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RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Xu Guo*; Production Department Director: *Xiang Li*; Editorial Office Director: *Jin-Lei Wang*.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

September 6, 2022

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

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

Han-Shi Zeng, Zhan-Hui Zhang, Yan Hu, Gui-Lang Zheng, Jing Wang, Jing-Wen Zhang, Yu-Xiong Guo

Specialty type: Medicine, research and experimental

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: De Raffele E, Italy; Moshref RH, Saudi Arabia

Received: November 24, 2021

Peer-review started: November 24, 2021

First decision: June 7, 2022

Revised: June 13, 2022

Accepted: July 11, 2022

Article in press: July 11, 2022

Published online: September 6, 2022



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Abstract

BACKGROUND

Alagille syndrome (ALGS) 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 ALGS. 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 ALGS, 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 mo. 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 ALGS associated with TAPVC and severe xanthomas. This study has enriched the clinical manifestations of ALGS 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 (ALGS) patients. These two symptoms have never appeared in the same patient at the same time. Here, we report a unique case of ALGS associated with TAPVC and severe xanthomas. This study has enriched the clinical manifestations of ALGS and emphasized the association between *JAG1* gene and TAPVC.

Citation: Zeng HS, Zhang ZH, Hu Y, Zheng GL, Wang J, Zhang JW, Guo YX. Alagille syndrome associated with total anomalous pulmonary venous connection and severe xanthomas: A case report. *World J Clin Cases* 2022; 10(25): 8932-8938

URL: <https://www.wjgnet.com/2307-8960/full/v10/i25/8932.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v10.i25.8932>

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

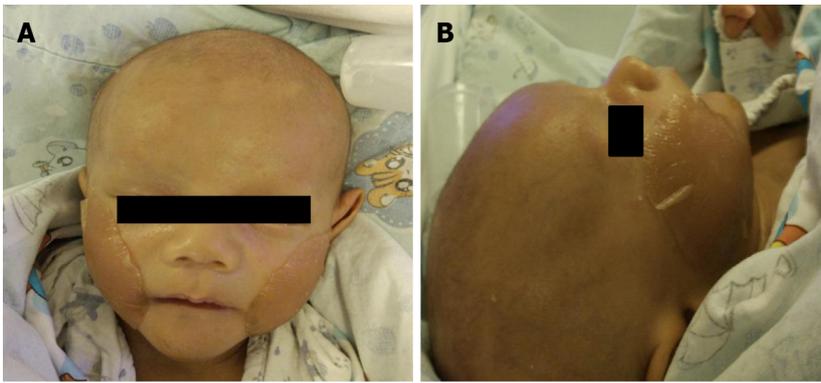
There was no history of past illness.

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.

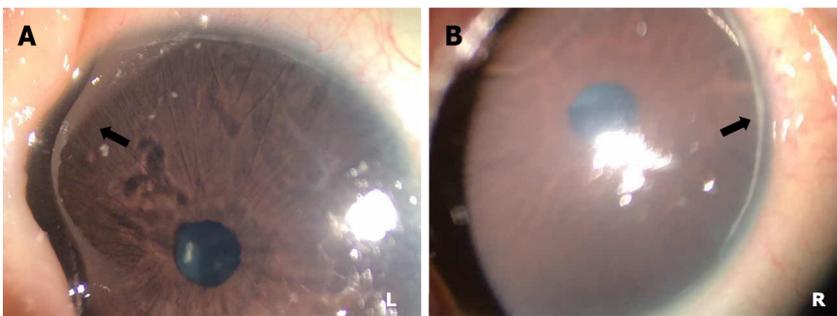
Physical examination

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.



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Figure 1 The patient shows characteristic faces of Alagille syndrome: Prominent forehead, deep-set eyes, mild hypertelorism, pointed chin, and saddle shape nose with a bulbous tip. A: Front image; B: Side image.



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Figure 2 Posterior embryotoxon. A: Posterior embryotoxon in left eye; B: Posterior embryotoxon in right eye. L: Left; R: Right.

