Imaging Findings in Alagille Syndrome - A Case Report with literature review

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Ethical Statement
Not applicable.

ABSTRACT

Alagille syndrome (AGS)is a rare disease with autosomal dominant inheritance and involves mutation of JAG 1(90%) and NOTCH 2(1-2%). The syndrome affects multiple systems, including the liver, eye, Vertebra, and cardiac, and has peculiar facial features. To diagnose AGS, three out of 5 clinical features or systems should be involved. Here we describe the imaging findings in a 13-year-old child who presented with tubercular spondylitis and cholestatic jaundice and had typical facies.

CASE REPORT

BACKGROUND

Alagille syndrome is a very rare case, and a constellation of clinical and imaging criteria is required to make the diagnosis. The case illustrates one of the rare differential diagnoses of jaundice in Childhood. Although it presents in the neonate, our case is unique as the presentation was late. Once the diagnosis is made, the final diagnosis requires liver biopsy and genetic testing.

CASE REPORT

A 13-year-old male was brought by his parents to the Paediatric neurology department with pain in the cervical region followed by paraparesis and difficulty in walking for 2 months with hyperreflexia of bilateral upper limbs followed by hyporeflexia of lower limbs. He was referred to our center for management of Potts spine which was diagnosed in a non-contrast MRI spine done outside.

At the presentation, he had a cholestatic picture with a basic evaluation of elevated Gamma-glutamyl transferase (GGT) with elevated transaminases. On reviewing the history, he had a history of jaundice at 1 month of age which was resolved with over-the-counter medications. Subsequently, by 5 months of age, he developed intense pruritis which has persisted to date, leading to lichenification of skin over the extremities (non-refractory to CAM medications which he received for the last 12 years, not properly evaluated for the same). He also had a characteristic triangular facies-broad forehead with a long pointed nose with a bulbous tip and deep-seated eyes. The child

was born out of a nonconsanguineous marriage and there was a history of 3 sibling death in the family (SIDS and cardiac disease in siblings) suggestive of an autosomal dominant mode of inheritance. He was short for his age and, per abdominal examination, showed mild hepatomegaly with the rest of the examination grossly normal. With the classical clinical presentation and clinical findings, the possibility of Alagille syndrome was kept and evaluated for the same.

Routine blood investigations, including hemogram and ESR, were within normal limits. Liver functions showed elevated GGT of 726 IU/L (0-51 IU/L) and transaminases (SGOT-163 IU/L (10-34IU/L), SGPT-186 IU/L (10-34 IU/L) with normal bilirubin levels (1.35mg/dl), and preserved albumin levels of 4.2 gm/dl (3.4-5.4 gm/dl) and PT/INR of 0.9. His cholesterol levels were also elevated at 235 mg/dl (Normal<200 mg/dl). Ophthalmology evaluation showed evidence of posterior embryotoxon and retinitis pigmentosa.

Due to pain in the cervical region, a non-contrast MRI was done which revealed altered marrow signal intensity involving the C6-T1 Vertebra with loss of Intervertebral disc space showing a hyperintense signal on T2W and hypointense signal on T1W with large pre and posterior paraspinal abscess with extradural extension and resultant compression of the spinal cord. The cord was of normal bulk and signal intensity. There was also significant wedging of the C7 Vertebra (Figure 1). Based on imaging features, tubercular spondylitis was kept, and the child was started with antitubercular therapy (modified therapy based on liver functions). To look for the bone status and as preoperative assessment for surgical fixation, CT cervical and thoracic spine was done in our institute, which showed similar findings and almost complete destruction of the C7 Vertebra. Additional findings which were depicted on CT were butterfly vertebra of D2-D4 Vertebra, and there was spina bifida in the lower lumbar and sacral Vertebra (Figure 2).

As the child had neonatal Cholestasis, the child underwent an Ultrasound abdomen with the color Doppler of the liver which revealed a small Gall bladder with an edematous wall. The common bile duct was not visualized. There was a well-defined area of increased echogenicity anterior to the porta (Figure 3). To look for the biliary status and for further characterization of liver lesions, a dynamic contrast-enhanced MRI was done. The common bile duct was not visualized. The liver lesion appeared isointense on T2w, and hypointense on T1w and showed poor arterial enhancement and also remained hypointense on other phases suggestive of the regenerative nodule. There was also the presence of two separate pancreatic ducts. The dorsal duct draining the body and tail of the pancreas was draining separately into the minor papilla while the ventral duct (draining the head and uncinate process) was draining into the major papilla (Figure 4). The spleen was normal in size. MRI findings were consistent with regenerative nodule, small gall bladder, and absent common bile duct with pancreatic divisum. HRCT temporal bone was also done which showed hypoplasia of bilateral Posterior semicircular canals (Figure 5).

