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The Role of Mutations on Gene PKHD1 in Caroli Syndrome

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1. Abstract

Caroli Disease (CD) or caroli syndrome is a rare congenital liver disease characterized by non-obstructive cystic dilatations of the intra-hepatic and rarely extra-hepatic bile ducts. Caroli disease can present at any age. CD ranges from simple ectasias of the larger intra-hepatic bile ducts (in this less common form the name Caroli disease is used) to a syndromic form (Caroli syndrome) that is more common and includes congenital hepatic fibrosis.

2. Generalities of Caroli Syndrome

Caroli syndrome is a rare genetic condition that causes the liver bile ducts to become larger than usual. Enlargement of the bile ducts in the liver (intrahepatic bile ducts) can cause gallstones, leading to jaundice and flu-like symptoms. People with Caroli syndrome can have many of these symptoms throughout their lives [1] (Figure 1).

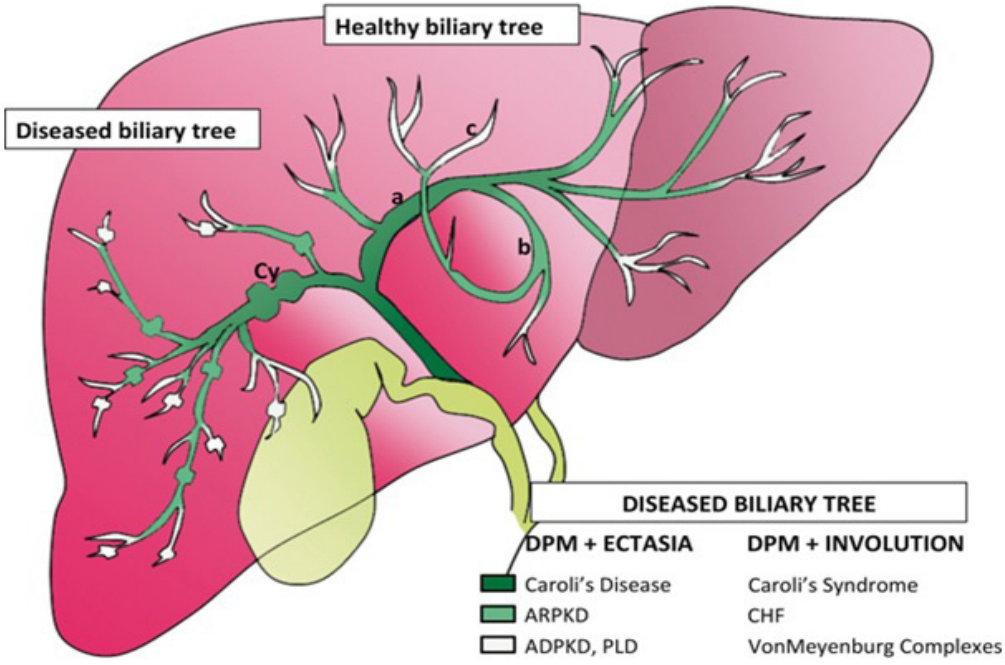

Figure 1: Schematic of hepatic bile duct disorders in Caroli Syndrome [1].

People with Caroli syndrome have scars on their liver (congenital liver fibrosis) that can cause high blood pressure in the veins of the liver (high blood pressure and portal) as well as bile duct problems in the liver. Occasionally, people with Caroli syndrome can develop cysts (polycystic kidney disease) in their kidneys. In addition, symptoms of Caroli syndrome can include blood in the stool, recurrent illnesses, and abdominal pain. Symptoms of this syndrome usually start at the age of 30, but can occur at any age. Treatment may include antibiotics or surgery to remove part of the liver, which is damaged depending on the symptoms and parts of the liver [1,2] (Figure 2).