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 (CT) angiography clearly shows that butterfly vertebra at the seventh thoracic vertebrae (Figure 3B). CT angiography 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 ALGS.

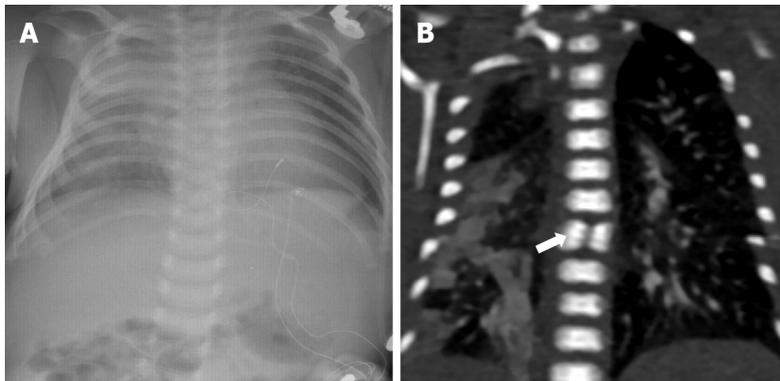
TREATMENT

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 mo. He responded well to treatment and was discharged 1.5 mo later.

Table 1 Biochemical alterations over time of the patient when he was in hospital

Biochemical indices	February 26, 2017	March 5, 2017	March 11, 2017	March 20, 2017	March 27, 2017	April 3, 2017	April 9, 2017
ALT (5-40 U/L)	107	198	266	527	256	324	444
AST (5-40 U/L)	221	382	457	620	233	378	525
GGT (8-50 U/L)	573		1015	1186	1065	1125	1114
ALP (20-500 U/L)	440		390	418	200	197	262
TP (60.0-83.0 g/L)	55.1	65.1	60.6	57.7	45.9	53.3	52.2
Alb (35.0-55.0 g/L)	36.5	40.2	38.2	38.8	30.4	34.3	35.5
Tbil (2-19 μ mol/L)	242.4	241.4	254.0	469.6	235.4	295.6	294.5
Dbil (0-6 μ mol/L)	165.5	163.6	133.1	245.9	149.0	138.7	124.4
Ibil (2.56-20.9 μ mol/L)	76.9	77.8	120.9	223.7	86.4	156.9	170.1
TBA (0-10 μ mol/L)	100	116.0	74.0	104.0	94.0	113.0	133.3

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; ALP: Alkaline phosphatase; TP: Total protein; Alb: Albumin; Tbil: Total bilirubin; Dbil: Direct bilirubin; Ibil: Indirect bilirubin; TBA: Total bile acid.



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Figure 3 X-ray and computed tomography examination. A: X-ray didn't discover obvious skeletal deformities; B: Chest computed tomography clearly showed that butterfly vertebra at the seventh thoracic vertebrae.

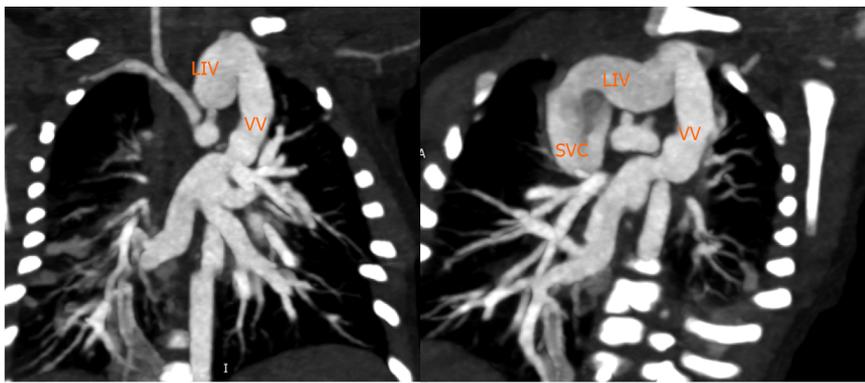
OUTCOME AND FOLLOW-UP

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, 339 U/L; aspartate aminotransferase, 396 U/L; alkaline phosphatase, 998 U/L; Tbil, 138.5 μ mol/L; Dbil, 112.3 μ mol/L; TBAs, 270.2 μ mol/L; total cholesterol level, 39.9 mmol/L; and triglyceride levels, 3.79 mmol/L.

