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Alagille syndrome associated with total anomalous pulmonary venous connection and severe xanthomas: A case report

ALGS with TAPVC and severe xanthomas

Abstract

BACKGROUND

Alagille syndrome is an autosomal dominant genetic disorder caused by mutations in the *JAG1* or *NOTCH2* gene. It is characterized by decreased intrahepatic bile ducts associated with a variety of abnormalities in many other organ systems, such as the cardiovascular, skeletal, and urinary systems.

CASE SUMMARY

We report a rare case of Alagille syndrome. A 1-month-old male infant presented with sustained jaundice and had a rare congenital heart disease: total anomalous pulmonary venous connection (TAPVC). Sustained jaundice, particularly with cardiac murmur, caught our attention. Laboratory tests revealed elevated levels of alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, total bilirubin, and total bile acids, indicating serious intrahepatic cholestasis. Imaging confirmed the presence of butterfly vertebra at the seventh thoracic vertebra. This suggested Alagille syndrome, which was confirmed by genetic testing with a c.3197dupC mutation in the *JAG1* gene. Ursodiol was administered immediately after confirmation of the diagnosis, and cardiac surgery was performed when the patient was 1.5 month old. He recovered well after treatment and was discharged at the age of 3 month. At the age of two years, the patient returned to our clinic because multiple cutaneous nodules with xanthomas appeared, and their size and number increased over time.

CONCLUSION

We report a unique case of Alagille syndrome associated with TAPVC and severe xanthomas. This study has enriched the clinical manifestations of Alagille syndrome and emphasized the association between *JAG1* gene and TAPVC.

Key Words: Alagille syndrome; JAG1 gene; Notch signaling pathway; Total anomalous pulmonary venous connection; severe xanthomas; Case report

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Core Tip: Total anomalous pulmonary venous connection （TAPVC） and severe xanthomas are rarely reported in Alagille syndrome patients. These two symptoms have never appeared in the same patient at the same time. Here, we report a unique case of Alagille syndrome associated with TAPVC and severe xanthomas. This study has enriched the clinical manifestations of Alagille syndrome and emphasized the association between *JAG1* gene and TAPVC.

INTRODUCTION

Alagille syndrome (ALGS, OMIM 118450) is a multiple system disorder that affects the face, eyes, liver, heart, bones and other organs[1-3]. ALGS is due to biallelic mutations in the Notch signaling pathway ligand JAG1 (JAGGED1) in 94% of patients and Notch receptors (NOTCH2) in 1%–2% of patients[4-6]. ALGS can be clinically diagnosed if three of the following features are present: cardiac murmur, posterior embryotoxon (eye abnormalities), butterfly-like vertebrae, renal abnormalities, and characteristic faces in the presence of bile duct paucity on liver biopsy[7,8]; or at least 4 of the 5 major features if liver biopsy is not performed[9,10]. In some atypical cases, molecular confirmation of ALGS diagnosis is valuable[7].

A high percentage (97%) of ALGS patients have cardiac murmur[11,12], including branch pulmonary artery stenosis, peripheral pulmonary stenosis, tetralogy of Fallot (TOF), valvar pulmonic stenosis, atrial septal defect, ventricular septal defect, coarctation of the aorta, and similar issues[13]. To our knowledge, the association of total

anomalous pulmonary venous connection (TAPVC) and ALGS has never been reported in any article, but it was reported in a conference by Sanchez-Lara *et al*[14].

CASE PRESENTATION

Chief complaints

A 20-day-old male neonate with unknown cause of jaundice since birth and TAPVC was referred to our hospital.

History of present illness

The patient had jaundice and TAPVC since birth, without a history of other ailments.

History of past illness

There was no history of past illness.

Personal and family history

There was no family history of other genetic diseases. The father showed characteristic facial features: a prominent forehead, deep-set eyes with mild hypertelorism, pointed chin, and saddle-shaped nose with a bulbous tip.

Physical examination

Physical examination revealed an infant weight of 3.2 kg. Jaundiced skin and sclera were observed along with a triangular appearance. The patient showed the same characteristic facial features as his father (Figure 1). He had abnormalities in both eyes (Figure 2) (posterior embryotoxon). No positive signs were found in the lungs. Abnormal sounds and murmurs were audible upon heart auscultation. The liver was palpable with a soft edge 4.0 cm below the right costal margin.

Laboratory examinations

Biochemical analysis showed increased levels of serum gamma-glutamyl transpeptidase, total bilirubin (TBil), direct bilirubin (DBil), and total bile acids (TBAs), indicating cholestasis (Table 1).

Imaging examinations

X-ray didn't discover obvious skeletal deformities(Figure 3A), while Chest computed tomography angiography (CT) clearly shows that butterfly vertebra at the seventh thoracic vertebrae(Figure 3B). Computed tomography angiography (CTA) showed that four pulmonary veins (PVs) joined together and drained into the vertical vein (VV). The VV flowed into the dilated left innominate vein (LIV), then into the superior vena cava (SVC), and finally into the right atrium (RA) (Figure 4).

