Received:
1 June 2017

Revised:
5 July 2017

Accepted:
7 July 2017

<https://doi.org/10.1259/bjr.20170406>

Cite this article as:

Han S, Jeon TY, Hwang SM, Yoo S-Y, Choe YH, Lee S-K, et al. Imaging findings of Alagille syndrome in young infants: differentiation from biliary atresia. *Br J Radiol* 2017; **90**: 20170406.

FULL PAPER

Imaging findings of Alagille syndrome in young infants: differentiation from biliary atresia

¹SOLBEE HAN, MD, ¹TAE YEON JEON, MD, ¹SOOK MIN HWANG, MD, ¹SO-YOUNG YOO, MD, ²YON HO CHOE, MD, ³SUK-KOO LEE, MD and ¹JI HYE KIM, MD

¹Department of Radiology and Center for Imaging Science, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

²Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

³Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Address correspondence to: Dr Tae Yeon Jeon

E-mail: hathor97.jeon@samsung.com

Objective: To compare the imaging findings using ultrasonography, MR cholangiopancreatography (MRCP), and intraoperative cholangiography (IOC) between Alagille syndrome (AGS) and biliary atresia (BA) in young infants with cholestatic jaundice.

Methods: The institutional review board approved this retrospective study. Ultrasonography ($n = 55$), MRCP ($n = 33$), and IOC ($n = 22$) studies were performed in 55 infants (all younger than 3 months) with AGS ($n = 7$) and BA ($n = 48$). The ultrasound images were reviewed focusing on gallbladder (GB) abnormalities, triangular cord sign, hepatic artery enlargement and signs of portal hypertension. Visualization of the extrahepatic biliary tree was assessed by MRCP and IOC.

Results: Six (86%) AGS patients showed a small GB on ultrasound; this was comparable to that in BA patients (81%, 35/43). The images were negative for triangular cord sign and hepatic artery enlargement in all AGS patients, whereas they were positive in 48% (23/48) ($p = 0.034$) and 77% (33/43) ($p < 0.001$) of the BA

patients, respectively. Signs of portal hypertension were less common in AGS patients than in BA patients ($p = 0.010$). Although non-visualization of the extrahepatic biliary tree by MRCP did not differ significantly between patients with AGS and BA, AGS patients showed a higher proportion of visible common bile ducts with IOC, compared to BA patients. The diagnosis of AGS was made in four infants (57%) before ultrasonography, based on extrahepatic manifestations.

Conclusion: The small GB visualized on ultrasonography and non-visualization of extrahepatic biliary tree by MRCP commonly occurred in patients with either AGS or BA. However, triangular cord sign, hepatic artery enlargement and signs of portal hypertension on ultrasonography and non-visualized common bile duct with IOC were less frequent in AGS patients than in BA patients.

Advances in knowledge: Atypical imaging findings for BA should prompt a meticulous evaluation for the extrahepatic manifestations of AGS to avoid possibly harmful surgery.

INTRODUCTION

Alagille syndrome (AGS) is an autosomal dominant disorder caused by defects in the *Notch* signaling pathway that affect multiple organ systems with phenotypic variability.^{1,2} AGS can be diagnosed clinically through the presence of at least three of five major features: chronic cholestasis, cardiac disease, ocular abnormalities, skeletal abnormalities and peculiar face phenotypes.³ Genetic analysis for mutations in *JAG1* or, rarely, in *NOTCH2* can be helpful in atypical and mild cases.⁴ A liver biopsy is no longer compulsory to diagnose AGS, although the syndrome is associated with a paucity of interlobular bile ducts histopathologically.^{1,2,5,6}

The clinical, laboratory, radiological and histopathological features of AGS may exhibit a considerable overlap with

biliary atresia (BA). However, discriminating AGS from BA in a timely manner is important, because Kasai portoenterostomy is unlikely to be of value when the surgery is performed on BA patients older than 3 months of age.⁷ Furthermore, Kasai portoenterostomy does not benefit infants with AGS and in fact, appears to worsen their outcomes.^{5,8-10} Most patients with AGS can be managed conservatively, and approximately 20–50% of AGS patients with severe cholestasis require liver transplantation before adulthood.^{2,5,8,11} Numerous imaging findings have been reported as valuable indicators for the diagnosis of BA, but studies on the imaging findings of AGS are few in number.

