Agenesis of the gallbladder: A multicenter case series and review of the bibliography

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ABSTRACT

Gallbladder agenesis is a rare condition in pediatrics that is usually asymptomatic and represents a diagnostic challenge for physicians seeing these cases for the first time. Some patients may, however, present with symptoms that mimic other diseases of the bile ducts, and many of them undergo surgery due to such suspicion. Still, a timely diagnosis of gallbladder agenesis allows for medical treatment that is often sufficient to resolve the patient's problem. Although it is a benign condition, patients often present with other associated, more serious malformations and should be actively studied for a timely referral to other specialists.

Here we describe our experience with the diagnosis and treatment of these patients and a brief review of the bibliography. We hope it will be helpful for physicians facing similar cases.

Keywords: gallbladder; congenital anomalies; pediatrics.

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INTRODUCTION

Gallbladder agenesis (GA) is a rare condition with a reported incidence of 10–65/100 000,^{1,2} but it may be higher given its asymptomatic nature. However, patients may present symptoms, such as dyspepsia, pain in the right upper quadrant, or intolerance to fatty foods, as well as other diseases of the bile ducts. It is more frequent in women (3:1) and is usually diagnosed during the third decade of life, frequently during a cholecystectomy.^{3,4}

It may be diagnosed with an ultrasound, but fibrous remnants of gallbladder agenesis may be interpreted as scleroatrophy in patients with recurrent cholecystitis. In uncertain cases, an MRI or an endosonography may help with the diagnosis.⁵ Although the bibliography about pediatric cases is scarce, GA seems to be associated with other malformations, although there are isolated cases.⁶

It is important for pediatricians to recognize GA because a timely diagnosis allows preventing unnecessary tests and procedures that increase morbidity and mortality.⁷ With this in mind, here we describe our experience with the diagnosis and treatment of these patients and a brief review of the bibliography.

POPULATION AND METHODS

Retrospective review of the medical records of CHU Sainte-Justine and Sanatorio de Niños de Rosario between 2015 and 2023. Patients with a diagnosis of GA were included, regardless of the diagnostic methodology. The results of supplementary tests, associated conditions, treatments, and course were registered. Uncertain diagnoses and bile duct atresia were excluded. Authorization was obtained from the participating sites to review the medical records and publication of results.

CASE REPORTS

Eight cases of GA were retrieved: 3 boys and 5 girls. The characteristics of patients are shown in *Table 1*. Patients' mean age was 5.7 years (\pm 2.1 years). Five patients were diagnosed during an investigation due to abdominal pain; in 4 of them, it was attributed to GA. Three of these cases improved with dietary changes and 1 with the administration of ursodeoxycholic acid (UDCA). One patient showed increased liver enzymes. Two had GA on the prenatal ultrasound.

Lab tests were abnormal in 3 patients: alanine aminotransferase (ALT) levels were up to 3 times the normal values and gammaglutamyltransferase (GGT) levels were up to 6 times the normal values. Bilirubin levels were normal in all patients. The ultrasound was diagnostic in all cases and demonstrated repeatedly and by different operators the absence of the gallbladder despite fasting for more than 6 hours.

A magnetic resonance cholangiopancreatography was done in 4 patients and corroborated the diagnosis. In 2 studies, dilated common bile duct was observed; 2 other studies found intrahepatic cystic lesions not communicating with the bile ducts. These were not compatible with hypoplastic or ectopic gallbladder. None of the patients had intrahepatic bile duct lesions (*Figure 1*).

A liver biopsy was done in 1 patient due to persistent hypertransaminasemia; F1 fibrosis with moderate inflammation and neoductular reaction was observed. This patient received UDCA and their biochemistry panel values returned to normal. No patient underwent surgery.

An associated condition was observed in 7 patients. Genetic mutations were found in 3 patients: a chromosome 12 deletion, a chromosome 16 deletion, and Beckwith-Wiedemann syndrome. Cryptorchidism and renal atrophy were observed in 1 patient, and hypospadias in another. Omphalocele with mesenteric *situs inversus* was observed in 1 patient, and *pancreas divisum* in another. A case of persistent left superior vena cava was found. One patient had clinodactyly that required surgical correction. Finally, 1 patient had hypoplasia of the right portal vein, umbilical cord cyst, and ventriculomegaly.