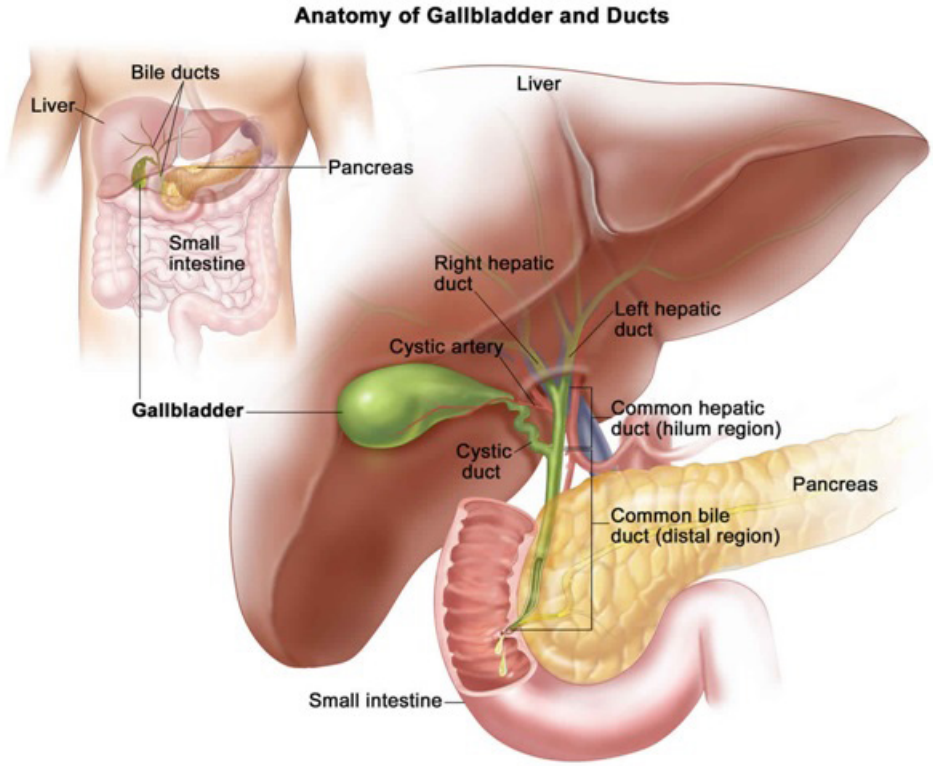

Figure 2: Schematic of the anatomy of the liver and bile ducts of the liver [1].

3. Clinical Signs and Symptoms of Caroli Syndrome

Caroli disease was first described in 1958 by a French physician named Dr. Jacques Carroll. He was a gastroenterologist who found that some people had dilated bile ducts in their liver. He also found that some people, in addition to having dilated bile ducts, have scars on their liver. Those with only wider bile ducts were later diagnosed with Caroli disease, and those with liver ulcers were diagnosed with Caroli syndrome. Caroli disease is a congenital dilatation of the intrahepatic bile duct, meaning that someone is born with bile ducts wider than normal in their liver [1, 3] (Figure 3).

Bile is made up inside the liver and sent through the ducts to the digestive system to help break down fatty foods for the body to use as energy. These bile ducts are important because they must be able to transport bile to other parts of the body. If these bile ducts become too large, bile begins to constrict and can swell the bile ducts inside the liver (cholangitis). Cholangitis can cause stomach pain, fever, fatigue, and nausea and vomiting [1, 3].

Caroli disease is usually diagnosed after the person first experiences the symptoms listed above. Having a diagnosis can help the medical team stop bile in the bile ducts in the future. Medications such as antibiotics can also be used to prevent irritation. Surgery is usually delayed until symptoms begin because it is an invasive procedure. Surgery can be used to remove part of the liver where the bile ducts are too large (hemiphectomy) and if the patient has too much cholangitis [1, 3] (Figure 4).

Another type of caroli syndrome causes tissue ulceration in the liver (congenital liver fibrosis), which causes the bile ducts to become wider than usual. It can also cause high blood pressure in the portal vein, which is the blood vessels of the liver (portal hypertension). Drugs such as beta blockers can be added to the portal to help with high blood pressure. People with Caroli syndrome are at higher risk for developing large cysts or growing cysts in their kidneys (polycystic kidney disease), so they may need medication and surgery to help their kidneys function properly [1, 4].