The purpose of our study is to compare the imaging findings using ultrasonography, MR cholangiopancreatography

(MRCP) and intraoperative cholangiography (IOC) between AGS and BA in young infants with cholestatic jaundice.

METHODS AND MATERIALS

Patients

This retrospective study was approved by our institutional review board, and the requirement for informed consent was waived. Cases were defined as infants with liver disease of AGS (AGS group), whereas controls were infants with BA (BA group). Inclusion criteria mandated that all patients undergo baseline ultrasonography at an age younger than 3 months.

The medical records of our institutional database between 2000 and 2014 were retrospectively searched, yielding 12 infants with liver disease of AGS and 127 infants with BA. Among the 12 patients with AGS, 5 patients were excluded because of non-availability of ultrasound images ($n = 2$) and age older than 3 months at initial ultrasound ($n = 3$). Among the 127 patients with BA, 79 patients were excluded because of non-availability of ultrasound images before Kasai portoenterostomy ($n = 55$), age older than 3 months ($n = 19$) and cystic BA (extrahepatic biliary atresia associated with choledochal cyst; $n = 5$). Finally, 55 consecutive children with AGS ($n = 7$, 1 boy and 6 girls) or BA ($n = 48$, 16 boys and 32 girls) were included in this study.

The diagnosis of AGS was founded on the presence of at least three of the five major features in all seven patients. Liver disease of AGS was diagnosed based on chronic cholestasis [hyperbilirubinemia (1.0 mg dl^{-1}) beyond 6 months of age ($n = 7$)]¹² and histopathologic analysis of the explanted liver ($n = 7$). In all cases of BA, the diagnosis was confirmed at laparotomy, the reference standard.

Clinical profiles and laboratory data

The medical charts were evaluated for patient demographics and clinical profiles, focusing on the frequencies of clay-coloured stool and the major clinical features of AGS. As a baseline investigation for neonatal cholestasis, biochemical hepatic function tests were evaluated, including bilirubin level, aspartate aminotransferase (AST), alanine aminotransferase, and gamma-glutamyl transpeptidase levels. The AST to platelet ratio index was determined as the ratio of (AST/upper limit of normal value: 45 IU l^{-1})/platelet counts (10^9 l^{-1}) $\times 100$.¹³

Image acquisition

All infants underwent a detailed hepatobiliary ultrasound examination by one of three paediatric radiologists using two ultrasonography systems (Sequoia, Siemens Healthcare, Erlangen, Germany; LOGIQ E9, GE Healthcare, Waukesha, WI). All infants were fasting for at least 3 h before ultrasound examination.

MR examinations ($n = 33$) were conducted using 1.5 or 3.0 T MRI systems (Signa Advantage Horizon; GE Medical Systems, Milwaukee, WI; Achieva, Philips Healthcare, Best, The Netherlands). The MRI sequences comprised axial and coronal turbo spin echo T_2 weighted images (TR/TE = 685–45925/67–150 ms, section thickness [ST] = 3–5 mm, matrix = 150–395 $\times$ 160–400,

field of view [FOV] = 140–270 mm), axial and coronal turbo spine echo heavily T_2 weighted images with non-breath hold and respiratory triggering (1008–43150/150–1002 ms, 3–5 mm, 130–256 $\times$ 82–256, 150–280 mm), and three-dimensional (3D) MRCP (1200–2000/580–650 ms, 2 mm, 148–256 $\times$ 130–180, 280 mm). We reformatted 3D acquisition images using a standard maximum intensity projection algorithm. The MR examinations were usually conducted under natural sleep, after feeding. If this was judged impossible, sedatives were offered by a skilled paediatric sedation team.

IOC ($n = 22$) was conducted by the surgical team. One or two radiographs were obtained after non-ionic contrast material was injected into the gallbladder (GB). The first radiograph permits the visualization of GB, cystic duct and common bile duct and passage of the contrast material to the duodenum. The second radiograph, after additional injection of contrast material with clamping of the proximal common bile duct, permits the visualization of the common hepatic duct and intrahepatic biliary tree.

