkhathat *et al*. studies reported NOTCH2 gene mutation as the confirmatory study of ALGS.[7,13,18] Summary of studies of patients with ALGS and the reported genetic results is shown in Table 2.

Two of our patients had liver transplantation at the age of 5 and 9 years due to sever pruritus that was affecting the quality of life in one patient and due to liver cirrhosis with suspicious hepatic nodules in the other patient. Ennaifer *et al*. study reported one patient who required a liver transplantation, and they explained the need for liver transplantation by the behavior of the liver lesions, which only occurs in 15%.[10]

The small sample size was the main limitation of this study. Another limitation was the small number of the study reports that are available to compare with. These limitations can be justified by the rarity of the disease.[2] Despite the limitations, this study is important being the first report to focus on such a rare syndrome from Bahrain.

In conclusion, Alagille syndrome is a rare autosomal dominant disorder. It is best diagnosed clinically and can be confirmed by the presence of abnormal liver functions and an associated *JAGGED1* or NOTCH2 mutation. This study reported five new patients who were diagnosed with ALGS. All five patients presented at the time of birth with low birth

Table 2: Summary of studies of patients with Alagille syndrome with available genetic results

Country	Author/Year	Period	Patient	Age (years)	Tested gene	Gene variations
Bahrain*	Isa and Alahmed (2023)	1994-2022	5	At birth	*JAG1*	c.703C>T (p.Arg235*) (heterozygous), heterozygous deletion of entire gene and c.551G>A (p.Arg184His)
China	Xie *et al*.[5] (2015)	2015	2	12 m	*JAG1*	Three within exon 22: c.2612C>G (p.Pro871Arg), exon 24: c.2957T>A (P.Leu986*), and exon 26: c.3417T>C (P.Tyr1139)
China	Huang[6] (2018)	2018	1	20	*JAG1*	NR†
China	Guo *et al*.[14] (2018)	2010-2017	11	<18	*JAG1*	Seven variants: c.1977G>A (P.Trp659*) and c.1106_1107delCC 2 patients. Both deletions involved the entire JAG1 gene P.Pro369fs)
Italy	Fischetto *et al*.[3] (2019)	2004-2015	1	3	*JAG1*	c.2026delT (*P*.Cys676AlafsTer6)
Italy	Micaglio *et al*.[1] (2019)	2019	1	12 days	*JAG1*	c.802del (p.His268Thrfs*144)
Thailand	Sangkhathat *et al*.[18] (2018)	2003-2016	4/20	NR	*JAG1*	c.2048G>A (p.Arg683His), c.703G>A (p.Arg235ST), c.2884A>G (p.Thr962Ala), c.133G>T (p.Val45Leu)
Mexico	Reyes-de la Rosa *et al*.[11] (2018)	2018	1	2 years and 7 months	*JAG1*	c.91dupG (heterozygous)
USA‡	Hannoush *et al*.[4] (2016)	2016	1	1	*JAG1*	p.Arg486Lysfs*5 (heterozygous)
USA	Brennan and Kesavan[7] (2017)	2017	1	6 m	*JAG1* *NOTCH2*	c.2729dupA (p.Cys911Valfs*41) c.4819C>T (p.Arg1607Cys)
USA	Shaul *et al*.[13] (2019)	2019	5	2-8 weeks	*NOTCH2*	One copy of VOUS
USA	Krantz *et al*.[19] (1998)	1998	54	NR	*JAG1*	Deletion of entire gene in 3 patients and mutations in 35 (9 nonsense, 2 missense, 11 small deletions, 8 small insertions, 1 complex rearrangement, and 4 splice site mutations)
USA	Krantz *et al*.[20] (1999)	1999	2	3.5 and 5.5	*JAG1*	684insG and deletion of entire gene

*The present study, †no record, ‡the United states of America

weight and cholestatic jaundice; three patients found to have only *JAG1* gene mutation, while patient 5 had both *JAG1* and NOTCH2 mutation. Although ALGS is a rare disorder in Bahrain, it causes a multisystem dysfunction with significant comorbidities. The diagnosis of ALGS is challenging as the disease can be associated with or misdiagnosed as biliary atresia. Patients with ALGS are at risk of high morbidity rate either by undergoing unnecessary intraoperative cholangiogram or by the unavoidable liver transplantation. These patients require long-term monitoring along with ursodeoxycholic acid and fat-soluble vitamins. Further studies are needed to understand more about the disease phenotype, long-term outcomes, and the different treatment modalities.

Ethical approval

This study was conducted in accordance with the principles of the Helsinki Declaration of 1975 (revised 2013), and it was ethically approved by the secondary care medical research subcommittee, Salmaniya Medical Complex, Government Hospitals, Kingdom of Bahrain (IRB number: 71090521).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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