DISCUSSION

The gallbladder develops during the fourth month of intrauterine life from a protrusion of the primitive gut, which divides into the liver and the primary cystic ducts. The latter are vacuolated and then migrate to their final position in the gallbladder fossa.⁸ Failures in these processes result in GA or ectopia.⁹

GA is characterized by the absence of the gallbladder in the presence of normally developed bile ducts, as opposed to bile duct atresia. Its presentation is varied: 35% of patients are diagnosed incidentally; 50% develop symptoms that, paradoxically, mimic those of cholecystitis or choledocholithiasis; and 15% of cases correspond to post mortem findings.¹ The pathophysiology of



FIGURE 1. Magnetic resonance cholangiopancreatography of several patients

Gallbladder agenesis in 4 different patients, with complete absence of the gallbladder and the cystic duct in all cases. A. Dilated common bile duct and left hepatic duct (thick arrow) with normal Wirsung duct and biliopancreatic duct (thin arrow). B. Non-communicating intrahepatic cystic lesion (thick arrow) with normal common bile duct and biliopancreatic duct (thin arrow). C and D. Dilated proximal common bile duct (thick arrow) with a normal distal common bile duct.

the symptoms is unknown, but it is hypothesized that they are caused by biliary stasis within the common hepatic duct, which is usually dilated as it functions as a bile reservoir. In our series, we found 2 patients with dilated common bile duct and normal biliopancreatic duct. Up to 60% of patients develop cholelithiasis.⁹ Another explanation is biliary dyskinesia, similar to that observed in post-cholecystectomy syndrome.¹⁰

The diagnosis of GA is of great importance because its management is not surgical, but with the administration of antispasmodics or UDCA.¹¹ Some authors have described the use of a sphincterotomy of Oddi in cases of medical treatment failure and persistent symptoms.¹² Minimally invasive procedures may be helpful, as many patients report resolution of symptoms, probably due to lysis of adhesions and fibrous remnants.⁹

An ultrasound is useful for the assessment of the hepatic and bile ducts, but its sensitivity is 61%. This is not caused by the inability to diagnose GA, but by the erroneous finding of the gallbladder when it is not present. The interposition of the duodenum in the gallbladder fossa, in addition to the expectation of finding the gallbladder in a patient without previous surgeries, accounts for these cases.^{1,5} Unfortunately, this results in symptomatic patients being diagnosed during an unnecessary surgery. Another useful diagnostic methodology is a magnetic resonance, and some authors recommend it after intraoperative suspicion of GA to exclude the presence of an ectopic gallbladder.^{4,13} It is worth noting that, although the bibliography considers a cholangiography (intraoperative or by magnetic resonance) as the gold standard procedure, in no case did invasive studies provide information that invalidated ultrasound findings. An endosonography allows the assessment of the bile ducts without the risks of a surgery, but its use as the main diagnostic method is uncommon and it is not free of complications.1,7

Although patients are usually asymptomatic, mild hypertransaminasemia or moderate cholestasis may be found incidentally, as was the case in 3 of our patients. This is probably due to biliary stasis, since dilated extrahepatic duct was observed in 2 patients, and the biopsy of 1 patient showed cholangiolar proliferation with some degree of focal inflammation.

GA has been described as part of malformation syndromes, such as tetralogy of Fallot, ventricular septal defects, duodenal atresia, intestinal