Image analysis

Two paediatric radiologists (with 14 and 7 years of experience in paediatric abdominal imaging) reviewed all images independently, and any disagreements were resolved by consensus. The reviewers were informed that all infants were referred with a chief complaint of cholestasis, but they were unaware of other clinical data.

The ultrasound images were assessed with emphasis on GB abnormalities, triangular cord sign, diameter of hepatic artery and signs of portal hypertension. Measurements using an electronic caliper were obtained twice and the average values were taken. When GB was observed, its length was measured on a longitudinal scan, with a description of any irregularities of the mucosa and contour. The GB was considered small when it was less than 1.9 cm long.^{14,15} The triangular cord sign was considered positive when a triangular or tubular echogenic thickening that was located anterior to the right portal vein was 4 mm or more thick.¹⁶ The diameter of the hepatic artery was measured at the level of the right proximal hepatic artery. A diameter of the hepatic artery larger than 1.5 mm was considered as hepatic artery enlargement.¹⁷ The presence of splenomegaly or ascites was considered a sign of portal hypertension. The size of the spleen was measured on a longitudinal scan at the level of the hilum. Splenomegaly was determined based on age.¹⁸

The visualization of the extrahepatic biliary tree was evaluated by MRCP or IOC. The extrahepatic biliary tree included the common bile duct, common hepatic duct and the confluence level of intrahepatic hepatic ducts.¹⁹

Statistical analysis

Statistical software (SPSS, version 23.0; SPSS, Chicago, IL) was used for statistical analyses. A p -value < 0.05 was considered as a statistically significant difference. Descriptive data were presented as the mean $\pm$ standard deviation or number

Table 1. Clinical profile and laboratory data

Variables	Alagille syndrome (n = 7)	Biliary atresia (n = 48)	p-Value
Gender, male:female	1:6	16:32	0.416
Clay stool ^a	3/5 (60%)	28/45 (62.2%)	1.000
Age at ultrasound, days	61.6 ± 14.7	58.7 ± 21.9	0.742
Kasai portoenterostomy ^a	3/7 (43%)	44/48 (92%)	0.006
Age at Kasai portoenterostomy, days	76 ± 22.3	67.1 ± 18.3	0.424
Liver transplantation ^a	7/7 (100%)	30/48 (63%)	0.082
Age at liver transplantation, months	11 ± 8.3	8.5 ± 20.3	0.149
Both Kasai portoenterostomy and liver transplantation ^a	3/7 (100%)	26/48 (54%)	0.696
Total bilirubin	12.9 ± 8.3	9.3 ± 3.2	0.437
Direct bilirubin	7.9 ± 1.6	6.8 ± 2.1	0.342
AST	244.7 ± 205.8	233.4 ± 204.6	0.915
ALT	202.0 ± 299.3	156.2 ± 129.0	0.497
GGT	665.9 ± 743.7	551.9 ± 453.2	0.920
AST:platelet	1.0 ± 0.7	1.7 ± 1.6	0.156

Unless otherwise noted, data are means ± standard deviation.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase.

^aData are numbers of patients with percentages in parentheses.

of individuals (percentage) with a condition. Statistical differences were compared using either Fisher's exact test for categorical variables and two-sample *t*-test or Mann-Whitney test for continuous variables.

RESULTS

Clinical profiles and laboratory data

The clinical profiles and laboratory data at the time of ultrasound examination in patients with AGS and BA are presented in [Table 1](#). Both groups showed a female predominance. Three patients with AGS underwent Kasai portoenterostomy at a median age of 83 days because AGS mimicked BA in early infancy. All AGS patients underwent liver transplantation, whereas 30 (63%) of the 48 BA patients underwent liver transplantation ($p = 0.082$). The frequency of clay-coloured stool showed no significant

difference between the two groups. No statistical difference was determined for the biochemical hepatic function tests.

The frequencies of major clinical features of patients with liver disease of AGS are as follows ([Table 2](#)): cardiac disease (7/7, 100%), skeletal abnormalities (3/7, 43%), ocular abnormalities (3/7, 43%) and a characteristic facial phenotype (6/7, 86%). Before initial ultrasound examination, the diagnosis of AGS was made in four infants (4/7, 57%) on the basis of extrahepatic manifestations. Six patients (86%) underwent molecular confirmation of AGS and all six had *JAG1* gene mutation.