Based on the constellation of clinical and imaging findings, the diagnosis of Alagille syndrome was kept (4 out of 5 criteria were present). A liver biopsy and genetic testing were planned for the final diagnosis. As the child's parents were apprehensive so a liver biopsy was deferred. Due to the high cost of genetic testing, parents could not afford for the same.

DISCUSSION

Etiology and Demographics

Alagille syndrome is a multisystem disorder with autosomal dominant inheritance, with the major gene affected in 97 % of cases being JAG1 and NOTCH 2 in less than 1 % of cases [1,2].

Clinical and Imaging Findings

Children present with cholestatic jaundice and conjugated bilirubinemia; however, to establish the diagnosis, classic criteria are defined, which are tabulated in table 1 [3].

Most syndromic children present with cholestatic jaundice (approx. 95%) with conjugated hyperbilirubinemia, pruritus, and growth failure [4]. All of these clinical features were seen in our patient. A liver biopsy can be done; however not necessary for diagnosis, which shows the paucity of intrahepatic bile ducts.

Cardiovascular anomalies are seen in approx. 90% of patients [5]. Peripheral pulmonary arterial stenosis is the most common congenital abnormality. ASD, VSD, TOF, aortic stenosis and coarctation of the aorta, and hypoplastic heart syndrome.

Posterior embryotoxon is the most common abnormality seen [6]. Segmentation anomalies in the form of butterfly vertebra are seen in most children, which is seen as a cleft in the body of the Vertebra on anteroposterior radiograph and occurs due to the non-fusion of the anterior arch. Other skeletal anomalies are spina bifida occulta, narrowing of the intervertebral foramen, pointing of anterior arch of atlas, absent 12th rib, and shortened distal phalanges of the hand [7]. Bony anomalies seen in the indexed case were butterfly vertebra involving the dorsal Vertebra and spina bifida occulta in the sacral Vertebra.

The dysmorphic facial feature is also one of the classic criteria, including a pointed chin, a straight nose with a bulbous tip, deep-seated eyes, and a prominent forehead. The child presented with characteristic facial features [3]. Various vascular anomalies can also be seen, including abnormality of major intracranial arteries, renal vessel anomalies, and moya moya disease [8]. Numerous other anomalies in the syndrome are growth retardation, renal anomalies, and pancreatic insufficiency. Pancreatic ductal anomalies such as pancreatic divisum can be associated with anomaly that was also seen in our case. Various inner ear abnormalities can also be seen. There was hypoplasia of bilateral Posterior semicircular canals in our case.

Treatment and Prognosis

Management requires a multidisciplinary approach with symptomatic treatment of each clinical feature. No management is done for Bony and eye abnormalities. Liver transplantation is the only cure for liver disease.

Differential Diagnosis

Biliary Atresia

Hepatobiliary involvement in Alagille syndrome has to be differentiated from biliary atresia as the management of both differs, and the Kasai operation done for BA worsens the disease. Non-visualization of the gall bladder or small rudimentary GB with triangular cord sign, nuclear scan, and biopsy can favor BA over Alagille syndrome. In our case, there was non-visualization of CBD, no triangular cord sign with a small gall bladder, and the presence of a regenerative nodule, which was suggestive of Alagille syndrome.

Distinguishing features of Alagille syndrome are summarized in table 2.

TEACHING POINTS

Diagnosis of Alagille syndrome requires high clinical suspicion with typical, imaging and biochemical features. Once the Classic criteria are met, investigation, follow up and family management should follow. Liver biopsy and genetic testing are not mandatory for the diagnosis.

QUESTIONS

Question 1: Which mutation is associated with Alagille syndrome?

