



The Childhood Liver Disease Research and Education Network strives to provide information and support to individuals and families affected by liver disease through its many research programs.

ALAGILLE SYNDROME

What is Alagille Syndrome?

Alagille syndrome (ALGS) is a condition affecting the liver, heart, spine, eye, face, kidneys and blood vessels that is caused by changes (mutations) in a gene called "Jagged1" in 94% of patients or "Notch2" in 1-2%. Most patients with ALGS have liver disease caused by "bile duct paucity," which means a decrease in the number of bile ducts in the liver. It is now recognized that ALGS is caused by abnormal development of many organs. In some patients, the heart problems caused by ALGS are much more important than the liver disease. Dr. Daniel Alagille, who recognized the organs affected in this disorder, described ALGS in 1969 and called it Syndromic Bile Duct Paucity. Since then, there have been great advances in the understanding and the therapy of ALGS, but there is much more to do.

What are the symptoms of the Liver Disease in Alagille Syndrome?

Infants with ALGS may show jaundice, pale stools, poor growth, or loose stools, and may have problems breathing or have pale or dusky skin color (if a heart problem is serious). Most patients with ALGS show signs and symptoms of liver problems at birth or soon after. They usually have a type of yellow eyes and skin called cholestatic jaundice (yellow color of the skin caused by decreased bile flow) in the first few months of life. Some infants are born small, and others have problems with gaining weight and growing. The lack of bile ducts causes a decrease in bile flow from the liver to the intestine. This lack of bile flow (cholestasis) causes a build-up in blood of substances that are normally eliminated from the body through the bile: bilirubin, bile salts, cholesterol and toxins. Too much bilirubin causes jaundice in the eyes and the skin. The build-up of bile salts in the skin may cause itching, which is sometimes severe and disruptive. Itching can interfere with sleep, and the scratching can damage the skin. Too much cholesterol causes fatty deposits in the skin (xanthomas). The buildup of toxins in the liver can also cause liver damage. In many patients, the symptoms of liver disease in ALGS (jaundice and itching) actually stop getting worse and even improve after a few years of age (this improvement is usually seen at around the time children start school). In others, the liver disease continues to get worse and may end up causing scarring of the liver (cirrhosis) or increased blood pressure in blood vessels going from the intestines to the liver (portal hypertension). If the liver disease is severe (as it is in approximately 20% of patients), liver transplantation may be needed. Some children and adults with ALGS have no symptoms of liver disease at all.



What is the Heart Disease in Alagille Syndrome?

Nearly all patients with ALGS have a heart murmur (an extra heart sound) at some time in their lives. The most common cause of this murmur is a narrowing of the arteries (blood vessels from heart to the lungs) in the lungs. This is called peripheral pulmonic stenosis or PPS. It usually causes no problems. ALGS can also cause more severe problems affecting the formation of the heart and blood vessels. The most important problems involve the right side of the heart. Two of these problems are called Tetralogy of Fallot (ToF) and pulmonary atresia (PA). In PA, the pulmonary artery (the blood vessel from the heart to the lungs) does not form normally. In some infants, the heart disease is identified by the first day of life, even before liver disease is noticed.

What Problems Can Alagille Syndrome Cause in Other Organs?

Alagille syndrome was first diagnosed only in infants who had too few bile ducts, but who also had at least three of five other problems. The other five problems are cholestasis, an extra line in the eye (posterior embryotoxon), unusually shaped spine bones (butterfly vertebrae), a heart murmur and a specific facial appearance. Posterior embryotoxon is a minor abnormality of the eye that usually does not affect vision. A medical eye doctor can best identify it. Butterfly vertebrae are a change in the shape of spine bones that can be seen on an x-ray of the spine. They generally do not cause any problems either, but they can help in the diagnosis of ALGS. Infants and children with ALGS have a "triangular face" with deep-set eyes and a large, noticeable forehead that can be recognized by experienced physicians. As the face matures into adulthood, the facial appearance changes but remains characteristic of an adult with ALGS. Other organs can be less commonly affected in ALGS. Kidney abnormalities can be seen in about half of patients. It is also possible to see abnormalities of blood vessels, including the pulmonary arteries, the aorta and blood vessels in the neck and brain. Other organs that can be involved include the pancreas and the long bones. In addition, patients with ALGS can have problems with poor absorption of nutrients (malabsorption). This causes malnutrition and poor growth and can lead to deficiencies of several vitamins. Special vitamins and infant formula are usually necessary to treat growth failure; however many patients are intrinsically short despite good nutrition.

How do you get Alagille Syndrome?

ALGS is dominantly inherited, which means that one parent can pass along the disease to a child. A single gene change (mutation) is all that is necessary for a child to develop ALGS. Mutations in the gene, *Jagged1*, are present in 95% of cases of ALGS. A small number of individuals have ALGS caused by another gene called *Notch2*. Both genes make proteins that are involved in human fetal development.