TABLE 1.	Patients'	' charact	teristics
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Sex	Age	Reason for consultation or symptom	Lab tests	Imaging tests	Biopsy	Associated Treat conditions	ment Res	ponse
М	4 years old	Cholestasis Hypertransaminasemia	ALT 2.5 x NV GGT 6 x NV	Ultrasound: absent GB in spite of fasting > 4 hours. Dilated common bile duct. MRCP: absent GB. Fusiform dilation of the common bile duct and right and left hepatic ducts. Normal intrahepatic bile duct.	 F1 Moderate inflammation Ductular reaction 	 Chromosome 12q15q2131 mutation Hydronephrosis Bilateral renal atrophy Vesicoureteral reflux Cryptorchidism Agenesis of the corpus callosum 	UDCA	Yes
F	15 days	Absence of GB in prenatal ultrasounds	Normal	Ultrasound: absent GB in spite of fasting > 4 hours. Normal intra- and extrahepatic bile ducts.	No	Partial 16p12.2 deletion Skin hemangiomas Persistent LSVC drainin into the coronary sinus	No g	NA
F	5 years old	Diffuse abdominal pain (incidental diagnosis)	Normal	Ultrasound: absent GB in spite of fasting > 4 hours. Normal intra- and extrahepatic bile ducts.	No	 Beckwith-Wiedemann syndrome Polyhydramnios Omphalocele Situs inversus 	Dietary changes	Yes
М	7 years old	Diffuse abdominal pain (incidental diagnosis)	Normal	Ultrasound: absent GB. MRCP: polyseptate cyst in gallbladder fossa. Simple liver cysts in segments V and VIII.	No	 Hypertrophic pyloric stenosis Hypospadias Chronic diarrhea 	Dietary changes	Yes
M (inc	7 years old idental diagn	Diffuse abdominal pain osis)	ALT NV GGT 1.5–2 x-NV	Ultrasound: absent GB in spite of fasting > 4 hours. MRCP: fusiform dilation of the common bile duct (common bile duct cyst, type I).	No	Pancreas divisum	UDCA	Yes
F	9 years old	Abdominal pain Dyspepsia (incidental diagnosis)	ALT 3 x NV GGT 6 x NV	Ultrasound: absent GB in spite of fasting > 4 hours. Multiseptate intrahepatic cystic lesion. MRCP: absent GB. Cystic lesion at the level of the porta hepatis.	No	Clinodactyly	UDCA	Yes
F	8 years old	Abdominal pain (incidental diagnosis)	Normal	Ultrasound: absent GB in spite of fasting > 4 hours. Normal intra- and extrahepatic bile ducts.	No	No	No	NA
F	Prenatal	Absence of GB in prenatal ultrasounds	Normal	Ultrasound: absent GB. Hypoplasia of the right portal vein. Normal umbilical vessels.	No	Umbilical cord cyst Ventriculomegaly	No	No

F: female; M: male; ALT: alanine-aminotransferase; GGT: gamma-glutamyltransferase; NV: normal value; GB: gallbladder; UDCA: ursodeoxycholic acid; LSVC: left superior vena cava; NA: not applicable; MRCP: magnetic resonance cholangiopancreatography.

malrotation, *pancreas divisum*, renal agenesis, cryptorchidism, and syndactyly.¹⁴ It has also been associated with genetic syndromes, such as trisomy 18 or Beckwith-Wiedeman syndrome.¹ The findings from our series of cases are compatible with those reported in the bibliography, with only 1 patient with GA as an isolated finding, with no other associated malformations.

GA remains an uncommon condition in the pediatric population and, therefore, its diagnosis is a challenge for pediatricians, surgeons or radiologists. Although some patients remain asymptomatic all their lives, half of them will develop symptoms not dissimilar to those of bile duct conditions. Given the diagnostic characteristics of GA via ultrasound, most patients undergo unnecessary invasive procedures during which the diagnosis is corroborated. It is worth recalling that an ultrasound done in adequate fasting conditions and in the hands of a skilled operator seems to be sufficient to diagnose GA. The presence of intestinal loops interposed in the gallbladder fossa may raise diagnostic doubts, as they may be confused with the aspect of a distended gallbladder. In these cases, more invasive procedures may be necessary to validate the diagnostic suspicion. Although the bibliography so far considers intraoperative cholangiography to be the gold standard for the diagnosis of GA, our experience shows that this is probably not the case. No author has reported a case where ultrasound has shown the absence of the gallbladder and then ruled out the diagnosis using more invasive methods. That is to say, all cases where the ultrasound showed the absence of the gallbladder were validated (possibly unnecessarily) by another procedure.

It should be noted that while GA itself is a benign condition, a dilated common bile duct may become symptomatic over time and even lead to the development of cholelithiasis. Some patients may also present with lab test alterations that may raise suspicion of other conditions. Therefore, an early recognition of GA is of vital importance, since surgical treatment is not indicated in most cases. More importantly, most of these patients have other associated malformations, which are usually more severe than GA and should be referred to the corresponding specialists. ■

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