Alagille syndrome is a multisystem disorder due to a mutation in JAG1gene (95%) and NOTCH2 gene (1%). It is an autosomal dominant disorder with variable expressivity. The characteristic features in various affected organ systems, the diagnostic approach, and the management is outlined in this article.

Introduction

Alagille syndrome is an **autosomal dominant genetic disorder with multisystem involvement**. 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 1:70000 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 true incidence is thus likely to be around 1:30000 live birth.

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>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Neonatal cholestasis</td>
<td>Preserved synthetic function</td>
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<tr>
<td>Heart</td>
<td>Pulmonary artery anomalies</td>
<td>Major determinant of early mortality</td>
</tr>
<tr>
<td></td>
<td>Tetralogy of Fallot (TOF)</td>
<td></td>
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<tr>
<td>Vascular system</td>
<td>Aneurysms of intracranial arteries</td>
<td>Screening MR angiography of head recommended for all</td>
</tr>
<tr>
<td>Skeletal system</td>
<td>Sagittal cleft or Butterfly vertebrae</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe metabolic bone disease with osteoporosis</td>
<td></td>
</tr>
<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>
</tr>
<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>
</tbody>
</table>

**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, an 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 of 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 a 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 and Management 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
5. As multiple organ systems are involved, multiple specialties are often involved in evaluation and management of this disorder

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. 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.

Review Questions

1. Alagille syndrome is a multisystem disorder. Neonatal cholestasis is one of the cardinal features of this syndrome. The most common gene mutation responsible for Alagille syndrome is
   A. SPINK1 gene
   B. NOTCH2 gene
   C. JAG1 gene
   D. FAP gene

2. Alagille syndrome is a multisystem disorder first described in 1969 by Daniel Alagille. He described children with cholestasis, cardiac skeletal renal and ocular abnormalities coupled with abnormal dysmorphic facial features. Which of the following is true regards inheritance of this disorder
   A. After defining the genotype, one can accurately predict the phenotype.
   B. Affected individuals have a 25% chance of passing the mutation to their offspring
   C. Affected individuals have a 50% chance of passing the mutation to their offspring
   D. Affected individuals have a 75% chance of passing the mutation to their offspring

3. Mary is an assistant professor of economics. She has no history of medical comorbidities. Mary has two elder brothers and an elder sister. She had a full term normal vaginal delivery in the month of March. There were no complications and she delivered a baby boy Bob. Bob cried well after birth. Mary has noticed yellowish discoloration of his eyes since birth. The discoloration is gradually increasing. The attending pediatrician notes a wide forehead and on auscultation notes the presence of a murmur. All the following are true except
   A. Bob needs further diagnostic evaluation and testing.
   B. Cardiac evaluation to rule out underlying abnormalities like pulmonary artery stenosis, tetralogy of Fallot (TOF) should be done.
   C. The jaundice is most likely physiological and will resolve gradually over next few days
   D. Slit lamp examination of the eye should be asked for to detect ocular anomalies like posterior embryotoxon, iris anomalies, optic disk anomalies and speaking of retinal pigment epithelium.

4. Jack was born with yellowish discoloration of his eyes. He was evaluated
further and was diagnosed to have Alagille syndrome with a mutation in JAG1 gene. His siblings and his parents were tested for the index mutation. His sister Jane who was 4 years old tested positive for the index mutation. Their parents were very anxious and visited the attending pediatrician for counseling. The best advice would be

A. As she is sure to develop a severe cholestatic disease in near future, she should be evaluated and urgently listed for liver transplantation at a high volume center.
B. She should be evaluated by a multispecialty team including cardiologist, nephrologist, ophthalmologists and hepatologist. She may or may not have manifestations of the features of Alagille syndrome.
C. When Jane grows up she has a 25 % risk of transmission of the mutation to her children.
D. None of the above.

5. All the following are characteristic features of Alagille syndrome except

A. Butterfly vertebrae
B. Gigantism
C. Posterior embryotoxon
D. Chronic cholestasis

6. Mark is 2 months old male child. Since the age of 2 weeks, he has progressively increasing yellowish discoloration of his eyes. His mother also complains that he is itching all over his body all the time. He has a wide forehead with deep set eyes. On further evaluation, he also has pulmonary artery stenosis, butterfly vertebrae, multiple xanthomas over palmar creases and nape of the neck and a primary posterior embryotoxon. Laboratory investigations reveal increased conjugated bilirubin levels with increased levels of alkaline phosphatase. The attending pediatrician strongly suspects him to be a case of Alagille syndrome. A percutaneous liver biopsy is done. Usually, all the following can be seen except

A. Paucity of bile ducts
B. Giant cell hepatitis
C. Prominent histologic cholestasis
D. Proliferation of bile ducts

References


**Correct answers:** 1C; 2C; 3C; 4B; 5B, 6D

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