Gallbladder agenesis with choledochal cyst—a rare association: a case report and review of possible genetic or embryological links

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SUMMARY

Gallbladder agenesis is a rare congenital anomaly. Choledochal cysts are uncommon. The combination of both these entities in a 56-year-old woman is reported. A previously fit and well woman, presented to the emergency department with a 3-day history of abdominal pain. Preoperative imaging and intraoperative findings confirmed gallbladder agenesis and a type I choledochal cyst. There were no other anomalies. She underwent a resection of the choledochal cyst and reconstruction by hepaticojejunostomy.

BACKGROUND

Congenital absence of gallbladder (agenesis) is a rare anomaly but presents important diagnostic and therapeutic dilemmas. Most patients are asymptomatic from gallbladder agenesis throughout life, but the condition is discovered incidentally when they present with abdominal symptoms, which may or may not be linked to the condition. Gallbladder agenesis may be associated with other biliary and/or extra-biliary anomalies. The combination of abnormalities makes diagnosis difficult on either ultrasound or MR cholangiopancreatography (MRCP). We report a case of gallbladder agenesis in a patient who also had a choledochal cyst, an association which has been reported only twice before in English literature. Tabibian *et al* described a case of an 82-year-old woman, who presented with duodenal obstruction secondary to a choledochal cyst stone. Goel *et al* described a case of gallbladder agenesis associated with a type IVA choledochal cyst. From both these cases it was noted that the combination of gallbladder agenesis and a choledochal cyst complicates surgical management. This is both due to the abnormal anatomy difficulties and also due to unusual complications caused by choledochal cysts.^{1 2}

CASE PRESENTATION

A 56-year-old woman presented to the emergency department with a few days history of dull epigastric pain. There was no history of present or previous episodes of fever and/or jaundice. The inflammatory markers, serum amylase and liver function tests were normal on admission. Abdominal examination showed minimal epigastric tenderness to deep palpation. There were no masses, or was there a hepatomegaly. An ultrasound revealed absence of the gallbladder consistent with congenital gallbladder agenesis. CT scan and MRCP confirmed the presence of a type I choledochal cyst and gallbladder agenesis (figure 1).

Gastroscopy revealed gastritis and the presence of *Helicobacter pylori* infection which was eradicated. A screening colonoscopy was normal. Apart from previous diagnoses of type II diabetes mellitus, hypertension and hypercholesterolaemia, she did not have any other significant comorbidities. She had no other detectable systemic congenital anomalies.

She underwent an elective laparotomy for management of her symptomatic choledochal cyst. At laparotomy, the gallbladder was not seen in its usual location. A thorough search was made in conjunction with preoperative and intraoperative ultrasound (IOUS) imaging to ensure that the gallbladder was neither intrahepatic nor ectopic in other locations such as on the left side. There was a fusiform choledochal cyst involving the extrahepatic bile duct, Todani type I,³ measuring 4.5 cm in its maximal diameter. The choledochal cyst extended from the hilum (but not involving the left or right hepatic ducts) to the distal bile duct at the level of the duodenum, but proximal to the entry of the pancreatic duct. There were no stones or mass lesions in the cyst. No other hepatopancreaticobiliary or gastrointestinal anomalies or pathology were noted. An excision of the choledochal cyst with the proximal resection margin distal to the confluence and the distal margin as close to the pancreatic duct as possible, was performed. Reconstruction was by Roux-en-Y hepaticojejunostomy. Histopathology results showed a dilated bile duct lined by normal biliary type epithelium with scattered inflammatory cells in keeping with a choledochal cyst. No

Figure 1 MR cholangiopancreatography image demonstrating a choledochal cyst in the absence of a gallbladder.

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dysplasia or malignancy was seen. The patient is still under routine follow-up and was last seen in clinic 2 years postoperation fit and well, with no significant complications.