1. Mutation in LMNA gene
2. Mutation in GDF1 gene
3. Mutation in MYH6 gene
4. Mutation in JAG 1 and NOTCH 2 gene (Applies)
5. Mutation in SOD1 gene

Explanation:

1. LMNA gene is associated with Hutchinson- Gilford progeria syndrome. [Alagille syndrome (AGS) is a rare disease with autosomal dominant inheritance and involves mutation of JAG 1(90%) and NOTCH 2(1-2%)]

2. GDF1 gene mutations are associated with a congenital heart defect in humans.[Alagille syndrome (AGS)is a rare disease with autosomal dominant inheritance and involves mutation of JAG 1(90%) and NOTCH 2(1-2%)]

3. MYH 6 gene mutation is associated with ASD. [Alagille syndrome (AGS)is a rare disease with autosomal dominant inheritance and involves mutation of JAG 1(90%) and NOTCH 2(1-2%)]

4. Alagille syndrome (AGS)is a rare disease with autosomal dominant inheritance and involves mutation of JAG 1(90%) and NOTCH 2(1-2%)

5. SOD1 gene mutation is associated with amyotrophic lateral sclerosis [Alagille syndrome (AGS)is a rare disease with autosomal dominant inheritance and involves mutation of JAG 1(90%) and NOTCH 2(1-2%)]

Question 2: What is the inheritance pattern of Alagille syndrome?

1. Autosomal dominant (applies)
2. Autosomal recessive
3. Co-dominant
4. X- linked recessive
5. X- linked dominant

Explanation:

1. Autosomal Dominant [Alagille syndrome is inherited in an autosomal dominant pattern, which suggests one copy of the altered or deleted gene is sufficient to cause the disorder. In approximately 30 to 50 % of cases, an affected person inherits the mutation or deletion from one affected parent.]

2. Autosomal Recessive [Alagille syndrome is inherited in an autosomal dominant pattern, which suggests one copy of the altered or deleted gene is sufficient to cause the disorder. In approximately 30 to 50 % of cases, an affected person inherits the mutation or deletion from one affected parent]

3. Co-dominant [Alagille syndrome is inherited in an autosomal dominant pattern, which suggests one copy of the altered or deleted gene is sufficient to cause the disorder. In approximately 30 to 50 % of cases, an affected person inherits the mutation or deletion from one affected parent]

4. X-linked recessive [Alagille syndrome is inherited in an autosomal dominant pattern, which suggests one copy of the altered or deleted gene is sufficient to cause the disorder. In approximately 30 to 50 % of cases, an affected person inherits the mutation or deletion from one affected parent]

5. X-linked Dominant [Alagille syndrome is inherited in an autosomal dominant pattern, which suggests one copy of the altered or deleted gene is sufficient to cause the disorder. In approximately 30 to 50 % of cases, an affected person inherits the mutation or deletion from one affected parent]

Question 3: All of the following organs are involved in Alagille syndrome except:

1. Liver
2. Heart
3. Kidney
4. Vertebral bodies
5. Ears(Applies)

Explanation:

1. Liver [Alagille syndrome not only affects the liver, but it also affects the heart, kidneys, vertebral bodies, and eyes. The syndrome affects multiple systems, including the liver, eye, Vertebra, and cardiac, and has peculiar facial features].

2. Heart [Alagille syndrome not only affects the liver, but it also affects the heart, kidneys, vertebral bodies, and eyes. The syndrome affects multiple systems, including the liver, eye, Vertebra, and cardiac, and has peculiar facial features].

3. Kidney [Alagille syndrome not only affects the liver, but it also affects the heart, kidneys, vertebral bodies, and eyes. The syndrome affects multiple systems, including the liver, eye,

Vertebra, and cardiac, and has peculiar facial features].

4. Vertebral Bodies [Alagille syndrome not only affects the liver, but it also affects the heart, kidneys, vertebral bodies, and eyes. [The syndrome affects multiple systems, including the liver, eye, Vertebra, and cardiac, and has peculiar facial features].

5. Ears [Alagille syndrome not only affects the liver, but it also affects the heart, kidneys, vertebral bodies, and eyes. The syndrome affects multiple systems, including the liver, eye, Vertebra, and cardiac, and has peculiar facial features].

Question 4: Which of the following is the close differential diagnosis of Alagille syndrome?

1. Choledochal cyst
2. Primary sclerosing cholangitis
3. Biliary atresia (Applies)
4. Budd Chiari syndrome
5. Choledocholithiasis

Explanation:

1. Choledochal Cyst [The entity has to be differentiated from biliary atresia as the management of both differs, and the Kasai operation done for BA worsens the disease. Non-visualization of the gall bladder or small rudimentary GB with triangular cord sign, nuclear scan, and biopsy can favor BA over Alagille syndrome].

