Alagille Syndrome

National Digestive Diseases Information Clearinghouse

U.S. Department of Health and Human Services

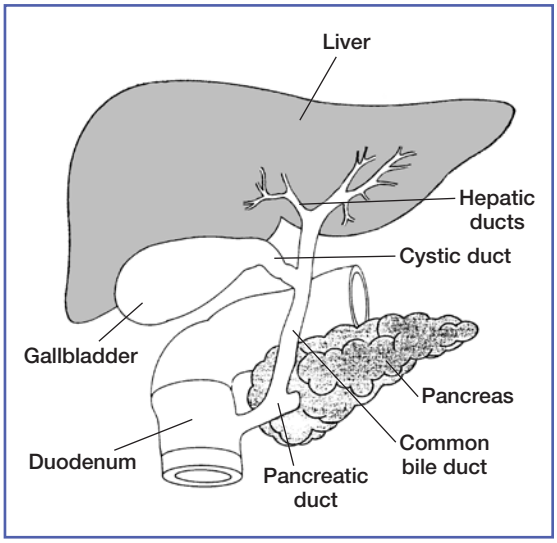
NATIONAL INSTITUTES OF HEALTH

NIDDK
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

What is Alagille syndrome?

Alagille syndrome is an inherited disorder in which a person has fewer than the normal number of small bile ducts inside the liver. Bile ducts, also called hepatic ducts, are tubes that carry bile from the liver cells to the gallbladder and eventually drain into the small intestine. Bile is a liquid produced in the liver that serves two main functions: carrying toxins and waste products out of the body and helping the digestion of fats and the fat-soluble vitamins A, D, E, and K. The decreased number of hepatic ducts causes bile to build up in the liver, leading to liver damage. Eventually the liver may stop working and a liver transplant is necessary.

Alagille syndrome is a complex disorder that can affect other parts of the body including the heart, kidneys, blood vessels, eyes, face, and skeleton. The syndrome occurs in about one in every 70,000 births[1] and is equally common in boys and girls. The symptoms of Alagille syndrome are usually seen in the first 2 years of life.



Normal liver and biliary system.

What causes Alagille syndrome?

Alagille syndrome is an autosomal dominant disorder, meaning it can be inherited from one parent who has the disorder. A child who has a parent with Alagille syndrome has a 50 percent chance of developing the disorder. Most people with Alagille syndrome have a mutation, or defect, in the *Jagged1 (JAG1)* gene. Mutations in the *NOTCH2* gene are seen in less than 1 percent of people with Alagille syndrome.

[1]Kamath BM, Krantz ID, Spinner NB. Alagille Syndrome. In: Pagon RA, ed. *GeneReviews*. Seattle (WA): University of Washington; 1993–2008. http://www.genetests.org. Accessed April 10, 2008.

What are the symptoms of Alagille syndrome?

The symptoms of Alagille syndrome and their severity vary, even among people in the same family.

Liver Symptoms

Infants with Alagille syndrome may have symptoms of liver disease and poor bile drainage from the liver in the first few weeks of life. These symptoms can also occur in children and adults with Alagille syndrome.

Jaundice. Bilirubin is the pigment that gives bile its reddish-yellow color. Jaundice occurs when the bilirubin content in the blood rises, causing yellowing of the skin and whites of the eyes. High levels of bilirubin in the blood can darken the urine, while stools may become pale, gray, or white from a lack of bilirubin in the intestines.

Many healthy newborns have mild jaundice due to immaturity of the liver. This type of jaundice disappears by the second or third week of life, whereas the jaundice of Alagille syndrome remains. Infants with jaundice that persists should be checked by a doctor.

Pruritus. The buildup of bilirubin in the blood may cause itching, also called pruritus. Pruritus usually starts after 3 months of age and can be severe.

Malabsorption and growth problems. People with Alagille syndrome may have diarrhea because of malabsorption, a condition in which the bowel does not properly absorb fats and fat-soluble vitamins. Malabsorption occurs because bile is necessary for their digestion. Malabsorption can lead to failure to thrive in infants and poor growth and delayed puberty in older children. People with Alagille syndrome and malabsorption may develop bone fractures, eye problems, blood-clotting problems, and learning delays.