Further diagnostic work-up

Based on these findings, ALGS was suspected and confirmed by genetic testing. A heterozygous variant (c.3197dupC) in the *JAG1* gene was identified (Figure 5). This is a frame shift mutation, and it has been reported previously[10]. It is expected that the protein products encoded by this gene will be cut off prematurely, which is considered pathogenic.

FINAL DIAGNOSIS

Based on the clinical, imaging, and genetic findings, the final diagnosis was Alagille syndrome.

TREATMENT

After a clear diagnosis of ALGS, the patient began ursodiol treatment, which he has been tolerating very well. The patient underwent surgical correction of his cardiac murmur at the age of 1.5 month. He responded well to treatment and was discharged 1.5 month later.

OUTCOME AND FOLLOW-UP

The patient did not attend regular follow-up visits at our hospital; thus, no follow-up data were obtained. He returned to our clinic due to severe xanthomas at the age of two years (Figure 6). Laboratory tests revealed increased levels of alanine aminotransferase (ALT), 339 U/L; aspartate aminotransferase (AST), 396 U/L; alkaline phosphatase (ALP), 998 U/L; Tbil, 138.5 μmol/L; Dbil, 112.3 μmol/L; TBAs, 270.2 μmol/L; total cholesterol level (TCHO), 39.9 mmol/L; and triglyceride levels (TRIG), 3.79 mmol/L.

DISCUSSION

Protein Jagged-1 encoded by the JAG1 gene is one of the ligands of the Notch receptor[1]. Notch signaling pathway plays an important role in cardiovascular development[15-16]. It coordinates the morphogenesis of the cardiac chambers and valves, and regulates the formation of the cardiac outflow tract[11,12]. Therefore, malformations related to right ventricular outflow tract obstruction (RVOTO), such as stenosis at some level of the pulmonary tree and TOF, have accounted for more than 80% of cardiac murmurs in these patients[13,16]. However, a few patients have other cardiac murmurs, such as valvar pulmonic stenosis, atrial septal defect, ventricular septal defect, patent ductus arteriosus, or double-chambered RV[16].

Our patient was confirmed to have ALGS by clinical examination and genetic testing. His cardiac murmur, TAPVC, has never been reported in any article on ALGS. TAPVC is a rare cardiac murmur in which the PVs fail to return to the RA. The incidence of this rare entity is approximately 7-9 per 100 000 Live births or 0.7-1.5% of all congenital heart diseases[17-20]. TAPVC is divided into four major types. Type I: supracardiac (approximately 55%), as in this case, which is the most common type. The PVs confluence behind the left atrium, then drain into the LIV through the VV, then into the SVC or sometimes into the azygos vein, and finally into the RA[17]. Type II: intracardiac (approximately 30%), all PVs drain directly into the RA or through the common trunk of the pulmonary veins to the coronary sinus[21,22]. Type III: infracardiac (approximately 12%), after confluence behind the LA, the PVs pass the diaphragmatic esophageal hiatus through the VV，then flow into the portal vein or its branches. [21,22].

Type IV: mixed (approximately 3%), the PVs enter the RA through multiple channels[21,22].

JAG1 gene mutations are mainly associated with the development of RVOTO, which is a spectrum of diseases associated with the pulmonary valve, branches of the pulmonary artery, and the RV[16]. Thus, stenosis at some level of the pulmonary tree and TOF are the most common causes of cardiac murmur in ALGS patients. However, a number of other types of cardiac murmur have been discovered in ALGS patients. This indicates that *JAG1* mutations have a multifaceted impact on cardiac development. TAPVC has not been reported in ALGS patients in any article; however, Sanchez-Lara *et al* reported three ALGS patients at the 2006 ASHG Annual Meeting[14]. Therefore, at least five ALGS patients and three mutation sites have been found to be associated with TAPVC. We suspect that *JAG1* is closely associated with TAPVC.

Biliary stricture is the main feature in most ALGS patients, and unusual structures can cause cholestatic liver disease. The dysfunctional liver often leads to an increase in serum total cholesterol and triglycerides. Thus, hypercholesterolemia is attributable to cholestasis and may finally lead to severe xanthomas[23]. Although some medicines have been reported to improve liver function in ALGS patients, the only way to resolve the problem is liver transplantation.

CONCLUSION

Bile duct paucity is the main characteristic feature in most cases of ALGS. Here, we report a more fatal and rarer feature, TAPVC, which requires surgical correction at an early age. We also report the unusual finding of severe xanthomas. These findings suggest that *JAG1* gene may be a pathogenic gene of TAPVC. Further research should be carried out to prove this hypothesis.

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