Bile should be able to move through the bile ducts without getting stuck. When these ducts become too large, bile can accumulate easily. As bile accumulates over time, its accumulation can lead to the formation of small stones. These small stones usually do not cause symptoms unless they block the bile ducts. When the bile ducts become blocked due to stones, the bile ducts become swollen (cholangitis). This can cause pain in the right side of the body, vomiting, fever and jaundice. People with caroli disease experience many parts of cholangitis. Rarely, tumors called cholangiocarcinomas can develop in the bile duct due to the accumulation of bile. Symptoms usually occur before the age of 30, but can occur at any age. Some people with caroli disease may have only one part of cholangitis, so it is

important to understand how the disease affects a person's life [1, 4].

The liver has its own bile ducts and its own blood vessels that make up the liver portal system. The portal system carries blood from the digestive organs to the liver to filter waste products. The liver must be properly formed to function. Occasionally, people are born with a disease that causes liver ulcers (congenital liver fibrosis). It also changes the way their bile ducts form in the liver, putting them at greater risk for cholangitis. Because the hepatic portal system is not properly formed in this syndrome, the blood pressure in these arteries is higher than normal. People with caroli syndrome have congenital liver fibrosis. Caroli syndrome is a progressive disease in which the liver is damaged over time. This condition can lead to liver failure and polycystic kidney disease [1, 4].

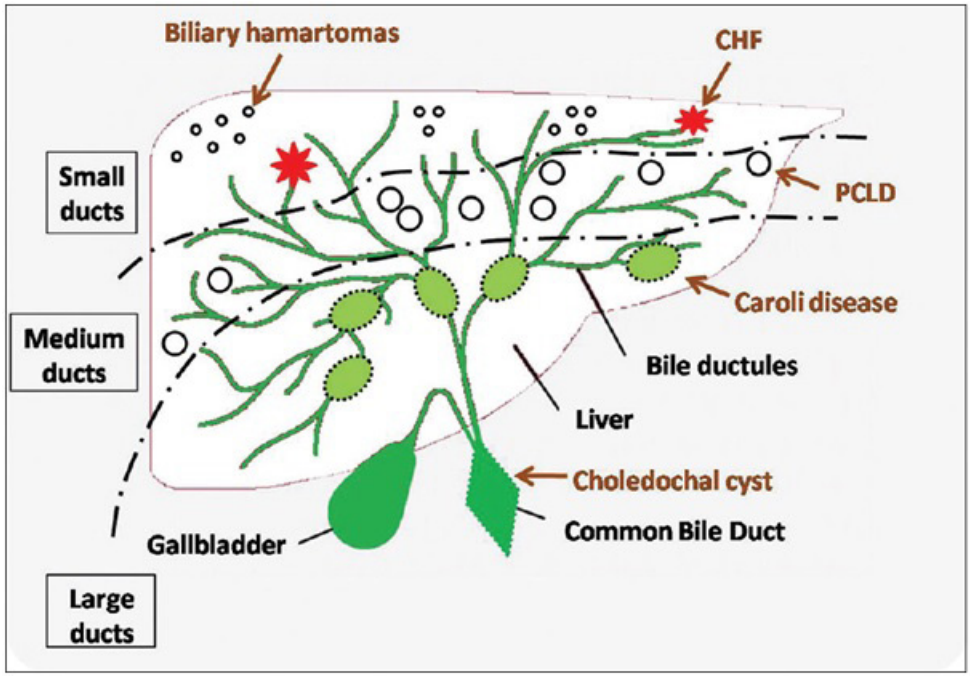

Figure 3: Schematic of the biochemical mechanism of Caroli syndrome in the bile ducts of the liver [1].