Xanthomas. Xanthomas are fatty deposits that appear as yellow bumps on the skin. They are caused by abnormally high cholesterol levels in the blood, which is common in people with liver disease. Xanthomas are found on the abdomen, knees, elbows, hands, and around the eyes and are harmless.

Unique Symptoms

Alagille syndrome can affect other parts of the body in ways that may help doctors distinguish it from other liver conditions.

Heart. A heart murmur is the most common sign of Alagille syndrome other than liver disease. Most people with Alagille syndrome have a narrowing of the pulmonary arteries, which carry blood from the heart to the lungs. This narrowing causes a murmur that can be heard with a stethoscope, but usually it does not cause problems. A small number of people with Alagille syndrome have more serious heart conditions involving problems with the walls or the valves in the heart. The more serious conditions may require medications and corrective surgery.

Face. Many children with Alagille syndrome have deep-set eyes; a straight nose; a small, pointed chin; and a prominent, wide forehead. These features are not usually recognized until after infancy. The face typically changes with age, and by adulthood the chin is more prominent.

Eyes. Posterior embryotoxon is a condition in which an opaque ring is seen in the cornea, the transparent covering of the eyeball. A specialist performs an eye examination, called the slit lamp test, to look for the

condition. The abnormality is common in people with Alagille syndrome and usually does not affect vision.

Skeleton. The shape of the bones of the spine may look abnormal on an x ray, but this abnormality rarely causes spine problems.

Kidneys. A wide range of kidney diseases can occur in Alagille syndrome. Some people have small kidneys or cysts in the kidneys. The kidneys can also have decreased function.

Spleen. The spleen is a small abdominal organ that cleans blood and protects against infection. Blood flow from the spleen drains directly into the liver. When liver disease is advanced, the blood flow backs up into the spleen and other blood vessels. This condition is called portal hypertension. The spleen may enlarge in the later stages of liver disease. A person with an enlarged spleen should avoid contact sports to protect the organ from injury.

Blood vessels. People with Alagille syndrome may have abnormalities of the carotid arteries—the blood vessels in the head and neck. This serious complication can lead to internal bleeding or stroke. If a person with Alagille syndrome suffers a head injury, prompt evaluation and magnetic resonance imaging (MRI) or a computerized tomography (CT) scan of the brain are needed to check for problems. Alagille syndrome can also cause narrowing or bulging of other blood vessels in the body.

How is Alagille syndrome diagnosed?

Because the symptoms of Alagille syndrome vary and because the syndrome is so rare, the disorder can be difficult to diagnose. The doctor will perform a thorough physical examination to look for clinical symptoms of the disorder. If Alagille syndrome is suspected, the doctor will order one or more of the following tests and examinations:

- blood tests to check liver function and nutritional status
- an abdominal ultrasound to look for liver enlargement and to rule out other conditions
- a liver biopsy to check for a decreased number of hepatic ducts
- a cardiology examination to check for heart problems
- an eye examination to check for posterior embryotoxon
- an x ray of the spine to look for abnormalities
- examinations of the blood vessels and kidneys to check for abnormalities

To make a diagnosis of Alagille syndrome, a positive liver biopsy and the presence of three of the following symptoms are usually required:

- liver symptoms
- heart abnormalities or murmurs
- skeletal abnormalities
- posterior embryotoxon
- facial features typical of Alagille syndrome

The doctor may also have a blood sample tested to look for the *JAG1* gene mutation. The gene mutation can be identified in 95 percent of people with a diagnosis of Alagille syndrome based on signs and symptoms.[2] A person can also be diagnosed with Alagille syndrome if the *JAG1* gene mutation alone is present—even when no major symptoms of the disorder are evident.

The doctor may refer a person suspected of having Alagille syndrome to a geneticist—a physician who specializes in genetic disorders—to review the findings and assist with diagnosis. The geneticist and a genetic counselor meet with family members to review the family medical history and provide information. Once a person is diagnosed with Alagille syndrome, the parents may be tested for the *JAG1* gene mutation. Siblings and other family members may also be tested. The specialists discuss the likelihood that family members and offspring will have the mutation. Prenatal testing is available at specialized centers.

How is Alagille syndrome treated?