DISCUSSION

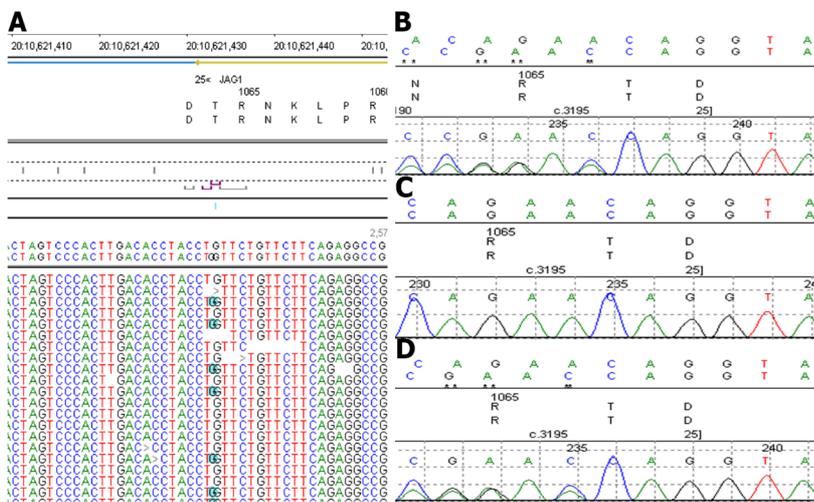
Protein Jagged-1 encoded by the *JAG1* gene is one of the ligands of the Notch receptor[1]. Notch signaling pathway plays an important role in cardiovascular development[15,16]. It coordinates the morphogenesis of the cardiac chambers and valves, and regulates the formation of the cardiac outflow tract[11,12]. 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 100000



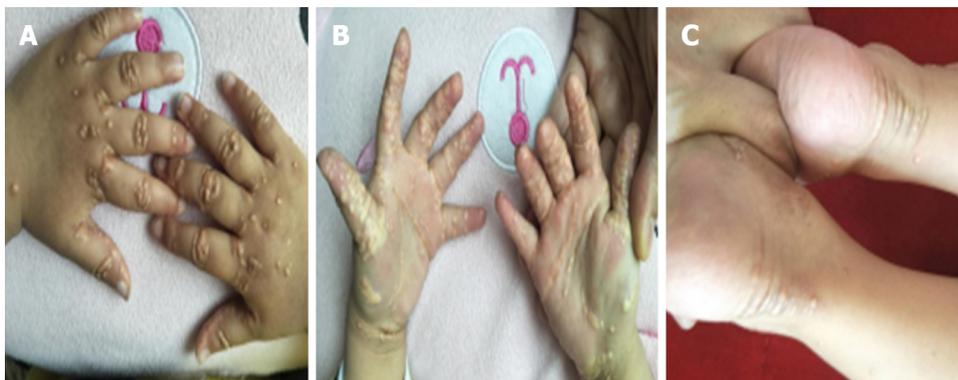
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Figure 4 The classic hemodynamic features of total anomalous pulmonary venous connection type I. LIV: Left innominate vein; VV: Vertical vein; SVC: Superior vena cava.



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Figure 5 Gene analysis results of the family. A: Next generation sequencing result of the patient; B-D: Sanger sequencing results of the patient, the mother and the father.



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Figure 6 Xanthomas seen in the surface of hands and feet. A and B: Hands; C: Feet.

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 PVs 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*[14] 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.

FOOTNOTES

Author contributions: Zeng HS conducted data curation and wrote the manuscript; Guo YX revised and approved the final manuscript; all authors contributed to the article and approved the submitted version.

Informed consent statement: The patient's guardian provided written informed consent to participate in this study. Written informed consent was obtained for the publication of any potentially identifiable images or data included in this article.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Country/Territory of origin: China

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S-Editor: Fan JR

L-Editor: A

P-Editor: Fan JR

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