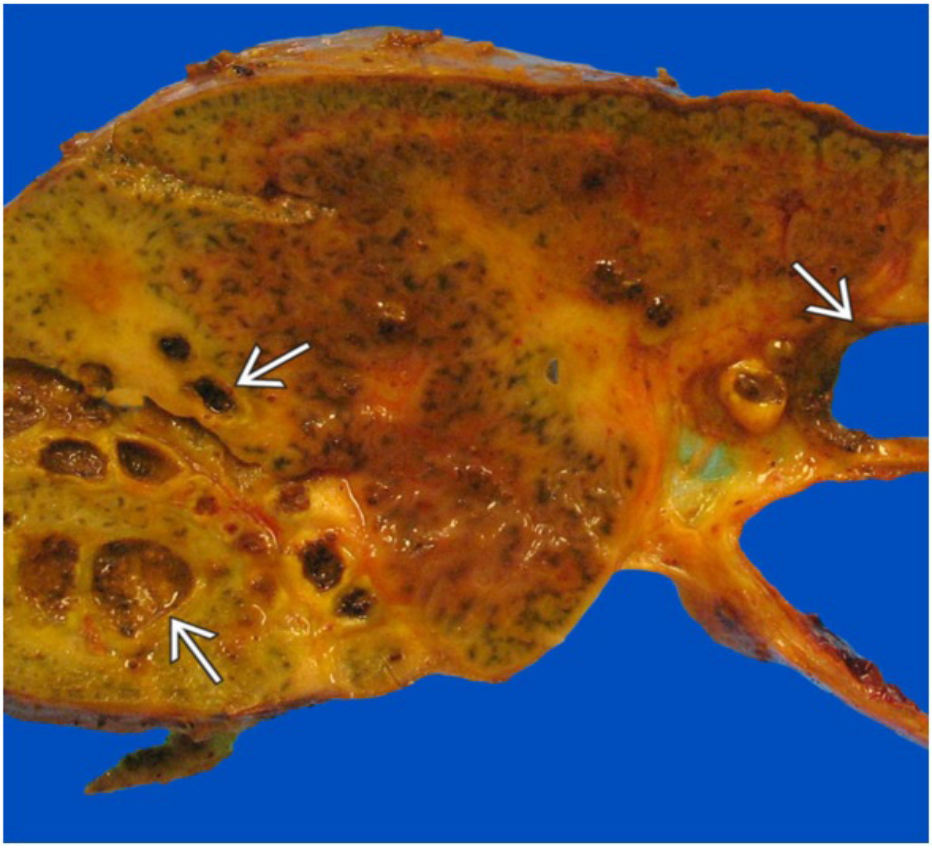

Figure 4: Picture of liver tissue with caroli syndrome with related disorder [1].

4. Etiology of Caroli Syndrome

Caroli syndrome is caused by a genetic mutation in the PKHD1 gene, which is located on the short arm of chromosome 6 as 6p12.3-p12.2. This gene synthesizes a protein that helps build the bile ducts as well as the kidneys. Mutations in this gene are also associated with kidney disease, called polycystic kidney disease. Caroli syndrome follows an autosomal recessive inherited pattern. Therefore, to develop this autosomal recessive syndrome, two copies of the mutated PKHD1 gene (one from the father and the other from the mother) are required, and the chance of having a child with the autosomal recessive syndrome is 25% for each possible is pregnancy [1, 5].

In addition, caroli syndrome follows an autosomal dominant inheritance pattern. Therefore, to develop this autosomal dominant syndrome, a copy of the PKHD1 mutant gene (either parent) is required, and the chance of having a child with this autosomal dominant syndrome is 50% for each possible pregnancy [1, 5] (Figure 5).

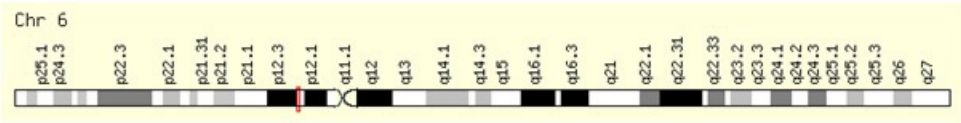

Figure 5: Schematic of chromosome 6 where the PKHD1 gene is located in the short arm of this chromosome as 6p12.3-p12.2.1.

