

# Caroli Disease Associated With Vein of Galen Malformation in a Male Child

## abstract

We report the first case of a male child with both Caroli disease and vein of Galen malformation. The neonate presented to our department with congestive heart failure as a result of the intracranial arteriovenous high-flow shunt. Over time, several endovascular embolizations led to a complete angiographic occlusion of the shunt. Additionally, the diagnosis of Caroli disease was made at the age of 2 months. He developed choledocholithiasis necessitating endoscopic sphincterotomy and stone extraction. As a prolonged medical treatment he received ursodeoxycholic acid and antibiotics. A coincidence of Caroli disease and vein of Galen malformation has not yet been described. Both diseases are very rare, leading to the question of whether there is a link in the pathogenesis. Based on the few previously described underlying mechanisms, we develop hypotheses about the relationship between both rare diseases. We consider overexpression of vascular endothelial growth factor and its receptors as a possible common molecular mechanism in their pathogenesis. We also highlight the critical role of increased expression of the Notch ligand Jagged 1 both in the development of cerebral arteriovenous malformations in general and in the formation of dilated intrahepatic bile ducts (eg, in Caroli disease). *Pediatrics* 2014;134:e284–e288

**AUTHORS:** Dominik Grieb, MD,<sup>a</sup> Axel Feldkamp, MD,<sup>b</sup> Thomas Lang, MD,<sup>c</sup> Michael Melter, MD,<sup>d</sup> Christian Stroszczynski, MD,<sup>e</sup> Friedhelm Brassel, MD,<sup>a</sup> and Dan Meila, MD<sup>a,f</sup>

Departments of <sup>a</sup>Radiology, and <sup>b</sup>Neuroradiology and <sup>b</sup>Pediatrics, Klinikum Duisburg–Sana Kliniken, Duisburg, Germany; <sup>c</sup>Department of Pediatrics, Hospital Barmherzige Brüder Regensburg, Regensburg, Germany; Departments of <sup>d</sup>Pediatrics, and <sup>e</sup>Radiology, University Medical Center Regensburg, Regensburg, Germany; and <sup>f</sup>Department of Diagnostic and Interventional Neuroradiology, Medical School Hannover, Hannover, Germany

### KEY WORDS

vein of Galen malformation, Caroli disease, intracranial aneurysms, VEGF

### ABBREVIATIONS

AVM—arteriovenous malformation  
VEGF—vascular endothelial growth factor  
VEGFR—vascular endothelial growth factor receptor  
VGM—vein of Galen malformation

Dr Grieb designed the study and drafted the initial manuscript; Dr Feldkamp coordinated data collection and reviewed and revised the manuscript; Dr Lang and Profs Melter and Stroszczynski reviewed and revised the manuscript; Prof Brassel supervised data collection and critically reviewed the manuscript; Dr Meila conceptualized the study and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Address correspondence to Dan Meila, MD, Department of Radiology and Neuroradiology, Klinikum Duisburg–Sana Kliniken, Zu den Rehwiesen 9, D-47055 Duisburg, Germany. E-mail: dan.meila@sana.de, dmeila@yahoo.de