Treatment for Alagille syndrome is aimed at increasing the flow of bile from the liver, promoting growth and development, and making the person as comfortable as possible. Ursodiol (Actigall, Urso) is the only drug approved by the U.S. Food and Drug Administration to increase bile flow. Other treatments address specific symptoms of the disease.

Pruritus. Itching may improve when the flow of bile from the liver is increased. Medications such as cholestyramine (Questran, Prevalite), rifampin (Rifadin), naltrexone (ReVia, Depade), or antihistamines may be prescribed to relieve pruritus. Hydrating the skin with moisturizers and keeping fingernails trimmed to prevent skin damage from scratching are important.

If severe pruritus does not improve with medication, a procedure called partial external biliary diversion (PEBD) may provide relief from itching. PEBD involves surgery to connect one end of the small intestine to the gallbladder and the other end to an opening in the abdomen—called a stoma—through which bile leaves the body and is collected in a pouch.

A liver transplant may be necessary for a person with liver failure and severe pruritus that does not improve with medication or PEBD.

[2]Warthen DM, Moore EC, Kamath BM, Morrissette JJ, Sanchez P, Piccoli DA, Krantz ID, Spinner NB. *Jagged1 (JAG1)* mutations in Alagille syndrome: increasing the mutation detection rate. *Human Mutation*. 2006;27(5):436–443.

Malabsorption and growth problems. Infants with Alagille syndrome are given a special formula that allows the absorption of much-needed fat by the small intestine. Infants, children, and adults can benefit from a high-calorie diet, calcium, and vitamins A, D, E, and K. If oral doses of vitamins are not well tolerated, a health care provider may need to give the person injections for a period of time. A child may receive additional calories through a tiny tube that is passed through the nose into the stomach. If extra calories are required for a long time, a tube, called a gastrostomy tube, may be placed directly into the stomach through a small opening made in the abdomen. The child's growth may improve if nutrition status improves and the flow of bile from the liver increases.

Xanthomas. These fatty deposits typically worsen over the first few years of life and then improve over time, or they may eventually disappear in response to PEBD or the medications used to increase bile flow.

Liver failure. In some cases, Alagille syndrome will progress to end-stage liver failure and require a liver transplant. A liver transplant is when the diseased liver is removed and replaced with a healthy one from an organ donor.

The health care team carefully considers the risks and benefits of a transplant and discusses them with the patient and family. People with Alagille syndrome and heart problems may not be candidates for a transplant because they could be at high risk for complications during and after the procedure.

What is the long-term outlook for people with Alagille syndrome?

The outlook for people with Alagille syndrome depends on several factors, including the severity of liver damage and heart problems and the early correction of malabsorption. Predicting who will experience improved bile flow and who will progress to end-stage liver failure is difficult. Fifteen percent of people with Alagille syndrome will eventually require a liver transplant.

Survival rates for people receiving liver transplants have improved over the past several years because of newer drugs that suppress the immune system and keep it from attacking and damaging the new liver.

Research studies report that 75 percent of children diagnosed with Alagille syndrome live to at least 20 years of age.[3] Because of improvements in liver and heart therapies, this survival rate is increasing. Many adults with Alagille syndrome who improve with treatment lead normal, productive lives. Deaths in people with Alagille syndrome are most often caused by liver failure, heart problems, and blood vessel abnormalities.

[3]Emerick KM, Rand EB, Goldmuntz E, Krantz ID, Spinner NB, Piccoli DA. Features of Alagille syndrome in 92 patients: frequency and relation to prognosis. *Hepatology*. 1999;29(3):822–829.