2. Primary Sclerosing Cholangitis [[The entity has to be differentiated from biliary atresia as the management of both differs, and the Kasai operation done for BA worsens the disease. Non-visualization of the gall bladder or small rudimentary GB with triangular cord sign, nuclear scan, and biopsy can favor BA over Alagille syndrome].

3. Biliary Atresia [The entity has to be differentiated from biliary atresia as the management of both differs, and the Kasai operation done for BA worsens the disease. Non-visualization of the gall bladder or small rudimentary GB with triangular cord sign, nuclear scan, and biopsy can favor BA over Alagille syndrome].

4. Budd Chiari syndrome [The entity has to be differentiated from biliary atresia as the management of both differs, and the Kasai operation done for BA worsens the disease. Non-visualization of the gall bladder or small rudimentary GB with triangular cord sign, nuclear scan, and biopsy can favor BA over Alagille syndrome].

5. Choledocholithiasis [The entity has to be differentiated from biliary atresia as the management of both differs, and the Kasai operation done for BA worsens the disease. Non-visualization of the gall bladder or small rudimentary GB with triangular cord sign, nuclear scan, and biopsy can favor BA over Alagille syndrome].

Question 5: Features of dysmorphic facies in Alagille syndrome except:

1. Broad forehead
2. Deep-seated eyes
3. Prominent ears (Applies)
4. Straight nose with a bulbous tip
5. Occipital plagiocephaly

Explanation

1. Broad Forehead [Dysmorphic facial feature is also one of the classic criteria of Alagille syndrome, including a pointed chin, straight nose with a bulbous tip, deep-seated eyes, and prominent forehead].

2. Deep-seated Eyes [Dysmorphic facial feature is also one of the classic criteria of Alagille syndrome, including a pointed chin, straight nose with a bulbous tip, deep-seated eyes, and prominent forehead].

3. Prominent Ears [Dysmorphic facial feature is also one of the classic criteria of Alagille syndrome, including a pointed chin, straight nose with a bulbous tip, deep-seated eyes, and prominent forehead].

4. Straight nose with bulbous tip [Dysmorphic facial feature is also one of the classic criteria of Alagille syndrome, including a pointed chin, straight nose with a bulbous tip, deep-seated eyes, and prominent forehead].

5. Occipital Plagiocephaly [Dysmorphic facial feature is also one of the classic criteria of Alagille syndrome, including a pointed chin, straight nose with a bulbous tip, deep-seated eyes, and prominent forehead

REFERENCES

1. Li L, Krantz ID, Deng Y, et al. Alagille syndrome is caused by mutations in human Jagged1, which encodes a ligand for Notch1. *Nat Genet.* 1997; 16: 243–251. PMID: 9207788.

2. Oda T, Elkahloun AG, Pike BL, et al. Mutations in the human Jagged1 gene are responsible for Alagille syndrome. *Nat Genet.* 1997; 16: 235–242. PMID: 9207787.

3. Turnpenny PD, Ellard S. Alagille syndrome: pathogenesis, diagnosis and management. *Eur J Hum Genet.* 2012; 20(3): 251-257. PMID: 21934706.

4 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: 822–829. PMID: 10051485.

5 McElhinney DB, Krantz ID, Bason L, et al. Analysis of cardiovascular phenotype and genotype-phenotype correlation in individuals with a JAG1 mutation and/or Alagille syndrome. *Circulation*. 2002; 106: 2567–2574. PMID: 12427653.

6. Hingorani M, Nischal KK, Davies A, et al. Ocular abnormalities in Alagille syndrome. *Ophthalmology*. 1999; 106: 330–337. PMID: 9951486.

7. Sanderson E, Newman V, Haigh SF, Baker A, Sidhu PS. Vertebral anomalies in children with Alagille syndrome: an analysis of 50 consecutive patients. *Pediatr Radiol.* 2002; 32: 114–119. PMID: 11819079.

8. Emerick KM, Krantz ID, Kamath BM, et al. Intracranial vascular abnormalities in patients with Alagille syndrome. *J Pediatr Gastroenterol Nutr.* 2005; 41: 99–107. PMID: 15990638.

