

A case report of intrahepatic bile duct confluence anomalies in VACTERL syndrome

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Abstract

Rationale: The clinical manifestations of VACTERL association include vertebral anomalies, anal atresia, congenital heart diseases, tracheoesophageal fistula, renal dysplasia, and limb abnormalities. The association of intrahepatic anomalies and VACTERL syndrome is a rare coincidence. VACTER syndrome and intrahepatic bile drainage anomalies might be genetically related.

Patient concerns: A 12-year-old girl presented with episodic colicky abdominal pain, nausea, and vomiting for several years. The individual episodes resolved spontaneously within a few days. She had a history of VACTERL syndrome, including a butterfly shape of the L3 vertebra, anal atresia, and an atrial septal defect.

Diagnoses: On laboratory findings, abnormal liver function tests included elevated total bilirubin, alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyltransferase. There was no significant abnormal finding in hepatobiliary system sonography except mild gallbladder wall thickening. We performed magnetic resonance cholangiopancreatography and demonstrated an abnormal intrahepatic bile duct confluence, which showed 3 bile ducts draining directly into the neck of the gallbladder.

Intervention: Her symptoms related to bile reflux during gallbladder contraction. Cholecystectomy with choledochojejunostomy was undertaken because segments of the bile drainage were intertwined.

Outcomes: After surgery, her symptoms decreased, but abdominal discomfort remained due to uncorrected left intrahepatic anomalies.

Lessons: Although hepatobiliary anomalies are not included in VACTERL association diagnostic criteria, detailed hepatobiliary work up is needed when gastrointestinal symptoms are present in VACTERL association patients.

Abbreviations: ALT = alanine aminotransferase, ASD = atrial septal defect, AST = aspartate aminotransferase, GGT = gamma-glutamyltransferase, MRCP = magnetic resonance cholangiopancreatography.

Keywords: gallbladder, intrahepatic bile duct, VACTERL syndrome

1. Introduction

The clinical manifestations of VACTERL association include vertebral anomalies, anal atresia, congenital heart diseases, tracheoesophageal fistula, renal dysplasia, and limb abnormalities, and a VACTERL diagnosis requires the presence of at least 3 of these symptoms.^[1,2] VACTERL incidence is estimated at approximately 1 in 10,000 to 40,000 live-born infants.^[1] Some VACTERL

malformations make their appearance early in the embryological period (23–30 days postconception), while others occur later in embryogenesis.^[1,3] In addition to these core component features, patients may also have other congenital anomalies including anorectal gastrointestinal anomalies in addition to the anal atresia tracheoesophageal anomalies, but bile duct anomalies with VACTERL association have not yet been reported.^[2]

The anatomical variability of the biliary system has been well described; however, most cases of drain variability involve portions of the right liver to join the main biliary tract, rather than the left liver and gallbladder.^[4–6] Direct drainage of the segment 3 bile duct into the neck of the gallbladder is also seldom reported.

The association of intrahepatic anomalies and VACTERL syndrome is a rare coincidence. Here, we report a case of VACTERL association with recurrent cholangitis due to anomalies of bile duct confluence.

2. Case report

A 12-year-old girl presented with episodic colicky abdominal pain, nausea, and vomiting for several years. The individual episodes resolved spontaneously within a few days. She had been diagnosed with VACTERL syndrome at birth based on the following symptoms; imperforate anus, atrial septal defect (ASD), and butterfly vertebra at lumbar 3. She underwent surgical correction of her imperforate anus (ectopic anus onto) at 6 months of age and also had ASD and patent ductus arteriosus closure corrective surgery at 6 years of age.

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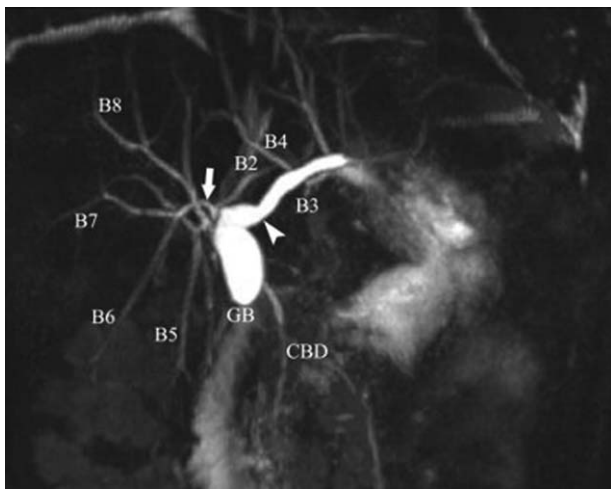


