Alagille Syndrome — Clinical Features and Diagnosis

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Alagille syndrome is a genetic disease characterized by abnormalities in the liver, heart, eye, kidneys, and skeleton with a typical facial appearance. It is an autosomal disorder caused by mutations in the JAG1 gene and NOTCH2 gene. Both sexes irrespective of geographic, racial or ethnic variations are equally affected by this disorder. Jaundice and heart murmurs with characteristic facial appearance are the main symptoms. Blood and urine analysis, ultrasonography, ECG, liver biopsy and genetic tests are the diagnostic measures. Both Therapeutic and surgical interventions are intended based on the patients’ conditions.

Introduction

Alagille syndrome is an autosomal dominant genetic disorder that can involve the liver, heart, skeleton, eyes, and kidneys. It was first described in 1969 by Daniel Alagille. Children with neonatal cholestasis, characteristic dysmorphic facies, and involvement of multiple organ systems should be suspected to have Alagille syndrome.

Definition of Alagille Syndrome

Diagnosis is based on demonstration of the paucity of bile ducts on liver biopsy in association with at least three of the following major clinical features:

1. Chronic cholestasis
2. Cardiac involvement—pulmonary artery stenosis
3. Skeletal abnormalities—Butterfly vertebrae
4. Ocular anomalies—primary posterior embryotoxon
5. Characteristic dysmorphic facies—prominent forehead, deep-set eyes, pointed chin, saddle straight nose with a bulbous tip

**Epidemiology of Alagille Syndrome**

Previous clinical studies had noted an incidence of 1:70,000 live births. With recent advances in diagnostics and wide availability of genetic testing facilities, a significant number of patients have been identified who have the disease-causing mutations but no neonatal cholestasis. The current estimated incidence of Alagille syndrome is between 1:30,000 and 1:45,000 with no difference in gender.

**Genetics of Alagille Syndrome**

It is an autosomal dominant disorder with variable expressivity. Alagille syndrome is caused by mutations in JAG1 (seen in 94%) and NOTCH2 (seen in 1%) genes. The affected notch signaling pathway plays a crucial role in the determination of cell fate during normal development.

The mutations affect the development of multiple systems leading to the various clinical manifestations seen. Being an autosomal dominant disorder the affected individual transmits the mutation to 50% of his kindred. The expressivity is highly variable. Many individuals carry the mutation and so technically have Alagille syndrome, but have no or minor manifestations. De novo mutations are responsible for 50—70% of cases.

**Clinical Features of Alagille Syndrome**

Alagille syndrome is a multisystem disorder. The various characteristic features are tabulated below:
<table>
<thead>
<tr>
<th>Organ system</th>
<th>Characteristic features</th>
<th>Miscellaneous</th>
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</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Neonatal cholestasis</td>
<td>Preserved synthetic function</td>
</tr>
<tr>
<td>Heart</td>
<td>Pulmonary artery anomalies</td>
<td>A major determinant of early mortality</td>
</tr>
<tr>
<td>Vascular system</td>
<td>Aneurysms of intracranial arteries</td>
<td>Screening MR angiography of head recommended for all</td>
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<tr>
<td>Skeletal system</td>
<td>Sagittal cleft or Butterfly vertebrae</td>
<td></td>
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<tr>
<td>Facial features</td>
<td>Prominent forehead, deep-set eyes, pointed chin, saddle straight nose with a bulbous tip. The combination of all gives a triangular appearance.</td>
<td>Features change with age</td>
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<tr>
<td>Ocular features</td>
<td>Primary posterior embryotoxon Axenfeld anomaly Iris anomalies Disc anomalies</td>
<td>Formal slit lamp examination recommended in infancy in suspected cases</td>
</tr>
<tr>
<td>Renal system</td>
<td>Renal dysplasia Renal tubular acidosis Vesicoureteric reflux</td>
<td>Now considered a disease-defining criterion</td>
</tr>
<tr>
<td>Growth</td>
<td>Severe growth retardation Short stature Neurocognitive and developmental delay</td>
<td>Multifactorial</td>
</tr>
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Hepatic Involvement

Cholestasis typically presents in the first year of life. There is a **gross derangement of conjugated bilirubin and bile acid levels are very high**, partly accounting for the intense accompanying pruritus. Hepatitis (Increased AST, ALT) is seen in many children but is less significant. The synthetic function of the liver is typically preserved. ALP and GGT are often elevated.

Due to cholestasis excretion of cholesterol is also impaired leading to very high levels in the blood. This typically manifest as multiple xanthomas on the skin.

The progress of liver dysfunction with age is variable. Some may have spontaneous resolution of cholestasis while others may progress to **end-stage liver disease. No known genotypic or radiologic markers predict the progression**. A recent study documented high bilirubin levels and high cholesterol levels before five years of age to be strongly associated with severe liver dysfunction in later life.

Eventually, about 25 % require **liver transplantation**. It is typically offered when there is synthetic dysfunction, intractable portal hypertension, recurrent bone fractures (especially of long bones like femur), severe pruritus and growth failure.