Points to Remember

- Alagille syndrome is an inherited disorder in which a person has fewer than the normal number of bile ducts in the liver. The symptoms of Alagille syndrome are usually seen in the first 2 years of life.
- Alagille syndrome is a complex disorder that can affect the liver and other parts of the body such as the heart, kidneys, blood vessels, eyes, face, and skeleton.
- Alagille syndrome is an autosomal dominant disorder, which means it can be inherited from one parent who has the disorder.
- Alagille syndrome is most often caused by a mutation, or defect, in the *Jagged1 (JAG1)* gene.
- Infants with Alagille syndrome may have symptoms of poor bile drainage from the liver in the first few weeks of life.
- Alagille syndrome can affect other parts of the body in ways that may help doctors distinguish it from other liver conditions.
- Because the symptoms of Alagille syndrome vary and because the syndrome is so rare, the disorder can be difficult to diagnose. The doctor may use the following to make a diagnosis: evaluation of the symptoms of Alagille syndrome, liver function tests, a liver biopsy, a blood test to look for a *JAG1* gene mutation, and a genetic workup.
- Treatment for Alagille syndrome is aimed at increasing the flow of bile from the liver, promoting growth and development, and making the person as comfortable as possible.
- In some cases, Alagille syndrome will progress to end-stage liver failure and require a liver transplant.
- Research studies report that 75 percent of children with Alagille syndrome live to at least 20 years of age. Deaths in people with Alagille syndrome are most often caused by liver failure, heart problems, and blood vessel abnormalities.

Hope through Research

The National Institute of Diabetes and Digestive and Kidney Diseases' Division of Digestive Diseases and Nutrition supports basic and clinical research into liver diseases, including Alagille syndrome. Studies are under way to

- explain the many ways Alagille syndrome presents in people
- focus on the interaction between *JAG1* and other genes and on identifying new genes that might cause Alagille syndrome
- translate findings about bile formation and secretion into treatments to reverse or cure Alagille syndrome
- target the exact cause of pruritus and develop a curative treatment
- develop a gene therapy for liver disease in newborns that could be used to treat Alagille syndrome

Participants in clinical trials can play a more active role in their own health care, gain access to new research treatments before they are widely available, and help others by contributing to medical research. For information about current studies, visit *www.ClinicalTrials.gov*.

For More Information

Alagille Syndrome Alliance
10500 SW Starr Drive
Tualatin, OR 97062
Phone: 503–885–0455
Email: alagille@alagille.org
Internet: www.alagille.org

American Liver Foundation
75 Maiden Lane, Suite 603
New York, NY 10038–4810
Phone: 1–800–GO–LIVER (465–4837)
or 212–668–1000
Fax: 212–483–8179
Email: info@liverfoundation.org
Internet: www.liverfoundation.org

Children's Liver Association for Support Services
25379 Wayne Mills Place, Suite 143
Valencia, CA 91355
Phone: 1–877–679–8256
Fax: 661–263–9099
Email: info@classkids.org
Internet: www.classkids.org

United Network for Organ Sharing
P.O. Box 2484
Richmond, VA 23218
Phone: 1–888–894–6361 or 804–782–4800
Fax: 804–782–4817
Internet: www.unos.org

Acknowledgments

Publications produced by the Clearinghouse are carefully reviewed by both NIDDK scientists and outside experts. This publication was reviewed by David A. Piccoli, M.D., Children's Hospital of Philadelphia.

You may also find additional information about this topic by visiting MedlinePlus at *www.medlineplus.gov.*

This publication may contain information about medications. When prepared, this publication included the most current information available. For updates or for questions about any medications, contact the U.S. Food and Drug Administration toll-free at 1–888–INFO–FDA (463–6332) or visit *www.fda.gov*. Consult your doctor for more information.

The U.S. Government does not endorse or favor any specific commercial product or company. Trade, proprietary, or company names appearing in this document are used only because they are considered necessary in the context of the information provided. If a product is not mentioned, the omission does not mean or imply that the product is unsatisfactory.

National Digestive Diseases Information Clearinghouse

2 Information Way
Bethesda, MD 20892–3570
Phone: 1–800–891–5389
TTY: 1–866–569–1162
Fax: 703–738–4929
Email: nddic@info.niddk.nih.gov
Internet: www.digestive.niddk.nih.gov

The National Digestive Diseases Information Clearinghouse (NDDIC) is a service of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The NIDDK is part of the National Institutes of Health of the U.S. Department of Health and Human Services. Established in 1980, the Clearinghouse provides information about digestive diseases to people with digestive disorders and to their families, health care professionals, and the public. The NDDIC answers inquiries, develops and distributes publications, and works closely with professional and patient organizations and Government agencies to coordinate resources about digestive diseases.

This fact sheet is also available at *www.digestive.niddk.nih.gov*.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

NIH Publication No. 09–6048
February 2009