FIGURES

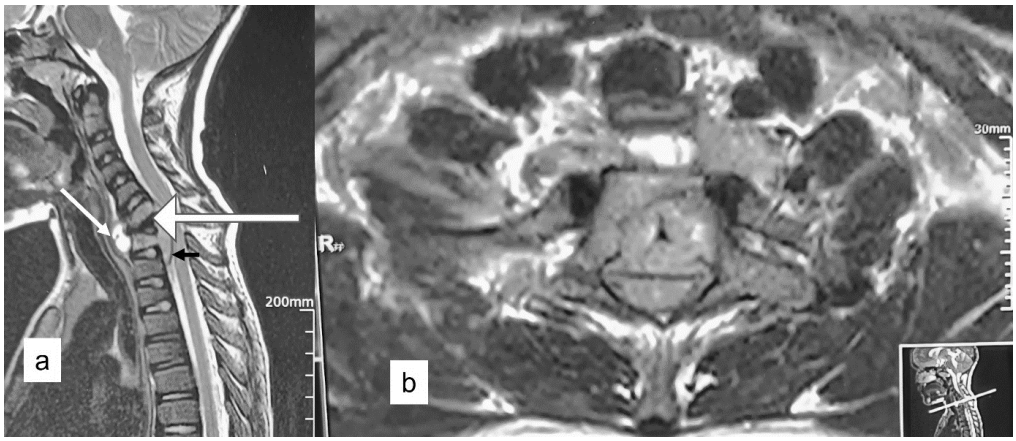

Figure 1: 16-year-old male with Alagille syndrome.

Findings: Sagittal and Axial T2W image of Cervical spine depicting the almost complete collapse of C7 Vertebra (block arrow in a) with T2 hyperintense marrow of C6-T1 Vertebra and reduce intervertebral disc space. There is also the presence of hetero intense pre and paraspinal collection (white arrow in a and b) which is compressing the spinal cord (black arrow in a and b)

Technique: Sagittal and Axial T2W MRI (done outside)

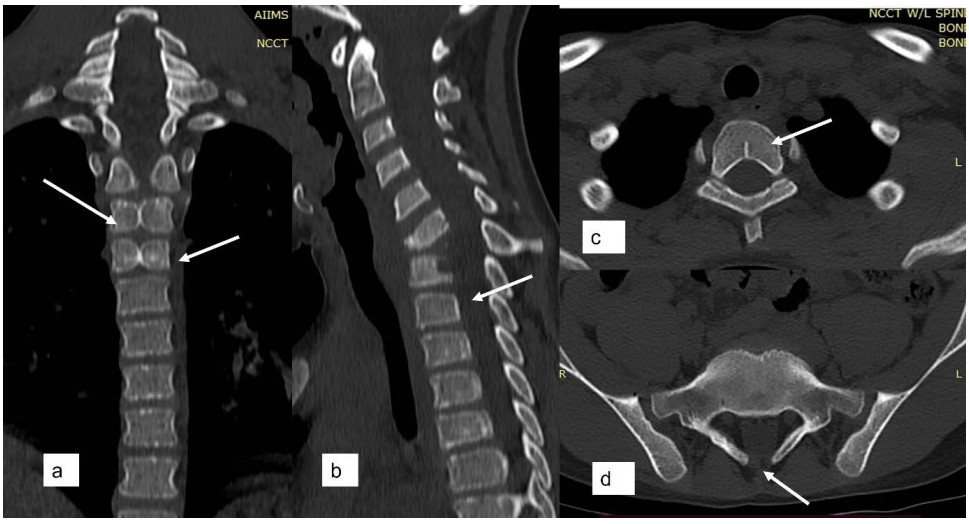

Figure 2: 16-year-old male with Alagille syndrome.

Findings: Coronal Reformatted and axial cervicothoracic spine (bone window) showing butterfly vertebra from the level of D-2 –D4 vertebra (white arrow in a and c). Posterior wedging of the D2 Vertebra is seen (arrow in b). A defect in the posterior elements is seen in the lower sacral Vertebra. (Arrow in d)

Technique: Axial and reformatted coronal and Sagittal CT scan. Dual source multidetector non-contrast CT of the cervicothoracic spine0201 mA, 120 kV; 0.6 mm slice thickness