Imaging findings

The imaging findings in both AGS and BA patients are presented in [Table 3](#). Of the GB that was visualized, the proportion of small

Table 2. Major clinical features and genetic mutations in seven infants with Alagille syndrome

No.	Sex/age ^a	Hepatic	Cardiac	Skeletal	Ocular	Facial	JAG1 mutation
1	F/43d	Cholestasis	PS, ASD	Normal	Retinitis pigmentosa	Peculiar	Identified
2	F/49d	Cholestasis	PS, ASD	Butterfly vertebra	NE	Normal	Identified
3	F/53d	Cholestasis	VSD	Butterfly vertebra	NE	Peculiar	Identified
4	F/58d	Cholestasis	PS	Normal	Posterior embryotoxon	Peculiar	Identified
5	F/69d	Cholestasis	PS	Butterfly vertebra	Iris abnormality	Peculiar	Identified
6	F/78d	Cholestasis	PS	Normal	NE	Peculiar	NE
7	M/81d	Cholestasis	PS	Normal	NE	Peculiar	Identified

ASD, atrial septal defect; d, days; NE, not evaluated; PS, pulmonary artery stenosis; VSD, ventricular septal defect.

^aAge at the time of ultrasound examination.

Table 3. Imaging findings between infants with Alagille syndrome and biliary atresia

Variables	Alagille syndrome (n = 7)	Biliary atresia (n = 48)	p-Value
Ultrasound	7/7 (100%)	48/48 (100%)	
GB abnormalities	7/7 (100%)	38/41 (93%)	1.000
Non-visualized GB	0/7 (0%)	5/48 (10%)	1.000
Small GB	6/7 (86%)	35/43 (81%)	1.000
GB wall irregularity	1/7 (14%)	33/43 (77%)	0.003
Triangular cord sign	0/7 (0%)	23/48 (48%)	0.034
Hepatic artery enlargement	0/7 (0%)	41/48 (85%)	<0.001
Signs of portal hypertension	1/7 (14%)	33/48 (69%)	0.010
Splenomegaly	3/7 (43%)	33/48 (68.8%)	0.219
Ascites	0/7 (0%)	7/48 (15%)	0.577
MRCP	4/7 (57%)	29/48 (60%)	
Non-visualized CBD	3/4 (75%)	27/29 (93%)	0.330
Non-visualized CHD	4/4 (100%)	28/29 (97%)	1.000
Non-visualized confluence level	4/4 (100%)	28/29 (97%)	1.000
IOC	3/7 (43%)	19/48 (40%)	
Non-visualized CBD	0/3 (0%)	15/19 (79%)	0.023
Non-visualized CHD	2/3 (67%)	18/19 (95%)	0.259
Non-visualized confluence level	3/3 (100%)	19/19 (100%)	1.000

Data are numbers of patients with percentages in parentheses.

CBD, common bile duct; CHD, common hepatic duct; GB, gallbladder; IOC, intraoperative cholangiography; MRCP, MR cholangio pancreatography.

GB (86% [6/7] versus 81% [35/43], $p = 1.000$; 1.4 ± 0.5 cm versus 1.6 ± 0.8 cm, $p = 0.390$) was not significantly different between AGS and BA patients. The GB wall irregularity was observed in only one patient with AGS but in 33 (77%) of the 43 patients with BA ($p = 0.003$). The triangular cord sign was positive in 48% (23/48) of the BA patients, but negative in all the AGS patients ($p = 0.034$) (Figures 1 and 2). The diameter of hepatic artery was significantly smaller in AGS patients (1.0 ± 0.2 mm) than in the BA patients (2.0 ± 0.5 mm) ($p = 0.030$) (Figures 1 and 2). The hepatic artery was not enlarged in all patients with AGS. The spleen length (4.9 ± 1.1 cm versus 6.0 ± 1.4 cm, $p = 0.538$) and presence of ascites (0% [0/7] versus 15% [7/48], $p = 0.577$) were not significantly different between the two groups, but the signs of portal hypertension were less common in patients with AGS than with BA ($p = 0.010$).