**Liver Biopsy**

The characteristic feature is a **paucity of bile ducts**. In bile duct paucity, bile duct to portal space ratio is < 0.9 in infants. The bile ductules are not to be included in the calculation. The biopsy specimen should be adequate and representative with at least six portal tracks seen.

**Giant cell hepatitis, histological cholestasis and rare progression to cirrhosis** are also characteristics of Alagille syndrome. Bile duct proliferation is characteristic of biliary atresia and helps differentiate between the two.
Cardiovascular Involvement

Cardiovascular involvement is fairly common (to the tune of 94% in some series). **Right-sided lesions** predominate. Most common anomaly identified is Pulmonary artery anomaly. **Tetralogy of Fallot** is also common.

The cardiac disease accounts for a majority of deaths in early infancy in Alagille syndrome. The case to case survival of cardiac lesions with Alagille syndrome is much worse than that of the same lesions without Alagille syndrome.

Apart from pulmonary artery intracranial arteries are also commonly involved. In fact, in diagnosed cases, a **screening MR Angiogram is recommended to pick up asymptomatic aneurysms** and treat them prophylactically.

Unexplained intracranial bleeds of various magnitudes are common and may be preceded by trivial trauma. Moyamoya disease, the involvement of celiac artery, renal artery, aorta, superior mesenteric artery, and the subclavian artery has also been described.

Skeletal Involvement

Vertebral anomalies are characteristic. Failure of fusion of anterior arches leads to the typical deformity of **Sagittal cleft** or **Butterfly vertebrae**. Severe metabolic bone disease and osteoporosis are also common. This is multifactorial. Severe chronic malnutrition, growth hormone resistance, chronic hepatic disease and deficiency of necessary nutrients all contribute. This often leads to recurrent fractures of long bones. Recurrent femur fractures is often an indication for liver transplantation.

Facial Features

Characteristic syndromic facies has been a part of the original description of this syndrome. There is a **typical triangular appearance with the broad wide forehead**. Children also frequently have **deep set eyes, saddle or straight nose, bulbous tip**
and pointed chin.

The facial characteristics often alter with age. Facies characteristics is a very subjective parameter with significant inter-observer variability and hence it is a relatively unreliable diagnostic marker for Alagille syndrome.

Involvement of the Ocular System

*Primary posterior embryotoxon* is a characteristic feature. A number of other anomalies like optic disc drusen, iris anomalies, Axenfeld anomaly, etc. have also been described. In suspected cases of Alagille syndrome, getting a formal slit lamp examination done on the infants can provide useful diagnostic clues and is recommended.

Renal involvement

Though not originally a part of major clinical diagnostic criteria, renal involvement is quite common and is now considered disease-defining criteria by many. The most common anomalies are renal dysplasia, vesicoureteric reflux, renal tubular acidosis, and urinary obstruction.

Growth and Development

*Severe growth retardation* is seen in the majority of children. Chronic malnutrition, malabsorption, growth hormone resistance contributes to growth failure. Failure to thrive, chronic wasting, suboptimal height for age and weight for age is common. The neurocognitive and developmental delay is also common.

Diagnosis of Alagille Syndrome

A high index of suspicion for Alagille syndrome should be maintained while evaluating a case of neonatal cholestasis. **Investigations** which help reach the diagnosis are:

1. Typical characteristic features in various organ system as previously described
2. Bile duct paucity on liver biopsy
3. HIDA scan, Intraoperative cholangiogram
4. Mutational analysis for JAG1 or NOTCH2 gene. In a small number of patients with Alagille syndrome, genetic testing may not reveal a JAG1 or NOTCH2 mutation.
5. As multiple organ systems are involved, multiple specialties are often involved in the evaluation and management of this disorder.

Treatment of Alagille Syndrome

Individuals with Alagille syndrome should receive

1. a **baseline echocardiogram to screen for heart involvement**
2. an **ultrasound of the abdomen**
3. a **screening eye exam**.

Children who are old enough to sit during a magnetic resonance imaging study should undergo a magnetic resonance angiography study to evaluate the blood vessels of the head.

**Supplemental treatment with vitamins** is needed in patients with malabsorption. The
administration of vitamins A, D, E, and K might be needed. Young infants and children with Alagille syndrome should be given formula milk with medium chain triglycerides as they are better absorbed in patients with cholestasis.

**Mild cholestasis is typically treated with medications.** Ursodeoxycholic acid is a choleretic and often prescribed in mild cholestasis. The severe accompanying pruritus is distressing. Antihistaminics, partial or total biliary diversion, skin emollients and keeping the nails trimmed to avoid injury are often advised. Rifampin, cholestyramine, and naltrexone can be also used to treat pruritus.

Kasai hepatoportoenterostomy has a detrimental effect on outcomes and is not to be done. Liver transplantation is advocated for severe cholestasis and end-stage liver disease.

Genetic counseling is indicated for affected individuals and their families. The main question is whether the mutation was a de novo one or an inherited one.

**References**


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