Figure 1. Magnetic resonance (MR) cholangiography. Thick slab T2-weighted MR cholangiography image shows complex anatomy variance of the biliary tree. A dilated segment 3 bile duct (B3, arrow head) drains into the neck of the gallbladder. In addition, the bile duct of the right posterior segment (arrow, conjoined B6 and B7) drains into the proximal portion of the segment 2 bile duct (B2). The right anterior segment of the bile duct (conjoined B8 and B5) and segment 2 bile duct (B2) join to form the common hepatic duct.

Her abdominal examination revealed normoactive bowel sounds; however, we further investigated mild right upper quadrant and epigastric tenderness. Laboratory findings indicated elevated liver enzymes, including gamma-glutamyltransferase (GGT), 586 IU/L; alanine aminotransferase (ALT), 119 IU/L; aspartate aminotransferase (AST), 19 IU/L; and total bilirubin 0.42 mg/dL. No specific findings were identified on abdominal x-ray, and no significant findings in the hepatobiliary system, except for mild gallbladder wall thickening, were identified on sonography. Decreased gallbladder ejection fraction (66.9%) was detected on a gallbladder scan. Differential diagnostic work-up was performed to rule out viral hepatitis, metabolic disease, and autoimmune disease, which were all found to be negative. Conservative treatment, including nothing by mouth, ursodeoxycholic acid, and antibiotics, was performed, and her symptoms

were resolved within 3 to 7 days. She was discharged a few days later; however, episodic abdominal pain developed frequently during a 6-month follow-up, and GGT level was intermittently elevated up to 700 IU/L.

Six months later, she was admitted again due to severe colicky abdominal pain with GGT at 706 IU/L, ALT at 733 IU/L, AST at 348 IU/L, and total bilirubin at 1.48 mg/dL. Magnetic resonance cholangiopancreatography (MRCP) was conducted and demonstrated an abnormal intrahepatic bile duct confluence. Segment 3,4 intrahepatic ducts were found to drain directly into the gallbladder, and the segment 6,7 intrahepatic ducts were draining into the left intrahepatic duct (Figs. 1 and 2).

Cholecystectomy with choledochojejunostomy was conducted for symptom relief due to several cholangitis relapses caused by intrahepatic duct confluence anomalies. After palliative operation, the frequency and intensity of abdominal pain were improved, and GGT, AST, and ALT levels were decreased relative to before surgery. However, after surgery, modest abdominal discomfort developed intermittently, most likely because the left hepatic duct anomalies were not corrected. Two years later, she experienced *Klebsiella pneumoniae* bacteremia due to cholangitis, and recovered from 2 weeks antibiotics treatment. At 3 years follow-up from surgery, we confirmed her GGT and AST/ALT was normalized, and her symptom was markedly decreased. This case study has been approved by the Institutional Review Board (IRB) of Korea University Ansan Hospital (IRB no: 2018AS0081). In addition, informed consent was obtained from the patient.

3. Discussion

The VACTERL syndrome includes gastrointestinal problems including anal atresia and tracheoesophageal fistula with esophageal atresia.^[2] Hepatobiliary problems are not included in diagnostic criteria because the coincidence of hepatobiliary issues with VACTERL syndrome is not common. This is the first case of intrahepatic bile duct confluence anomalies with VACTERL syndrome.

In cases of repeated undiagnosed abdominal pain with elevated liver enzyme levels without definite abdominal abnormalities on ultrasonography, physicians should consider further diagnostic