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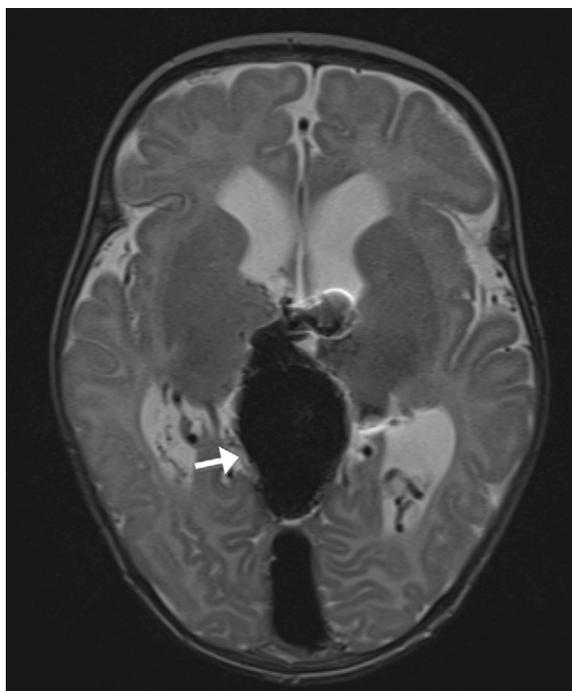
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Caroli disease is a congenital disorder characterized by intrahepatic bile duct ectasia, often accompanied by congenital hepatic fibrosis.<sup>1</sup> Bacterial cholangitis is the dominant complication in the clinical course and the main cause of morbidity and mortality.<sup>2</sup> Vein of Galen malformation (VGM) is a severe neurovascular disease in childhood that is characterized by arteriovenous shunting between numerous choroidal arteries and the precursor of the vein of Galen, the median prosencephalic vein of Markowski.<sup>3</sup> Untreated children have a very bad prognosis. Neonates with high-flow shunts often die of consequences of congestive heart failure or multiorgan failure.<sup>4</sup> Here, we report the first case of Caroli disease associated with a VGM in a male child.

## CASE REPORT

The male neonate was delivered by cesarean section at a gestational age of 41 weeks. His birth weight was 4530 g, his length was 58.0 cm, his head circumference was 38.0 cm, and his Apgar score was 8/10/10. This was the mother's first pregnancy. There was no history of biliary disease or arteriovenous malformation (AVM) in the patient's family. On the third day of his life the infant developed progressive dyspnea and had a significant drop in oxygen saturation. Plain chest radiography showed cardiomegaly, and a systolic bruit was detected (Levine 3/6). Echocardiography revealed pulmonary hypertension and a persistent foramen ovale. Head sonography revealed a choroidal type of VGM as the reason for the increasing congestive heart failure. Additional MRI of the head demonstrated a VGM with a huge dilated median prosencephalic vein of Markowski (Fig 1).

Symptoms worsened despite maximum medical treatment with catecholamines. Therefore, the patient was intubated and placed on mechanical ventilation.



**FIGURE 1**

Axial T2-weighted MRI of the VGM showing a huge dilated median prosencephalic vein of Markowski (white arrow).

On the next day the infant was transferred to our department with progressive cardiorespiratory failure. Consequently, emergency endovascular embolization was performed the same day. A combined transvenous and transarterial approach with coiling of high-flow arteriovenous fistulous connections was performed. A notable shunt reduction with a significantly lower level of pulmonary hypertension was achieved.

After a second successful embolization the next day, the patient's cardiorespiratory status had improved remarkably. He was extubated at 15 days of age. However, mild pulmonary hypertension persisted, and the patient underwent continuous medical therapy with 2 diuretics and a cardiac glycoside to achieve additional clinical improvement and cardiac stabilization. At the age of 4 weeks the patient was transferred back in a stable general condition. Over time, several embolizations were necessary and led to

a complete angiographic occlusion of the shunt.

On the last follow-up at the age of 3, the young patient showed an inconspicuous neurologic status and markedly improved cardiovascular status. When the child was admitted to the hospital with acute obstructive cholestasis at the age of 2 months, the mother reported that the child had brownish urine and discolored stools, poor oral intake, and failure to gain weight. The patient was not jaundiced. The liver was not enlarged, and the spleen was not palpable. Laboratory testing revealed an elevated total bilirubin level of 8.0 mg/dL, an elevated direct bilirubin level of 6.6 mg/dL, and elevated levels of aspartate aminotransferase (96 U/L), alanine aminotransferase (59 U/L), and  $\gamma$ -glutamyltransferase (1488 U/L). Inflammatory parameters and levels of lipase and amylase were unremarkable. Ultrasound of the abdomen revealed severe dilatation of the intrahepatic and extrahepatic bile ducts,

finally leading to the diagnosis of Caroli disease. The duct of Wirsung and pancreas were unremarkable.