DISCUSSION

There are a number of reports of both gallbladder agenesis and choledochal cysts separately in the literature, despite both conditions being extremely rare. However, a MEDLINE search at the time of writing this paper, only revealed the two reports, aforementioned, of synchronous congenital gallbladder agenesis and choledochal cyst. Including our case, all three patients required operative management to resolve their symptoms.^{1 2}

The incidence of gallbladder agenesis is 10–65 per 100 000 in the general population, whereas choledochal cysts occur in about 1 in 100 000 live-births in the Western world. Although there is a wide geographical variation in the reported incidence of choledochal cyst, which ranges from as high as 1:1000 live-births in Asian populations. While there is no gender predominance in any autopsy series, in surgical series, women are three times as likely to have gallbladder agenesis.⁴ As with gallbladder agenesis there is an unexplained preponderance in women for choledochal cyst, with a female:male ratio of 3:1.^{2 5–9}

We present a review of both conditions with an overview of possible common embryological and genetic causes.

Choledochal cyst

A choledochal cyst is a dilation of part or all of the bile ducts. In 1977, Todani *et al* classified choledochal cysts into five categories as below. Recent classifications have included further subtypes within these groups. Type I is fusiform or saccular with 50–80% incidence. Type II has a diverticulum of bile duct 2% incidence. Type III is a choledochocoele with a 3% incidence. Type IV has intra and extrahepatic cysts of biliary tree with a 15–35% incidence. Type V has intrahepatic cysts of biliary tree (Caroli's disease) with a 20% incidence.³

Several theories have been put forward to explain the formation of choledochal cysts either acquired after birth or genetic. Bearing in mind women's preponderance for the disease one theory suggests either an X linked dominant trait or an autosomal dominant trait with a relatively low penetrance in men. One possible mechanism for acquiring choledochal cysts is the long common channel theory, which focuses on the abnormal pancreaticobiliary duct junction as the primary defect. This leads to progressive proximal dilation of the biliary tree due to a combination of increased pressure, pancreatic fluid reflux with enzyme activation, inflammation and infection. Abnormal pancreaticobiliary duct junction is defined as the confluence of the bile duct and pancreatic duct outside the sphincter of Oddi creating a long common channel that ranges in length from 10 to 45 mm.^{10 11}

Choledochal cysts, like gallbladder agenesis, have been associated with other anomalies in and outside the pancreaticobiliary tree. The pancreaticobiliary anomalies include multiseptate gallbladder, pancreatic arteriovenous malformation, heterotopic pancreas, pancreas divisum, pancreatic aplasia and congenital absence of portal vein. The gastrointestinal associations reported are colonic atresia, duodenal atresia, imperforate anus and familial adenomatous polyposis. Cardiac anomalies such as ventricular septal defect and aortic aplasia are also known.¹²

Gallbladder agenesis

Gallbladder agenesis is a rare congenital abnormality and was first described by Lemery in 1701.⁶ The clinical importance of gallbladder agenesis lies in clinical uncertainty and the risks it

poses if the diagnosis is not entertained. The absence of gallbladder on abdominal ultrasound, which is the standard initial imaging investigation, clinches the diagnosis. However, it is important to recognise that not all reports of non-visualisation of gallbladders imply a diagnosis of gall bladder agenesis. Though ultrasound examination has a high sensitivity and specificity for gallbladder pathology, it is operator dependant and other variables such as a contracted gallbladder, the body habitus and bowel gas affect the performance characteristics of diagnostic ultrasound. In this context appropriate use of additional investigative modalities such as CT scan, MRCP, endoscopic ultrasound, ERCP and HIDA scan, will often provide the anatomical information necessary to make a preoperative diagnosis and help avoid unwarranted surgery. Preoperative diagnosis is not always achieved and those who undergo surgery may suffer morbidity from the exploration. In patients diagnosed intraoperatively, a thorough search for all potential ectopic sites for the gallbladder such as intrahepatic, left sided, falciform ligament, between the leaves of the lesser omentum, retrohepatic, retroperitoneal, retroduodenal and retropancreatic areas, should be made, if this could be done safely, before accepting a diagnosis of gallbladder agenesis.^{7 13}

Up to 50% of patients with gallbladder agenesis present with non-specific abdominal symptoms, others may never have symptoms or present during childhood, often with additional malformations. While it is estimated that 25–50% of patients with gallbladder agenesis may develop choledocholithiasis.^{4 5 8 13 14}