5. Frequency of Caroli Syndrome

Caroli syndrome can affect people of all races and ethnicities. Symptoms usually begin in adulthood, but can sometimes begin in childhood. Caroli disease is rarer than Caroli syndrome, but it is estimated that 1 in 1,000,000 people has Caroli disease. It is estimated that caroli syndrome affects about 1 in 100,000 people, but it is difficult to identify people with caroli syndrome because the features may overlap with other caroli conditions [1, 5].

6. Disorders Associated with Caroli Syndrome

Many conditions have the same symptoms as caroli syndrome. It is important to know the conditions that can be mistaken for two types of disease and caroli syndrome:

Caldochal cysts grow on the bile ducts that are present from birth. A cyst or growth can occur anywhere in the bile duct, causing bile to return to the liver and pancreas, causing cholangitis and pancreatitis. Symptoms can occur in childhood or later. Symptoms include jaundice, abdominal mass, fever, and pain in the upper abdomen. Cholangiocarcinoma may also form [1, 6] (Figure 6).

Recurrent pyogenic cholangitis is a chronic infection that causes cholangitis. It is caused by parasites known as ascaris lumbricoides and C. Sinesis ascaris lumbricoides. The disease mainly affects people who live or are living in Southeast Asia [1, 7].

Primary Sclerosing Cholangitis (PSC) is an autoimmune disease that causes the bile ducts of the liver to become hard and inflamed over time. This condition can lead to end-stage liver disease, portal hypertension, and is associated with inflammatory bowel disease. People with PSC are at higher risk for colon cancer as well as cholangiocarcinomas [1, 8].

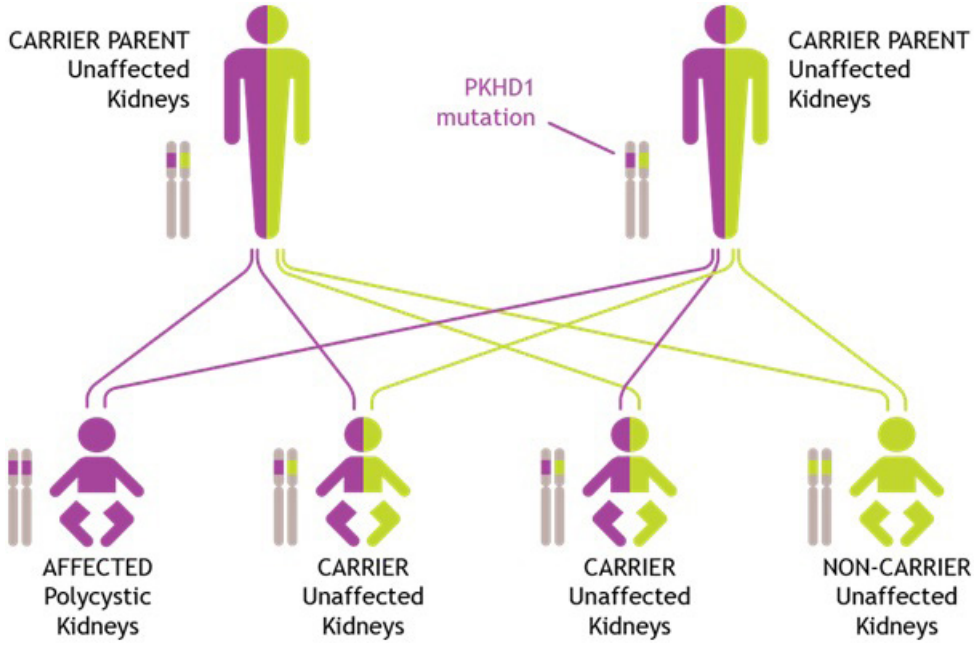

Figure 6: Schematic of the autosomal recessive inherited pattern that Caroli syndrome follows [1].

7. Diagnosis of Caroli Syndrome

Depending on the symptoms, imaging may be done to see if there is a problem with the liver or bile ducts. Ultrasound, CT scan, ERCP, MRCP and MRI are required for diagnosis. ERCP (Retrograde Endoscopic Cholangiopancreatography) is a procedure that uses a small, flexible tube (endoscope) that is inserted through the mouth and into the stomach. ERCP is able to look at the bile ducts and liver to detect scarring or lumps. ERCP is an invasive method, but it can help rule out other conditions. This method is accurate in diagnosing carroli syndrome [1, 8] (Figure 7).

