

# Regression of Antenatally Diagnosed Localized Caroli's Disease

By Ioana Bratu, Jean-Martin Laberge, Samir Khalifé, and Ana Sinsky  
Montreal, Quebec

The authors report on an infant who had a multiloculated cystic lesion located in segment IV of the liver, consistent with Caroli's disease diagnosed, by routine prenatal ultrasound at 25 weeks' gestation, and confirmed by hepatobiliary HIDA scan and computed tomography soon after birth. Because there was no sign of biliary obstruction, the patient was observed initially, with gradual regression of the cysts noted by serial sonograms. Caroli's disease in older children and adults often is associated with recurrent cholangitis and

cirrhosis, mandating resection when the disease is unilobar. However, the natural history of Caroli's disease diagnosed in utero is unclear, and a period of observation appears warranted in the asymptomatic patient.

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INDEX WORDS: Caroli's disease, antenatal diagnosis, choledochal cyst, fetal, liver cyst.

**C**AROLI'S DISEASE, as initially described by Caroli in 1958, consists of congenital cystic dilations of the intrahepatic bile ducts that communicate with the biliary system<sup>1</sup>; it also corresponds to the type V choledochal cyst as classified by Todani.<sup>2</sup> Caroli's disease may be diffuse or unilobar, and its extent determines treatment. Although Caroli's disease usually is diagnosed in early adulthood, there have been at least 22 cases of antenatally diagnosed choledochal cysts, most of them being type I.<sup>3-5</sup> To our knowledge, there has only been 1 case reported of antenatally diagnosed Caroli's disease at 28 weeks' gestation.<sup>3</sup> We report a case of localized Caroli's disease diagnosed at 25 weeks' gestation that increased in size until birth and then gradually regressed postnatally.

## CASE REPORT

At 17 weeks into her pregnancy, a 32-year-old primigravida of Portuguese origin, with no significant family history, had 1 episode of mild, transient bleeding per vagina, upon which ultrasound scan showed a normal fetus and a small separation of the membranes. The mother was advised to rest, and no further antenatal issues arose until the 25th week of gestation when on routine follow-up obstetric ultrasound, a right biloculated cyst anterior to the gallbladder was observed measuring 1.2 × 2.7 × 1.5 cm. It was thought to be either a choledochal cyst or perhaps even a mesenteric cyst. Otherwise, the rest of the fetal ultrasound examination findings were normal, most notably, the kidneys were normal. The ultrasound was repeated at 28 weeks, and the same cyst was found in same location, with stable dimensions at 1.4 × 2.1 × 1.7 cm (Fig 1). A fetal echocardiogram was normal. Then,

the right intraabdominal biloculated cyst began to grow in size as shown by ultrasound scan at 32 and 37 weeks' gestation to be 1.5 × 3.0 × 2.5 cm, and 1.9 × 3.8 × 2.8 cm, respectively. At 40 weeks' gestation, the cystic structure had further grown to 2.8 × 3.4 × 3.4 cm, and was observed to have 4 lobulations (Fig 2). No other fetal abnormalities were noted except for mildly increased amniotic fluid. At 41 weeks and 4 days of gestation, labor was induced, and a healthy-looking baby girl was delivered with a birth weight of 3,790 g, and Apgar scores of 9 at 1 minute, 9 at 5 minutes. The neonatal physical examination findings were within normal: there was no jaundice, the abdomen was soft, and no abdominal masses were palpated. Breast feeding was started soon after birth without any problems. On the second day of life, the baby was noticed to be jaundiced but was otherwise afebrile and doing well. The total bilirubin level then was 270 μmol/L (normal, 5 to 100 μmol/L), with a direct bilirubin level of 10.7 μmol/L (normal, 0 to 25 μmol/L), AST was 33 U/L (normal, 0 to 100 U/L), ALT was 16 U/L (normal, 0 to 50 U/L), and GGT was 165 U/L (normal, 34 to 263 U/L). The mother's blood type is O positive, and the baby's is B positive. The baby's direct Coombs test was positive, and indirect Coombs versus "O" cells was negative, whereas the indirect Coombs versus "B" cells was positive. This was consistent with hemolysis from maternal-fetal ABO incompatibility. Subsequently, the baby had 2 days of phototherapy for the indirect bilirubinemia. She did well, and was discharged home on the fourth day of life with outpatient investigations of the intrahepatic cyst at our institution. On the day of discharge, an ultrasound scan confirmed the presence of a 3.6 × 3.4 × 4.5-cm multiloculated intrahepatic cyst within segment IV, with normal liver parenchyma, extrahepatic bile ducts, pancreas, and kidneys (Fig 3). At day 9 of age, a hepatobiliary HIDA scan confirmed that the cystic structure detected on ultrasound was compatible with Caroli's disease because there was communication with the biliary tree, with normal uptake and excretion, and with no evidence of obstruction in the bile flow (Fig 4). The following day, a computed tomography (CT) scan of the abdomen and pelvis with intravenous contrast showed multiple cystic lesions in segment IV, and possibly crossing into segment VIII of the liver (Fig 5). The largest cyst measured 2.4 × 1.8 cm and had a low density (3 to 7 Hounsfield Units). The gallbladder, and the rest of the examination findings were normal. A liver resection was entertained at the time, but because the baby was asymptomatic, it was decided to observe her closely. At follow-up at 3.5 months, and 1 year of age, the baby was growing well, was asymptomatic, and had normal physical examination findings, and normal bilirubin and liver enzyme levels. An ultrasound scan at 3.5 months and 1 year of age showed that the liver cysts, with a partially echogenic wall posteriorly and located just anterior to the portal vein