Non-visualization of the extrahepatic biliary tree by MRCP did not significantly differ between the two groups. However, the common bile duct was more commonly seen with IOC in AGS patients than in BA patients (100% vs 21%, $p = 0.023$). The common bile duct was not visualized by MRCP in three of four (75%) AGS patients, but small or hypoplastic common bile duct was seen with IOC in all three (100%) AGS patients (Figure 1). The common hepatic bile duct was not visualized by MRCP and the confluence level of the intrahepatic duct was not visualized with either MRCP or IOC in all patients in both groups.

DISCUSSION

Our study revealed that 86% (6/7) of the AGS patients showed small GB on ultrasonography; this percentage was comparable to that observed in BA patients (81%, 35/43). AGS is characterized by lack of triangular cord signs, smaller hepatic artery diameter and lower proportion of GB wall irregularities and signs of portal hypertension when compared to ultrasound evaluation of BA. The non-visualization of the extrahepatic biliary tree by MRCP did not significantly differ in both groups. However, in our study, visible common bile duct was encountered more frequently with IOC in the AGS patients than in the BA patients.

A decreased number of or an absence of interlobular bile ducts is a characteristic histopathological feature in the liver disease of AGS, with a reported incidence of 58–100%.^{1,2,5} The phenotypic spectrum of liver disease of AGS varies in its severity and clinical significance, ranging from subtle biochemical abnormalities to profound cholestasis and synthetic hepatic failure requiring liver transplantation.^{2,11} The diagnostic investigation can reflect the phenotypic variability of AGS. For example, Emerick et al² reported that 39% (14/36) of AGS patients showed normal or delayed excretion based on hepatobiliary scans, but 61% (22/36) of the AGS patients showed no excretion after 24 h. In addition, 26% (5/19) of the AGS patients had visible intrahepatic bile ducts with IOC, but 74% (14/19) of the AGS patients had non-visualized intrahepatic bile ducts. AGS patients with minimal or subclinical liver disease may show negative imaging findings.²⁰

Figure 1. Alagille syndrome in a 49-day-old girl. (a) Ultrasound image shows a small gallbladder measuring 1.4 cm (arrowheads). (b) Diameter of right hepatic artery is 0.8 mm (arrow) and triangular cord sign is negative. (c) 3D MR cholangiopancreatography image shows no visible extrahepatic biliary tree and small gallbladder (arrow) (asterisk: duodenum). (d, e) Intraoperative cholangiography shows patent common bile duct (long arrow) and common hepatic duct (short arrow) (d) and no visible confluence level of intrahepatic bile ducts (arrowhead) (e).

Figure 2. Biliary atresia in a 72-day-old girl. (a) Ultrasound image shows a small gallbladder measuring 1.3 cm, which has wall irregularity (arrow). (b) Diameter of the right hepatic artery is 1.8 mm (arrowheads) and triangular cord sign is positive (arrow). (c) 3D MR cholangiopancreatography image shows a small gallbladder (arrow) and no visible extrahepatic biliary tree (asterisk: duodenum). (d) Intraoperative cholangiography shows no visible extrahepatic biliary tree.

Previous studies on AGS reported GB abnormalities including small length or abnormal shape at ultrasonography, in concordance with our study.^{20,21} However, in contrast to a prior study by Cho et al²⁰ the incidence of GB abnormalities was much higher in our study (100% vs 57%). Plausible explanations for the higher proportion of GB abnormalities in our AGS patients include the following. First, all our AGS cases may have had more severe liver disease, considering that all seven AGS patients ultimately underwent liver transplantation. Second, the pathogenesis of GB abnormalities in AGS can be speculated by the diminished bile production and storage as well as inflammatory processes.²⁰ AGS shows less thickened portal septa and lesser degree of fibrosis or cirrhosis than BA because of the near absence of reactive ductular cells, hepatic progenitor cells and peribiliary gland hyperplasia in AGS, compared to BA.^{22,23} These differences in hepatic reparative mechanisms may explain the different ultrasound findings of triangular cord sign, hepatic artery diameter and signs of portal hypertension between AGS and BA.