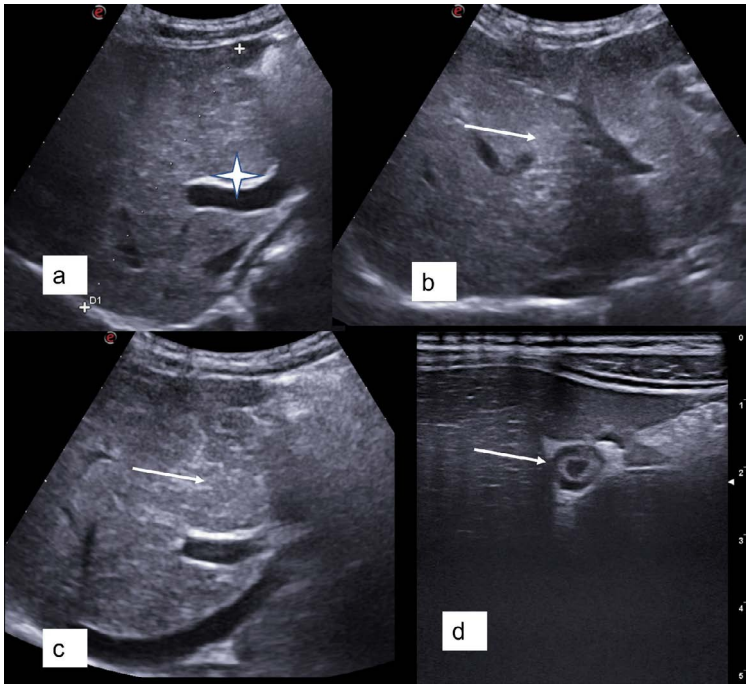

Figure 3:16-year-old male with Alagille syndrome.

Findings: Transverse Grey scale Ultrasound abdomen through the liver shows mild hepatomegaly with non-visualization of CBD (asterisk in a). The Hyperechoic area is seen anterior to the porta (arrow in b and c). The gall bladder is also small in size with pericholecystic edema (arrow in d)

Technique: Ultrasound of the epigastric region of the abdomen, using a 2-8 MHz convex array transducer (Esoate My Lab 9XP), in the transverse plane in an image (4a,b, and c). Ultrasound of the epigastric region of the abdomen, using a 7-12 MHz linear array transducer (Esoate My Lab 9XP), in the transverse plane in the image (4d).

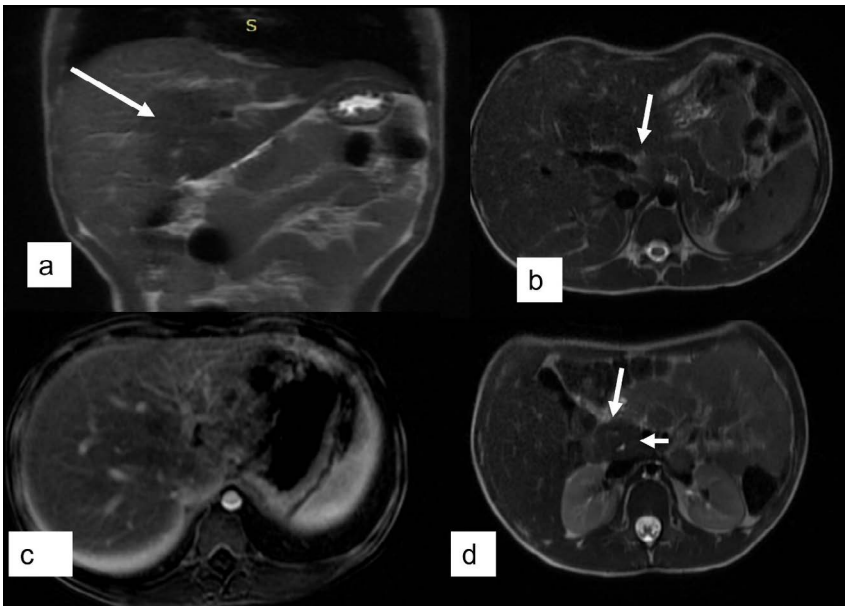

Figure 4:16-year-old male with Alagille syndrome.

Findings: Dynamic contrast-enhanced MRI through the upper abdomen. (a)Coronal T2W image through the liver shows an isointense intraparenchymal lesion anterior to the porta causing a mass effect on the hepatic vasculature. (b)Axial T2W images through the upper abdomen also reveal the absence of a common bile duct (arrow in b). (c) No post-contrast enhancement is seen in the lesion. (d)There was also the presence of two pancreatic ducts opening separately into major and minor papilla (arrows in d) suggestive of pancreatic divisum.