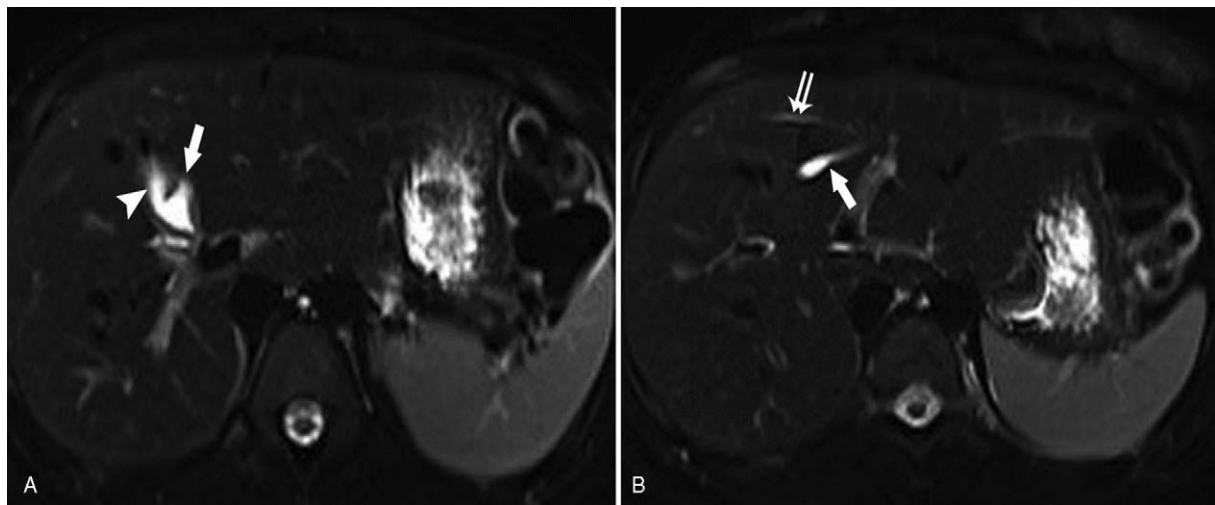


Figure 2. Fat saturated T2-weighted axial Magnetic resonance images show a dilated left intrahepatic bile duct (arrow) that drains into the gallbladder neck (arrow head, A). A dilated segment 4 bile duct (double arrow) conjoins to the segment 3 bile duct (arrow, B).

evaluation to seek definite diagnosis or etiology. In this 12-year-old patient, her abdominal pain relapsed most likely due to hepatobiliary problems, which we identified with MRCP. It is important to recognize that recurrent abdominal pain and abnormal lab findings indicate hepatobiliary problems.

In this case, anomalous drainage of the segmental biliary ducts led to difficulties in biliary system drainage, causing recurrent cholangitis. In development of the human embryo, the hepatic diverticulum appears in the ventral wall of the primitive midgut early in the 4th week of intrauterine life.^[7] This small diverticulum is the anlage of the liver, extrahepatic biliary ducts, gallbladder, and ventral pancreas. By the 5th week, all elements of the biliary tree are recognizable.

The terminal bile ducts grow out into the mesenchymal tissue of the septum transversum, which will produce the fibrous architecture of the liver, and the development of an intrahepatic duct system is completed by the 10th week.^[7]

The anatomical structures involved in VACTERL association are uniformly absent prior to the 6th week (23 days) postconception and are more or less fully formed by the 8th week (56 days) postconception.^[3] The overlapping time of the embryological hepatobiliary system and affected VACTERL association suggest the possibility of a relationship of VACTERL syndrome and intrahepatic duct anomalies.

In addition, exposure to teratogenic materials could disturb the molecular pathways or induce mutations of single genes and mitochondrial changes that are critical for VACTERL association anomalies and hepatic confluence anomalies.^[1,8] Additionally, resulting malformations may involve a vicious cycle in which mitochondrial dysfunction begets oxidative stress, causing damage to the same respiratory chain-deficient cells that show increased vulnerability to the same oxidative stress for which they are responsible. Oxidative stress may cause damage to many organs, including the liver system; therefore, it is possible that mitochondrial dysfunction affects VACTERL association with hepatobiliary system anomalies.^[8]

Atypical branching patterns of both the right and left hepatic ducts were found in 14% and 8% of patients, respectively, but direct draining of the segment 3 bile duct into the neck of the gallbladder is not rare.^[5,6,9] Also, some syndromes are related to intrahepatic duct paucity, but intrahepatic confluence anomalies are not common.^[10] However, the case of intrahepatic bile duct anomaly and VACTERL syndrome we present here is quite rare, and this is the first report of this new syndrome.

In conclusion, although hepatobiliary anomalies are not included in VACTERL association diagnostic criteria, detailed physical examination is needed when gastrointestinal symptoms are present in VACTERL association patients. Therefore, further study about the etiology of VACTERL syndrome is needed.

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