MRCP is a well-established and non-invasive modality for the assessment of hepatobiliary disease, even in children. Previous investigations have documented the diagnostic performance of MRCP in the diagnosis of BA by reporting a sensitivity of 75–100%, specificity of 36–96% and accuracy of 71–100%.^{19,24–26} However, MRCP may have some potential pitfalls, leading to erroneous diagnosis. For example, inadequate bile production in the patent biliary tree can result in false positive diagnoses,²⁷ whereas high signals from the intestinal tract can mimic the normal biliary tree.²⁶ In our study, MRCP could not differentiate AGS from BA. The non-visualization of the extrahepatic biliary tree by MRCP in AGS can be speculated to arise from the

insufficient production and secretion of bile due to the paucity of interlobular bile ducts.

The GB abnormalities seen on ultrasonography and the non-visualization of the extrahepatic biliary tree including the confluence level with MRCP and/or IOC may masquerade as BA. Moreover, liver biopsy is not always diagnostic for distinguishing AGS from BA. The histopathological results from liver specimens in early infancy may reveal portal inflammation and ductular proliferation.^{2,5,6} The paucity of interlobular bile ducts in AGS increases with age and worsening of liver disease.^{2,6} The potential diagnostic confusion causes AGS to be misdiagnosed as BA and the patients to undergo Kasai portoenterostomy. The performance of Kasai portoenterostomy in AGS patients has a poor hepatic outcome.^{5,8–10} AGS patients who undergo the Kasai portoenterostomy exhibit higher rates of liver transplantation and mortality, compared to those who do not. In agreement with prior studies, our study also revealed that the three AGS patients who underwent Kasai portoenterostomy ultimately underwent liver transplantation because of profound cholestasis and/or failure to thrive. Among them, two patients died because of acute rejection leading to hepatic failure. Kaye et al⁵ presumed that Kasai portoenterostomy itself has a detrimental stimulus. The exposure to intestinal contents will trigger intrahepatic inflammatory processes that act as additional insults to the already damaged intrahepatic bile ducts.

The major extrahepatic manifestations of AGS are cardiac disease (most commonly peripheral pulmonary stenosis, 85–97%), peculiar face (70–100%), butterfly vertebrae (33–87%) and ocular abnormalities (most commonly posterior embryotoxon,

56–88%). The minor clinical manifestations of AGS include renal disease, growth/mental retardation, pancreatic insufficiency or intracranial abnormalities.^{2,28} Expression of extrahepatic manifestations also varies in AGS from mild phenotype to life-threatening condition, even in family members carrying same gene mutations.^{1,2,11,28} Careful assessment to recognize subtle manifestations of AGS should be a part of the initial surveillance in infants with cholestatic jaundice. Kamath et al²⁹ reported that severe hepatic and cardiac disease occurred at a lower rate in *JAG1* mutation carriers than in the probands. Identification of genetic mutations for the diagnosis of AGS is of great importance in mild or subclinical cases, and it may permit prenatal diagnosis and precise evaluation of family members as potential living liver donors.^{4,30}

Limitations of our study may include the small number of infants with AGS and retrospective study design. A large-scale research of AGS including a range of severity of phenotypic findings may be necessary for generalization of our findings.

In conclusion, although observation of small GB with ultrasonography and non-visualization of extrahepatic biliary tree with MRCP were common in infants with either AGS or BA less than 3 months of age, the triangular cord sign, hepatic artery enlargement, GB wall irregularity and signs of portal hypertension with ultrasonography and non-visualization of the common bile duct with IOC were less common in AGS patients than in BA patients. Atypical imaging findings for BA in infants younger than 3 months with cholestatic jaundice should prompt a meticulous evaluation for the extrahepatic manifestations of AGS to avoid unnecessary and possibly deleterious surgery.