From the Divisions of Pediatric Surgery, Pediatric Radiology, and Obstetrics, The Montreal Children's Hospital and The Royal Victoria Hospital, McGill University, Montreal, Quebec, Canada.

Address reprint requests to Jean-Martin Laberge, MD, Division of Pediatric General Surgery, The Montreal Children's Hospital, 2300 Tupper St, Suite C1129, Montreal, Quebec, Canada H3H-1P3.

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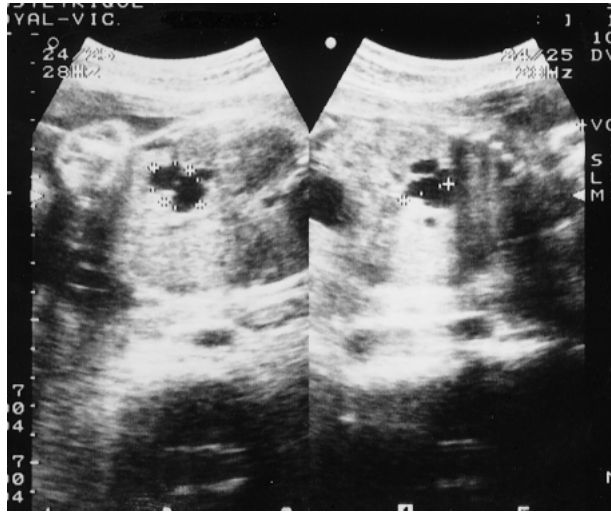


Fig 1. Ultrasound at 28 weeks' gestation shows a loculated cyst in the area of the liver (left, transverse; right, longitudinal, with acoustic shadowing from the ribs seen to the far right). The white markers outline the cysts, measuring  $1.4 \times 2.1 \times 1.7$  cm overall.

bifurcation, had decreased in size to  $1.5 \times 0.9 \times 1.6$  cm, and then  $1.0 \times 1.0 \times 0.5$  cm, respectively (Fig 6). There is no clinical or radiologic evidence of congenital hepatic fibrosis. The plan is further observation and follow-up a year later with repeat liver function tests and abdominal ultrasound scan, unless jaundice develops.