MRCP (magnetic resonance cholangiopancreatography) is a special type of test that can measure the size of the bile ducts. MRCP can also look at gallstones. Other types of imaging, including CT scans, can detect ulcers in the liver. It is difficult to tell if a liver ulcer is due to caroli syndrome or another unrelated illness [1, 9].

A complete blood count (CBC) is a blood test that may also be done to check if someone has Carol's disease or Carol syndrome. People with caroli syndrome may have lower white blood cells, lower red blood cells, or lower platelets than people with caroli disease. The combination of imaging and blood tests can help determine the type of caroli disease or Caroli syndrome in a person, because the symptoms are similar [1, 9].

8. Clinical Trial

Tests are prescribed based on the type of symptoms a person is experiencing. If someone has symptoms of caroli disease, they will have an ERCP, MRCP, CT scan, or other type of scan. It is important to measure the bile ducts in the liver to see if they are wider than usual, as this is the main symptom of caroli disease. These tests can rule out caroli syndrome [1, 9] (Figure 8).

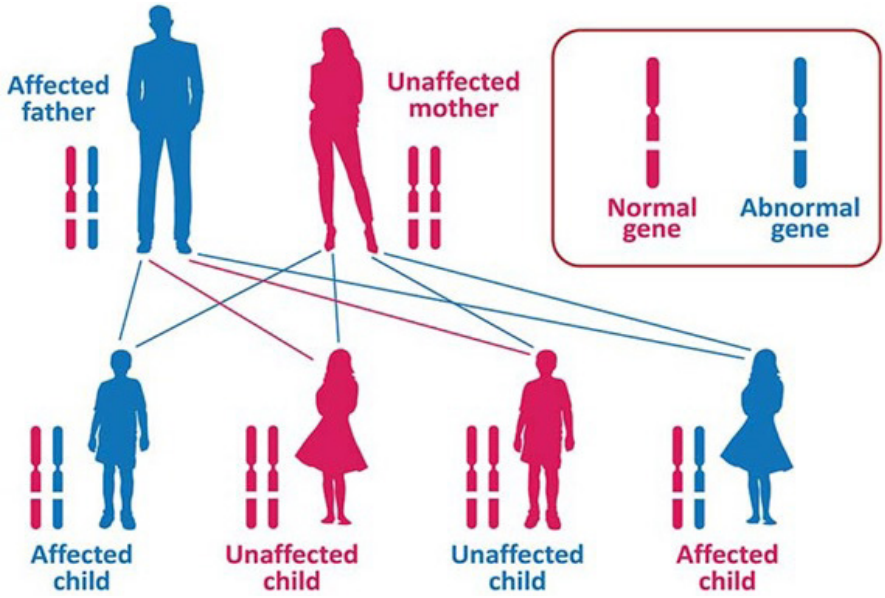

Figure 7: Schematic of the dominant autosomal inherited pattern that caroli syndrome also follows [1].