Gallbladder agenesis occurs as an isolated feature, in two-thirds of diagnosed patients. In one-third of patients, it occurs in association with additional malformations, which fall into one of two broad patterns: one subgroup have atresia of the bile ducts, and the other have normal bile ducts but manifest distant multiple congenital anomalies (12–21%). Gallbladder agenesis has been reported to be associated with many other gastrointestinal, skeletal, cardiovascular and genitourinary malformations, such as ventricular septal defect, imperforate anus, duodenal atresia, malrotation of the gut, pancreas divisum, hypoplasia of the right hepatic lobe, duplication cysts of the hepatic flexure, renal agenesis, undescended testes and syndactyly. A possible link has also been demonstrated with trisomy 22, thyroid isthmus agenesis and gallbladder agenesis.^{15 16}

Hepatobiliary embryology and the pathogenesis of gallbladder agenesis and choledochal cysts

At week 3 or 4 of gestation the hepatobiliary system or liver bud appears as an outgrowth of endodermal epithelium distal to the junction of the foregut and midgut. This hepatic diverticulum or outpouching from the ventral surface of the primitive gastrointestinal tract, then sprouts into two distinct entities; the hepatic primordium and the primordium of the bile ducts and gallbladder. From the latter, the primitive gallbladder and cystic duct arise as a bud. This gallbladder bud starts to develop attached to the common bile duct. In the seventh week, luminal development or canalisation is evident within the biliary tree, via vacuolisation.

Agenesis of the gallbladder results due to failure of the gallbladder bud to develop or proliferate or there may be a failure to canalise. Other gallbladder pathologies in embryonic development, including choledochal cysts may be due to failure of the gallbladder bud to form off from the common bile duct such as ectopic gallbladders or abnormalities may occur during elongation or canalisation.^{4 8 17–19}

Choledochal cysts may form by two possible mechanisms. First, the embryological over proliferation theory involving over

proliferation of the gallbladder buds and subsequent vacuolisation.¹⁰ Second, the aganglionosis theory where there is focal aganglionosis of the distal bile duct leading to proximal cystic dilation.¹¹ However, there is no single theory which could satisfactorily explain all the types of cysts.

Gallbladder agenesis has been noted to occur in familial clusters suggesting a genetic predisposition.¹⁹ Recent research by Yamashita *et al* showed that Lgr4 (leucine-rich repeat-containing G protein-coupled receptor 4) gene trapped mice demonstrated gallbladder agenesis during gestation. These mice developed without any other abnormality to the hepatic primordium or pancreatic buds, with normal common and intrahepatic bile ducts. Therefore, only the gallbladder and cystic duct were absent, apparently failing to elongate or proliferate without the Lgr4 gene.²⁰

Other relevant human genetic causes of hepatobiliary abnormalities

While the mutation in the APC (adenomatous polyposis coli) gene responsible for familial adenomatous polyposis is known to cause decreased cell–cell adherence in the biliary epithelium, which may theoretically result in dilatation of the bile ducts, no definite unifying genetic link has so far been identified which could explain the association of other anomalies often seen with choledochal cysts.²¹

Alagille syndrome is an autosomal dominant condition, caused by a mutation in the JAG 1 (jagged 1) gene. It results in abnormalities of the bile ducts among other abnormalities. It is possible that a part of the role of this gene may contribute to both gallbladder agenesis and choledochal cysts, however there is no supporting evidence for this at the present time.²²

A recent case series suggests that an autosomal recessive trait may cause a hereditary syndrome that causes gallbladder agenesis and biliary atresia, among numerous other abnormalities. However, no specific genetic mutations have yet been identified, although mutations in the HNF6 (hepatocyte nuclear factor 6) gene have been shown to cause biliary abnormalities.²³

The synchronous existence of biliary atresia and choledochal cyst has been identified in antenatal screening. This perhaps suggests that it may be genetically and embryologically sustainable to suffer both a dilatation of one part of the biliary system while a loss or reduction occurs in another part.²⁴

Learning points

- ▶ The combination of gallbladder agenesis and a choledochal cyst is extremely rare.
- ▶ It is important to remember that in the presence of either gallbladder agenesis or a choledochal cyst, other abnormalities may also be present.
- ▶ MR cholangiopancreatography imaging provided the diagnosis in our case.
- ▶ Operative management was required in each case previously reported and in our case the choledochal cyst was excised and hepaticojejunostomy was performed.
- ▶ No single or multiple genetic cause has been identified for either gallbladder agenesis or choledochal cysts, in humans, at the time of publication.

Competing interests None.

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