#### DISCUSSION

Caroli's disease is a rare congenital disorder, with an estimated incidence of 1 in 1,000,000,<sup>6</sup> characterized by cystic dilatations of the intrahepatic bile ducts that are in communication with the biliary tree. There are 2 forms of Caroli's disease: the pure type, as originally described by Caroli,<sup>1</sup> that occurs alone is called *Caroli's disease* and is observed in 13% of cases.<sup>7</sup> The more common type is associated with congenital hepatic fibrosis and also may

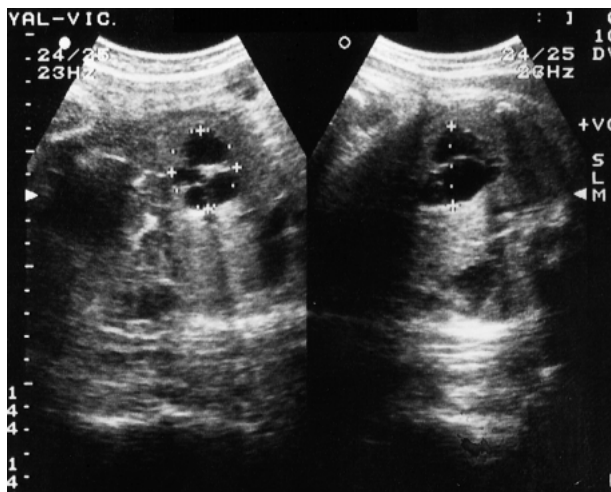


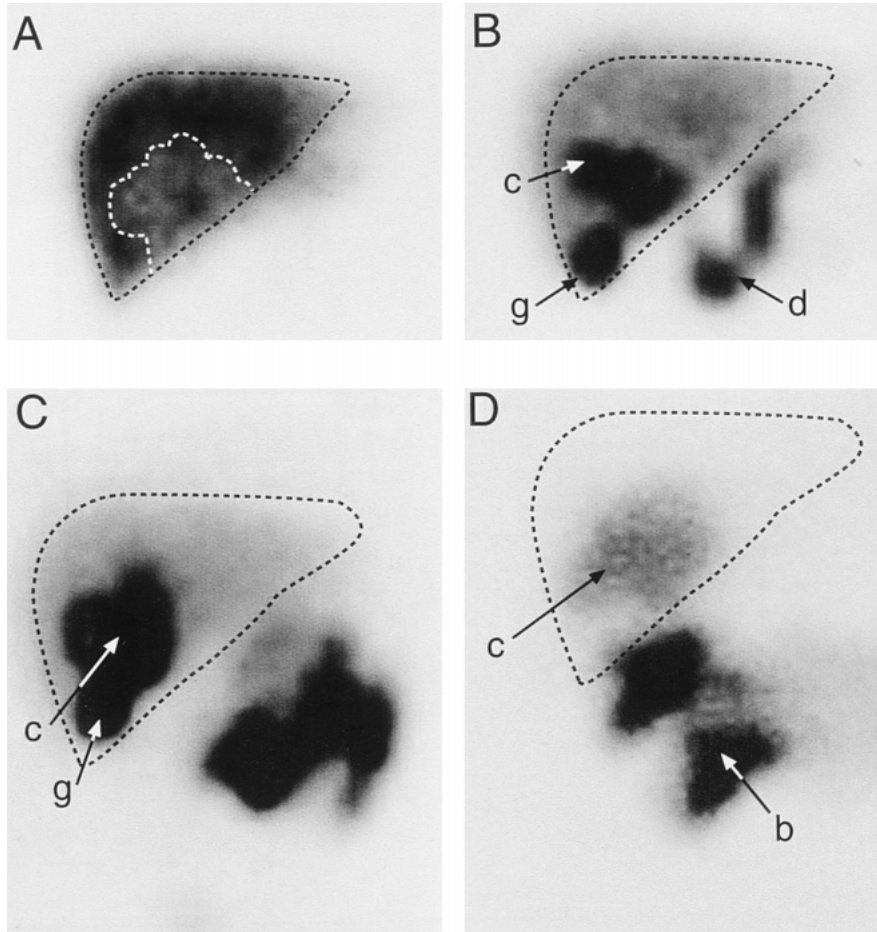
Fig 2. Ultrasound scan at 40 weeks' gestation. The multicystic area now measures  $2.8 \times 3.4 \times 3.4$  cm.



Fig 3. Ultrasound at 4 days of age. This longitudinal view shows several intrahepatic cysts, measuring  $3.6 \times 3.4 \times 4.5$  cm overall, just anterior to the portal vein bifurcation (v).