The discovery of the Jagged1 gene has led to a new understanding of ALGS. Jagged1 gene testing is now available. Notch2 testing is only recommended in individuals suspected of having ALGS in whom a Jagged1 mutation cannot be identified and this test is less widely available.

Gene testing can be used to confirm the diagnosis of ALGS in cases where the diagnosis cannot be made on examining the patient and looking at lab tests and x-rays alone. Gene testing can also be used to figure out if other family members with only mild signs and symptoms of ALGS carry a changed gene. If the parents of an ALGS child want to have more children, it may be important to know if they also carry a Jagged1 (or Notch2) mutation. Gathering this information, learning how it will affect a family's future children and deciding how to handle the results is known as "genetic counseling." It has been shown that about 60% of ALGS mutations are new in the first affected child. This means the parents of the ALGS child do not carry the gene. In these families, the risk of ALGS occurring in the next child is extremely low. In the other 40% of families, a parent carries the changed gene and the risk of the next child having ALGS is 50%. The severity of ALGS in the parent does not determine how mildly or severely their children will be affected. It is also possible that ALGS could be more or less severe in a second child than it was in the first child.

How is Alagille Syndrome found and diagnosed?

ALGS liver disease is found by a physical exam by a doctor and by blood tests and other special tests. The blood and urine tests include measuring the amount of bilirubin in the blood and how well the liver and kidneys work. An ultrasound of the liver may be performed. Ultrasound is a painless procedure using sound waves (sonar) through the skin to make a picture of the liver and kidneys. Another common test for the diagnosis of ALGS is a needle biopsy of the liver. In ALGS, the biopsy usually shows a decrease in bile ducts (bile duct paucity), particularly after an infant is six months old. Tests may also be performed to look at the spine (Xray), the eye (an examination by an eye doctor) and the heart (echocardiogram: a painless procedure using sound waves through the skin to make a picture of the heart). These are the most common organs, besides the liver, that may be involved in ALGS. ALGS may also be diagnosed by a blood test that looks for a mutation in the Jagged1 (or Notch2) gene.

What is the Treatment for Alagille Syndrome?

There is no known cure for ALGS, but there are ways to prevent or reduce health problems related to ALGS.

Therapy for children with ALGS is individualized, but most patients with ALGS require



treatment for their liver disease. Cholestasis causes bilirubin, bile salts and cholesterol to build-up in the body. Medications such as ursodeoxycholic acid (ursodiol) can help to improve bile flow and reduce itching. Ursodiol also helps to reduce blood cholesterol levels and jaundice. The build-up of bile salts may cause itching, which is sometimes severe. Antihistamines (such as diphenhydramine and hydroxyzine) can be used to control itching and improve sleep. Rifampin and other medications also help in some cases. Many patients take medications (such as cholestyramine and colesevelam) to help remove bile salts from the body. In severe cases, surgery to remove excess bile (partial external biliary diversion or ileal exclusion) can help with severe itching.

Most patients with ALGS are unable to absorb enough fat and the fat-soluble vitamins (A, D, E and K) due to inadequate levels of bile salts getting into the intestine. This leads to poor growth and malnutrition. Special formulas in infancy are made with MCT (medium chain triglyceride) oil, which is much better absorbed by children with cholestatic liver diseases. Also, supplements containing vitamins E, D and K (and sometimes A) are usually necessary because of the body's inability to absorb enough of these vitamins on its own. Low levels of these vitamins can lead to serious problems of the eyes, nerves, muscles, bones and blood clotting. Blood levels of these vitamins must be monitored closely and doses adjusted when needed.

What is the Outlook for someone with Alagille Syndrome?

Most patients with ALGS can lead long and productive lives. However, those with severe heart problems or progressive liver disease may have a shortened life span. Congenital heart disease that requires surgery is the most important problem affecting life expectancy. A small percentage of patients are born with severe heart defects. Patients with PPS generally have no important heart problems. In most patients with severe liver disease, liver transplantation leads to good long-term results. Bleeding around the brain and strokes (caused by abnormal blood vessels in the brain) can sometimes be a serious complication of ALGS and may be a cause of death.

The liver disease in AGS can improve over time in some patients. For this reason, liver transplantation should be considered for patients with AGS that have significant complications of their liver disease. Liver transplantation can be highly successful in ALGS. However, consideration of appropriateness for transplantation needs to carefully weigh the impact of the non-liver manifestations AGS patients may have on the results of liver transplantation. The heart and kidney disease seen in ALGS can make transplantation more challenging, and do not improve after liver transplantation.

In some patients, the heart disease or the blood vessel disease is the most important part of ALGS. These children may also need to be cared for by a heart doctor (cardiologist).



In every patient with ALGS, careful attention to taking medications and improving nutrition leads to markedly improved quality of life.