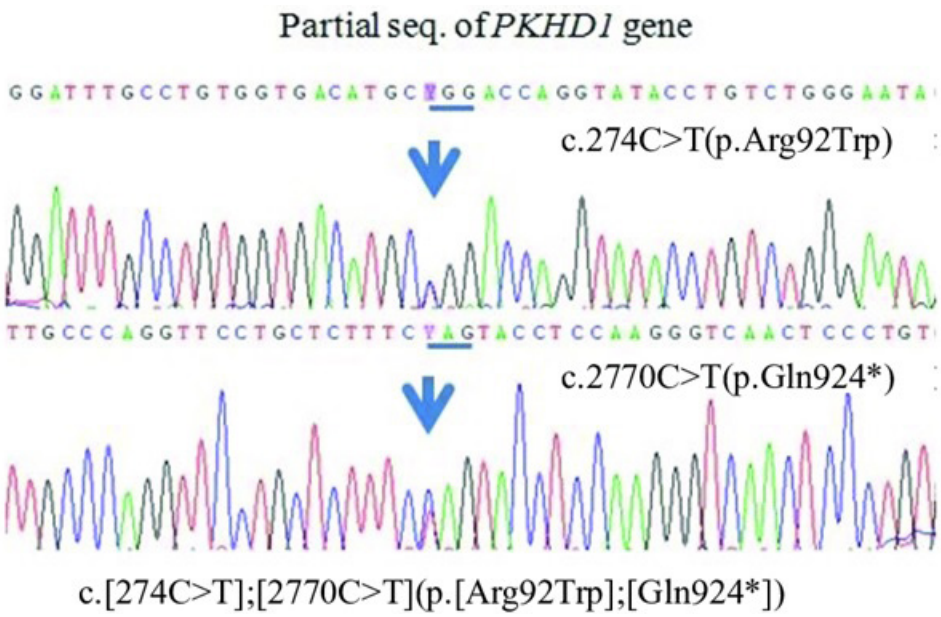

Figure 8: Schematic of a mutation sample in the PKHD1 gene [1].

9. Treatment Routes for Caroli Syndrome

The treatment for caroli disease is based on the location of the extensive bile ducts inside the liver. If the bile ducts are wider in the left or right half of the liver, that part of the liver can be surgically removed. People who have had a part of their liver removed (hemi-hepatectomy) to treat caroli disease often do not experience any symptoms in the future [1, 10].

If dilated bile ducts are located throughout the liver, the use of antibiotics can prevent cholangitis. Surgery can also be done to help remove bile from the liver (internal biliary bypass). For some people, this condition is difficult to manage, so a liver transplant may be the best option. People with caroli disease usually need a care team consisting of gastroenterologists, liver specialists, and surgeons. They may also be cared for by a liver transplant surgeon [1, 10].

10. Discussion and Conclusion

Caroli syndrome is a rare genetic condition that causes the liver bile ducts to become larger than usual. Enlargement of the bile ducts in the liver (intrahepatic bile ducts) can cause gallstones, leading to jaundice and flu-like symptoms. Some patients remain asymptomatic throughout the disease course. Some develop intra- or extra-hepatic calculi, leading to recurrent cholangitis (with bacteremia and sepsis), and acute pancreatitis. Manifestations are those of complications, mostly bacterial cholangitis, and include abdominal pain and biliary colic, fever with chills, and jaundice. Hepatomegaly, cirrhosis and portal hypertension (with splenomegaly) are also frequently reported to develop. Caroli syndrome is caused by a genetic mutation in the PKHD1 gene, which is located on the short arm of chromosome 6 as 6p12.3-p12.2. This gene synthesizes a protein that helps build the bile ducts as well as the kidneys. The treatment for caroli disease is based on the location of the extensive bile ducts inside the liver. If the bile ducts are wider in the left or right half of the liver, that part of the liver can be surgically removed. Antibiotics are used for cholangitis. Radiological, endoscopic, and surgical intervention may be required for patients with biliary obstruction, abscess formation and liver or bile duct stones. Patients with severe disease may be candidates for liver transplantation Quality of life may be significantly affected by recurrent cholangitis. Prognosis depends on the clinical course and the risk of cholangiocarcinoma. Choledochal cysts are growths on the bile duct that are present from birth. A cysts or growth can form anywhere in the bile duct which then causes bile to back up into the liver and the pancreas, which can cause cholangitis and swelling of the pancreas (pancreatitis). Symptoms can occur in childhood or later. Symptoms include jaundice, abdominal mass, fever, and pain in the right upper abdomen. Cholangiocarcinomas may also form. Primary sclerosing cholangitis (PSC) is an autoimmune condition that causes the bile ducts of the liver to become harder and inflamed over time. This condition can lead to end-stage liver disease, portal hypertension, and has been associated with inflammatory bowel disease. People with PSC are at an increased risk to develop colorectal cancer as well as cholangiocarcinomas [1, 10].

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