To prevent biliary infections, prophylactic medical treatment with antibiotics (cephalosporin of the second generation) was administered. Administration of ursodeoxycholic acid (3× per day, 30 mg) led to a slight decrease in total and direct bilirubin levels in a short time. Magnetic resonance cholangiopancreatography was performed at the age of 9 months, demonstrating the affected liver with the dilated intrahepatic bile ducts. Additionally, the magnetic resonance cholangiopancreatography revealed 2 stones in the common bile duct (Fig 2). The patient had no jaundice, abdominal pain, or fever. However, laboratory testing revealed markedly elevated levels of lipase (11 775 U/L) and amylase (3062 U/L) with normal inflammatory parameters. Therefore, endoscopic sphincterotomy and stone extraction were performed. This led to a normalization of lipase and amylase levels. After the endoscopic intervention, the child showed no clinical or laboratory signs of obstructive cholestasis or hepatobiliary infection. Medical treatment

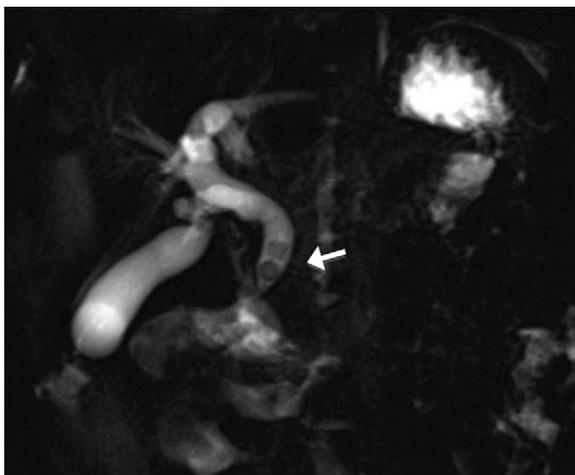
with ursodeoxycholic acid and antibiotics was continued.

## DISCUSSION

Caroli disease and VGM are both rare diseases in childhood. A coincidence of both disorders has not yet been described. Caroli disease is a developmental anomaly characterized by multiple saccular, cystic dilatations of the intrahepatic bile duct and has an incidence of 1 in 1 000 000 births.<sup>5</sup> The illness is often accompanied by varying degrees of portal fibrosis, leading to congenital hepatic fibrosis. The clinical presentation of the disease is dominated by complications of cholangitis, choledocholithiasis, hepatic abscess formation, and portal hypertension.<sup>2</sup> Its clinical progression has varying degrees of severity, and symptoms may appear late in life. Treatment of Caroli disease is limited and depends on the clinical features. Symptomatic patients with biliary infections should undergo aggressive antibiotic therapy to prevent dangerous sepsis. Bile duct dilatation increases the risk of lithiasis, often necessitating endoscopic sphincterotomy and stone extraction.<sup>6</sup> Additionally, ursodeoxycholic acid has

been proved to treat and prevent intrahepatic bile stones.<sup>7</sup> A large number of Caroli disease cases are associated with autosomal recessive polycystic kidney disease. Furthermore, VGM is a rare cerebral choroidal AVM that most often results in congestive heart failure and without medical treatment leads to multiorgan failure in the neonatal period. Untreated children have a very bad prognosis.<sup>3,4</sup> Early endovascular embolization has become the therapy of choice.<sup>8</sup>