Technique: GE discovery MR750 3T machine T2W (TR-3000MS and TE-80 ms) coronal (5a) and axial (5b,c, and d) sequences with a slice thickness of 3 mm

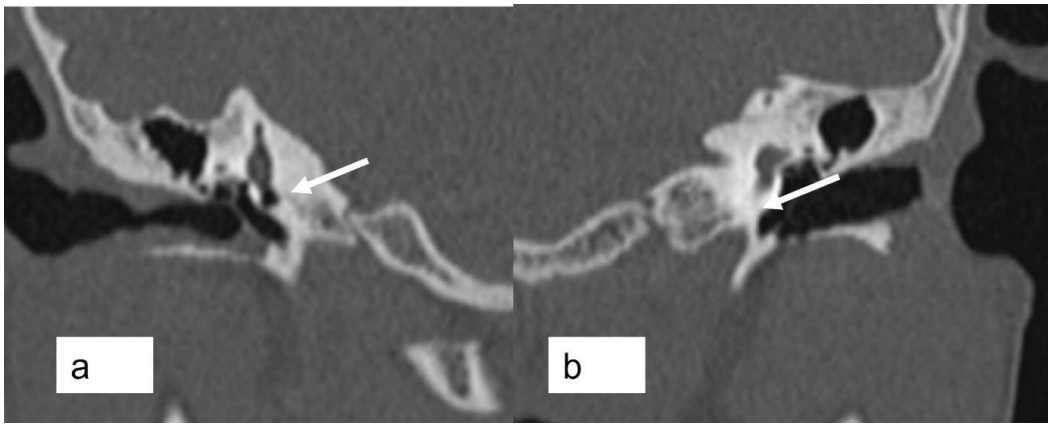

Figure 5: 16-year-old male with Alagille syndrome.

Findings: HRCT temporal bone coronal reformatted sections depicting rudimentary and blunted bilateral posterior semicircular canals bilaterally (arrow in a and b).

Technique: Dual-source multidetector non-contrast CT of the cervicothoracic spine, 201 mA, 120 kV; 0.6 mm slice thickness in images (6a and b).

Table 1: Classic criteria for Alagille syndrome based on 5 organ systems (adopted from Turnpenny PD, Ellard S 2005)

System/Organ	**Clinical/imaging/biochemical features**
Liver	Cholestatic jaundice with hyperbilirubinemia
Dysmorphic facies	Broad forehead Deep-seated eyes Prominent ears Straight nose with a bulbous tip Pointed chin
Cardiac	Peripheral pulmonary artery stenosis ASD VSD TOF
Vertebral anomalies	Butterfly vertebra Hemivertebra Fusion anomalies Spina Bifida occulta
Eye/ocular	Posterior Embryotoxon

Table 2: Summary table of Alagille Syndrome

Etiology	Rare disease with autosomal dominant inheritance and involves mutation of JAG 1(90%) and NOTCH 2(1-2%).
Incidence	Rare
Gender Ratio	1:6(M:F)
Age Predilection	Wide range -Infants up to adolescence
Risk factors	Genetic inheritance
Treatment	Multidisciplinary approach. No Treatment is required for bone and eye involvement. Liver transplantation is the cure for Liver Involvement.
Prognosis	Depends on the system involved. Worse Prognosis for hepatobiliary involvement
Imaging Findings	Cardiac abnormality-ASD, VSD, TOF Spine -Segmentation anomalies Liver-Non visualization of Common bile duct. Regenerative nodules can be present.

KEYWORDS

Alagille syndrome; Bile ducts; Cholestasis; Facies; Magnetic Resonance Imaging

ABBREVIATIONS

ASD = ATRIAL SEPTAL DEFECT
BA = BILIARY ATRESIA
CBD = COMMON BILE DUCT
CAM = COMPLEMENTARY AND ALTERNATIVE MEDICATIONS
C6 = 6TH CERVICAL VERTEBRA
D2 = SECOND THORACIC VERTEBRA
D6 = 6TH DORSAL VERTEBRA
GB = GALL BLADDER
GGT = GAMMA GLUTAMYL TRANSFERASE
INR = INTERNATIONAL NORMALIZED RATIO
HRCT = HIGH RESOLUTION CT SCAN
MRI = MAGNETIC RESONANCE IMAGING
PT = PROTHROMBIN TIME
SIDS = SUDDEN INFANT DEATH SYNDROME
T1W = T1 WEIGHTED MRI
T2W = T2 WEIGHTED MRI
TOF = TETRALOGY OF FALLOT
VSD = VENTRICULAR SEPTAL DEFECT

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