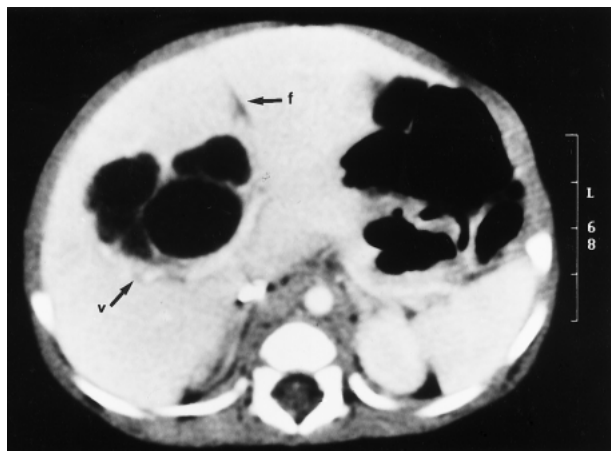
be called *Caroli's syndrome*.<sup>7</sup> However, this terminology is not widely used, and we will simply refer to it as *Caroli's disease with congenital hepatic fibrosis*. They also are labelled under the Todani choledochal cyst classification as type V, or as type IVA if they are associated with an extrahepatic choledochal cyst as they are in 21% of cases.<sup>2,7</sup> The cystic changes are diffuse in 60% to 80% of cases, but may be localized to 1 lobe or segment of the liver, of which the left side is more common.<sup>8</sup> Monobar disease is most likely not to be associated with congenital hepatic fibrosis.<sup>9</sup> The mode of inheritance is debated<sup>10</sup>: some believe that isolated Caroli's disease is not hereditary and not associated with renal anomalies, whereas Caroli's disease with congenital hepatic fibrosis either may be autosomal recessive and associated with the autosomal recessive polycystic kidney disease or it may have autosomal dominant inheritance.<sup>11</sup> The pathogenesis of Caroli's disease is thought to involve arrest of remodelling of the embryonic ductal plate of the larger intrahepatic bile ducts, and is thus part of the ductal plate malformations.<sup>10</sup>

The mean age of onset of symptoms is around 20 years,<sup>11</sup> but can be as early as the neonatal period,<sup>12</sup> especially in cases associated with congenital hepatic fibrosis. Cholangitis is the main presenting symptom in 64% of patients; portal hypertension in 22%; recurrent abdominal pain in the right upper quadrant in 18%; and pyelitis, systemic hypertension, and hematuria in 2%.<sup>11</sup> However, some, especially those without congenital hepatic fibrosis, may remain asymptomatic well into their 70s.<sup>8</sup> Liver function results may be normal or show a cholestatic picture. Age at diagnosis usually is 6 years after symptoms have appeared,<sup>11</sup> but is quite variable,



**Fig 4.** HIDA scan at 9 days of age. (A) During uptake, there is a central filling defect outlined by the white dots. (B) In the early phase of excretion, the cysts (c) fill first, followed by the gallbladder (g), and the duodenum (d). (C) At 1 hour, most of the activity is in the small bowel, but there is stasis in the cysts (c), and persistent activity in the gallbladder (g). (D) At 2 hours, there is further emptying of the cysts (c). Most of the radioactivity has disappeared from the liver which is outlined by the black dots. b, bowel loops.

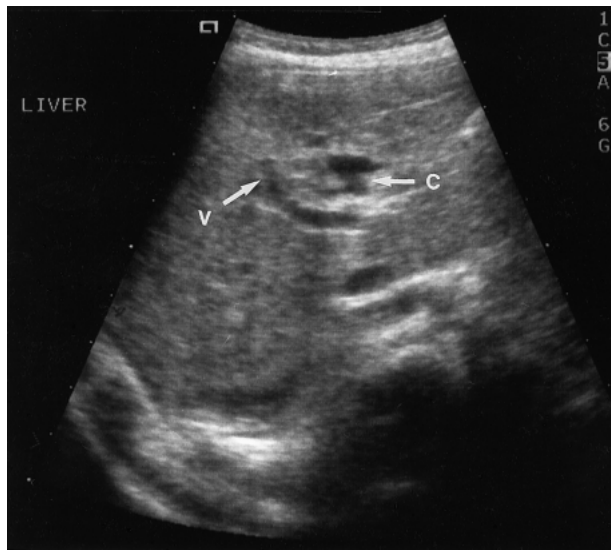
with 1 case being diagnosed prenatally at 28 weeks' gestation.<sup>3</sup> Diagnosis not only relies on detection of intrahepatic anechoic cystic areas on ultrasound examination, or water dense cysts on CT scanning, but also on