REFERENCES

1. Alagille D, Estrada A, Hadchouel M, Gautier M, Odièvre M, Dommergues JP. Syndromic paucity of interlobular bile ducts (Alagille syndrome or arteriohepatic dysplasia): review of 80 cases. *J Pediatr* 1987; **110**: 195–200. doi: [https://doi.org/10.1016/S0022-3476\(87\)80153-1](https://doi.org/10.1016/S0022-3476(87)80153-1)
2. Emerick KM, Rand EB, Goldmuntz E, Krantz ID, Spinner NB, Piccoli DA. Features of alagille syndrome in 92 patients: frequency and relation to prognosis. *Hepatology* 1999; **29**: 822–9. doi: <https://doi.org/10.1002/hep.510290331>
3. Subramaniam P, Knisely A, Portmann B, Qureshi SA, Aclimandos WA, Karani JB, et al. Diagnosis of alagille syndrome–25 years of experience at King's College Hospital. *J Pediatr Gastroenterol Nutr* 2011; **52**: 84–9. doi: <https://doi.org/10.1097/MPG.0b013e3181f1572d>
4. Li L, Krantz ID, Deng Y, Genin A, Banta AB, Collins CC, et al. Alagille syndrome is caused by mutations in human Jagged1, which encodes a ligand for Notch1. *Nat Genet* 1997; **16**: 243–51. doi: <https://doi.org/10.1038/ng0797-243>
5. Kaye AJ, Rand EB, Munoz PS, Spinner NB, Flake AW, Kamath BM. Effect of kasai procedure on Hepatic outcome in alagille syndrome. *J Pediatr Gastroenterol Nutr* 2010; **51**: 1–21. doi: <https://doi.org/10.1097/MPG.0b013e3181df5fd8>
6. Dahms BB, Petrelli M, Wyllie R, Henoch MS, Halpin TC, Morrison S, et al. Arteriohepatic dysplasia in infancy and childhood: a longitudinal study of six patients. *Hepatology* 1982; **2**: 350S–8. doi: <https://doi.org/10.1002/hep.1840020311>
7. Jonas MM, Perez-Atayde AR. *Liver disease in infancy and childhood*. 10th ed. Philadelphia, PA: Lippincott Williams and Wilkins, 2007.
8. Kamath BM, Schwarz KB, Hadzić N. Alagille syndrome and liver transplantation. *J Pediatr Gastroenterol Nutr* 2010; **50**: 11–15. doi: <https://doi.org/10.1097/MPG.0b013e3181c1601f>
9. Lee HP, Kang B, Choi SY, Lee S, Lee SK, Choe YH. Outcome of alagille syndrome patients who had previously received kasai operation during infancy: a Single center study. *Pediatr Gastroenterol Hepatol Nutr* 2015; **18**: 175–9. doi: <https://doi.org/10.5223/pghn.2015.18.3.175>
10. Markowitz J, Daum F, Kahn EI, Schneider KM, So HB, Altman RP, et al. Arteriohepatic dysplasia. I. pitfalls in diagnosis and management. *Hepatology* 1983; **3**: 74–6. doi: <https://doi.org/10.1002/hep.1840030112>
11. Lykavieris P, Hadchouel M, Chardot C, Bernard O. Outcome of liver disease in children with alagille syndrome: a study of 163 patients. *Gut* 2001; **43**: 51–5. doi: <https://doi.org/10.1136/gut.49.3.431>
12. Hoffenberg EJ, Narkewicz MR, Sondheimer JM, Smith DJ, Silverman A, Sokol RJ. Outcome of syndromic paucity of interlobular bile ducts (Alagille syndrome) with onset of cholestasis in infancy. *J Pediatr* 1995; **127**: 220–4. doi: [https://doi.org/10.1016/S0022-3476\(95\)70298-9](https://doi.org/10.1016/S0022-3476(95)70298-9)

13. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* 2003; **38**: 518–26. doi: <https://doi.org/10.1053/jhep.2003.50346>
14. Mittal V, Saxena AK, Sodhi KS, Thapa BR, Rao KL, Das A, et al. Role of abdominal sonography in the preoperative diagnosis of extrahepatic biliary atresia in infants younger than 90 days. *AJR Am J Roentgenol* 2011; **196**: W438–W445. doi: <https://doi.org/10.2214/AJR.10.5180>
15. Tan Kendrick AP, Phua KB, Ooi BC, Tan CE. Biliary atresia: making the diagnosis by the gallbladder ghost triad. *Pediatr Radiol* 2003; **33**: 311–5. doi: <https://doi.org/10.1007/s00247-003-0867-z>
16. Lee HJ, Lee SM, Park WH, Choi SO. Objective criteria of triangular cord sign in biliary atresia on US scans. *Radiology* 2003; **229**: 395–400. doi: <https://doi.org/10.1148/radiol.292020472>
17. Kim WS, Cheon JE, Youn BJ, Yoo SY, Kim WY, Kim IO, et al. Hepatic arterial diameter measured with US: adjunct for US diagnosis of biliary atresia. *Radiology* 2007; **245**: 549–55. doi: <https://doi.org/10.1148/radiol.2452061093>
18. Megremis SD, Vlachonikolis IG, Tsilimigaki AM. Spleen length in childhood with US: normal values based on age, sex, and somatometric parameters. *Radiology* 2004; **231**: 129–34. doi: <https://doi.org/10.1148/radiol.2311020963>
19. Norton KI, Glass RB, Kogan D, Lee JS, Emre S, Shneider BL. MR Cholangiography in the evaluation of neonatal cholestasis: initial results. *Radiology* 2002; **222**: 687–91. doi: <https://doi.org/10.1148/radiol.2223010969>
20. Cho HH, Kim WS, Choi YH, Cheon JE, Lee SM, Kim IO, et al. Ultrasonography evaluation of infants with alagille syndrome: in comparison with biliary atresia and neonatal hepatitis. *Eur J Radiol* 2016; **85**: 1045–52. doi: <https://doi.org/10.1016/j.ejrad.2016.03.023>
21. Farrant P, Meire HB, Mieli-Vergani G. Ultrasound features of the gall bladder in infants presenting with conjugated hyperbilirubinaemia. *Br J Radiol* 2000; **73**: 1154–8. doi: <https://doi.org/10.1259/bjr.73.875.11144791>
22. Fabris L, Cadamuro M, Guido M, Spirli C, Fiorotto R, Colledan M, et al. Analysis of liver repair mechanisms in alagille syndrome and biliary atresia reveals a role for notch signaling. *Am J Pathol* 2007; **171**: 641–53. doi: <https://doi.org/10.2353/ajpath.2007.070073>
23. Carpino G, Cardinale V, Renzi A, Hov JR, Berloco PB, Rossi M, et al. Activation of biliary tree stem cells within peribiliary glands in primary sclerosing cholangitis. *J Hepatol* 2015; **63**: 1220–8. doi: <https://doi.org/10.1016/j.jhep.2015.06.018>
24. Han SJ, Kim MJ, Han A, Chung KS, Yoon CS, Kim D, et al. Magnetic resonance cholangiography for the diagnosis of biliary atresia. *J Pediatr Surg* 2002; **37**: 599–604. doi: <https://doi.org/10.1053/jpsu.2002.31617>
25. Jaw TS, Kuo YT, Liu GC, Chen SH, Wang CK. MR Cholangiography in the evaluation of neonatal cholestasis. *Radiology* 1999; **212**: 249–56. doi: <https://doi.org/10.1148/radiology.212.1.r99jl13249>
26. Liu B, Cai J, Xu Y, Peng X, Zheng H, Huang K, et al. Three-dimensional magnetic resonance cholangiopancreatography for the diagnosis of biliary atresia in infants and neonates. *PLoS One* 2014; **9**: e88268. doi: <https://doi.org/10.1371/journal.pone.0088268>
27. Siles P, Aschero A, Gorincour G, Bourliere-Najean B, Roquelaure B, Delarue A, et al. A prospective pilot study: can the biliary tree be visualized in children younger than 3 months on Magnetic resonance cholangiopancreatography? *Pediatr Radiol* 2014; **44**: 1077–84. doi: <https://doi.org/10.1007/s00247-014-2953-9>
28. Cho JM, Oh SH, Kim HJ, Kim JS, Kim KM, Kim GH, et al. Clinical features, outcomes, and genetic analysis in Korean children with alagille syndrome. *Pediatr Int* 2015; **57**: 552–7. doi: <https://doi.org/10.1111/ped.12602>
29. Kamath BM, Bason L, Piccoli DA, Krantz ID, Spinner NB. Consequences of JAG1 mutations. *J Med Genet* 2003; **40**: 891–5. doi: <https://doi.org/10.1136/jmg.40.12.891>
30. Warthen DM, Moore EC, Kamath BM, Morrisette JJ, Sanchez-Lara PA, Sanchez P, et al. Jagged1 (JAG1) mutations in alagille syndrome: increasing the mutation detection rate. *Hum Mutat* 2006; **27**: 436–43. doi: <https://doi.org/10.1002/humu.20310>