Recently, the combined transarterial and transvenous method, called the kissing microcatheter technique, has been reported to have good results and is a safe alternative to the single transarterial or transvenous approach.<sup>9</sup> To date there are few data about associated diseases or malformations. The child described in this report has Caroli disease and VGM. Both diseases are characterized by pathologic variances of vessels or bile ducts, leading to the hypothesis that common features in their pathogenesis might exist. Although the molecular pathogenesis of Caroli disease is not fully understood, it has been proved that ductal plate malformation is a key factor in the formation of dilated intrahepatic bile ducts in Caroli disease. This developmental process takes place at around the eighth week of gestation.<sup>6,10</sup> During the same period, arteriovenous shunting between numerous choroidal arteries and the precursor of the vein of Galen, the median prosencephalic vein of Markowski, begins to develop.<sup>3</sup> Little is known about the underlying molecular mechanisms causing this AVM. Several investigations on cerebral AVMs in general revealed overexpression of the vascular endothelial growth factor (VEGF) and its receptors VEGFR-1 and VEGFR-2 on endothelial cells in patients with cerebral AVMs.<sup>11</sup> VEGF is a signal protein that plays a key



**FIGURE 2**

Coronal view of magnetic resonance cholangiopancreatography, maximum intensity projection, of the liver affected with Caroli disease, demonstrating dilatation of the intrahepatic bile duct. Note choledocholithiasis (white arrow).

role in vasculogenesis and angiogenesis. Its plasma level is also elevated (eg, in patients with intracranial aneurysms).<sup>12</sup> These aneurysms have a significantly higher detection rate in patients with polycystic kidney diseases, which in turn are associated with Caroli disease. Interestingly, cholangiocytes derived from livers affected with Caroli disease have been shown to overexpress VEGF and its receptors. In addition, both a proliferative effect of VEGF on cholangiocyte growth and a paracrine stimulation of the vascular supply of the biliary epithelium are described.<sup>13</sup>

Furthermore, in comparison with cells of normal cerebral vessels, Notch 1 signaling is activated in smooth muscle and endothelial cells of cerebral AVMs. This equally applies to the Notch ligand Jagged 1.<sup>14</sup> Notch signaling is a highly conserved pathway that plays an important role in cell fate specification throughout embryonic development. It is also suggested that activation of Notch 1 and its ligand Jagged 1 in normal vessels induces abnormal angiogenesis, leading to AVM formation.<sup>14</sup> Notch signaling and especially the

interaction with its downstream ligand Jagged 1 are also essential for adequate development of the intrahepatic bile ducts.<sup>15</sup> Mutations of Jagged 1, for example, result in a lack of intrahepatic bile ducts, called Alagille syndrome.<sup>16</sup> In addition, it is assumed that an increased expression of Jagged 1 in periductal and periportal myofibroblasts may lead to the formation of bile duct lesions and dilatation of intrahepatic bile ducts in an animal model of Caroli disease.<sup>17</sup>

These observations might link the molecular pathogenesis of cerebral AVMs such as VGM and Caroli disease. In this regard, it is also conceivable that a common genetic disorder causing pathologic variances of both intracranial vessels and bile ducts exists. A feasible link between VGM and an endoglin mutation, originally identified in patients with hereditary hemorrhagic telangiectasia, was reported recently.<sup>18</sup> Other studies focusing on the genetics of VGM describe an anomaly of the *RASA1* gene, which is associated with capillary malformation AVM.<sup>19</sup> Recent investigations of Caroli

disease, on the other hand, showed an *NPHP3* mutation in a patient presenting with Caroli disease, leading to the assumption that Caroli disease is a ciliopathy.<sup>20</sup> Its association with other ciliopathies, the polycystic kidney diseases, has been established. Polycystic kidney diseases and intracranial aneurysms are also known to be associated. Hence, there is a notable link between Caroli disease and another intracerebral angiopathy, confirming the hypothesis that common molecular or genetic mechanisms provoke pathologic variances in both bile ducts and intracranial vessels. At this time, it remains an open question whether the mentioned genes play a role in both VGM and Caroli disease. Consequently, additional genetic studies are necessary to detect possible common genetic mutations in VGM and Caroli disease. This is the first report of Caroli disease associated with a VGM. We discuss possible links in the pathogenesis of both rare diseases. However, additional research is warranted to gain a better understanding of both diseases.

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