**Fig 5.** Computed tomography scan with intravenous contrast at 10 days of age shows multiple liver cysts located centrally in segment IV, and possibly segment VIII (f, falciform ligament), just anterior to the portal vein bifurcation (v). The density of the cysts is close to that of water, measured at 3 to 7 Hounsfield Units.

showing that the cysts are in communication with the biliary tree to distinguish Caroli's disease from polycystic liver disease, simple liver cysts, lymphangioma, or multiple liver abscesses, that are noncommunicating. This usually is and most easily done with a hepatobiliary HIDA scan, but also can be done with direct imaging of the biliary tract with endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC). It is important to note that several investigators believe ERCP or PTC should not be done in asymptomatic patients with Caroli's disease because there is an increased risk of biliary sepsis.<sup>13</sup> A new and noninvasive method available to image the biliary system is magnetic resonance imaging.<sup>14</sup>

Obstetric ultrasound has permitted the antenatal detection of several disorders involving the biliary tree. Cystic dilations of the biliary system diagnosed antenatally are mainly type I choledochal cysts, and some turn out to be biliary atresia.<sup>5</sup> To differentiate between the 2, it was observed that the size of the choledochal cyst increased in size over gestation, whereas the size of the dilated biliary region associated with the congenital biliary atresia remained the same.<sup>5</sup> Only 1 case of antenatal Caroli's



**Fig 6.** Ultrasound scan at 1 year of age. This longitudinal section shows a dramatic regression of the cysts (c), the area now measuring  $1 \times 1 \times 0.5$  cm, just anterior to the portal vein bifurcation (v).

disease was reported previously.<sup>3</sup> The differential diagnosis of a cystic malformation in the right upper quadrant of the abdomen is extensive but may include duodenal atresia, duodenal duplication, and mesenteric, ovarian, omental, pancreatic, or renal cysts.<sup>15</sup>

There are 3 situations that require special attention in terms of management: monolobar Caroli's, diffuse Caroli's, and antenatally diagnosed Caroli's. For monolobar Caroli's disease, hepatic resection is the preferred treatment because this gives complete and long-lasting reso-

lution of symptoms, and there have been no reports of carcinoma arising in the remaining liver after resection.<sup>9</sup> The diffuse form of Caroli's has several treatment options.<sup>8</sup> Cholangitis is treated with antibiotics and drainage of the biliary tract. In some instances, ursodeoxycholic acid has been used to dissolve intrahepatic stones. ERCP with sphincterotomy, stone extraction, and then stenting, external biliary drainage, and internal biliary drainage operations have been used to remove the biliary obstruction, even though the latter often results in incomplete drainage of the biliary tree and its high morbidity with recurrent cholangitis. When complications such as biliary cirrhosis, severe portal hypertension, or cholangiocarcinoma arise, liver transplant then is the only option.<sup>13</sup> The youngest patient with cholangiocarcinoma in Caroli's disease was 32 years old,<sup>16</sup> whereas the youngest reported patient with a choledochal cyst to develop cholangiocarcinoma was 12 years old.<sup>17</sup> The treatment of prenatally diagnosed Caroli's disease has so far been conservative. There has been only one case of Caroli's disease diagnosed antenatally. That patient remained asymptomatic at 3 years, but the size of the intrahepatic cyst during follow-up was not mentioned.<sup>3</sup> In our patient, the localized intrahepatic cysts actually are regressing. We believe that for now, as long as the patient remains asymptomatic and undergoes regular follow-up with liver function tests and imaging studies, then there is no cause for any intervention. Should cholangitis develop, especially if combined with an increase in the size of the cysts, surgical resection of the diseased liver area would be indicated.

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