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

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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

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Caroli disease is a congenital disorder characterized by intrahepatic bile duct ectasia, often accompanied by congenital hepatic fibrosis. Bacterial cholangitis is the dominant complication in the clinical course and the main cause of morbidity and mortality. 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. Untreated children have a very bad prognosis. Neonates with high-flow shunts often die of consequences of congestive heart failure or multiorgan failure. 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. 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 γ-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.

FIGURE 1
Axial T2-weighted MRI of the VGM showing a huge dilated median prosencephalic vein of Markowski (white arrow).
finally leading to the diagnosis of Caroli
disease. The duct of Wirsung and pan-
creas were unremarkable.

To prevent biliary infections, pro-
phylactic medical treatment with anti-
biotics (cephalosporin of the second
generation) was administered. Admin-
istration 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 per-
formed at the age of 9 months, dem-
onstrating the affected liver with the
dilated intrahepatic bile ducts. Addi-
tionally, 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 inflamma-
tory parameters. Therefore, endoscopic
sphincterotomy and stone extraction
were performed. This led to a normali-
zation of lipase and amylase levels. After
the endoscopic intervention, the child
showed no clinical or laboratory signs
of obstructive cholestasis or hep-
atobiliary infection. Medical treatment
with ursodeoxycholic acid and anti-
biotics 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 develop-
mental anomaly characterized by
multiple saccular, cystic dilatations of
the intrahepatic bile duct and has an
incidence of 1 in 1 000 000 births. The
illness is often accompanied by varying
degrees of portal fibrosis, leading to
congenital hepatic fibrosis. The clinical
presentation of the disease is domi-
nated by complications of cholangitis,
choledocholithiasis, hepatic abscess
formation, and portal hypertension. 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 under-
go aggressive antibiotic therapy to
prevent dangerous sepsis. Bile duct
dilatation increases the risk of lithia-
sis, often necessitating endoscopic
sphincterotomy and stone extraction.
Additionally, ursodeoxycholic acid has
been proved to treat and prevent
intrahepatic bile stones. A large
number of Caroli disease cases are
associated with autosomal recessive
polycystic kidney disease. Further-
more, VGM is a rare cerebral choroidal
AVM that most often results in con-
gestive heart failure and without
medical treatment leads to multiorgan
failure in the neonatal period. Un-
treated children have a very bad
prognosis. Early endovascular embolization has become the therapy of
choice.

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.
To date there are few data about as-
sociated diseases or malformations.
The child described in this report has
Caroli disease and VGM. Both diseases
are characterized by pathologic var-
ciances of vessels or bile ducts, leading
to the hypothesis that common fea-
tures in their pathogenesis might exist.
Although the molecular pathogenesis
of Caroli disease is not fully under-
stood, it has been proved that ductal
plate malformation is a key factor in
the formation of dilated intrahepatic
bile ducts in Caroli disease. This de-
velopmental process takes place at
around the eighth week of gestation.
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.
Little is known about the underlying
molecular mechanisms causing this
AVM. Several investigations on cerebral
AVMs in general revealed overex-
pression of the vascular endothelial
growth factor (VEGF) and its receptors
VEGFR-1 and VEGFR-2 on endothelial
cells in patients with cerebral AVMs.
VEGF is a signal protein that plays a key

![FIGURE 2](https://example.com/image.png)

**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).19 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.15

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 1.14 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.14 Notch signaling and especially the interaction with its downstream ligand Jagged 1 are also essential for adequate development of the intrahepatic bile ducts.15 Mutations of Jagged 1, for example, result in a lack of intrahepatic bile ducts, called Alagille syndrome.16 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.17

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.18 Other studies focusing on the genetics of VGM describe an anomaly of the RASA1 gene, which is associated with capillary malformation AVM.19 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.20 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.

REFERENCES


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