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Alagille syndrome: an uncommon cause of intrahepatic cholestasis in adults

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ABSTRACT

Alagille syndrome (ALGS) is an autosomal-dominant multisystem disorder caused by mutations in *Jagged 1 (JAG1)* or *NOTCH2.* The penetrance is low but highly variable. It is almost exclusively diagnosed in children with cholestasis and, more rarely, in their adult relatives. Here, we report the case of a patient diagnosed with ALGS in adulthood. The patient was a 28-year-old male who presented with characteristic facial features, an eye abnormality, chronic cholestasis with bile duct paucity on liver biopsy, atrial defects and stenosis of the left internal carotid artery. A novel frameshift mutation, c.2087_2088insAAAAATGG (p. W697Kfs*49), in *JAG1* was identified. To our knowledge, this is the first case of ALGS diagnosed in adulthood in China. ALGS should be considered as a differential diagnosis for intrahepatic cholestasis in adult patients with a wide variety of clinical manifestations, including cardiac disease, skeletal abnormalities, ocular abnormalities and characteristic facial

features.

Key words: Alagille syndrome. Cholestasis. *JAG1*. Adult.

INTRODUCTION

Alagille syndrome (ALGS) is an autosomal-dominant disorder caused by mutations in *Jagged 1 (JAG1)* or *NOTCH2* (1). The penetrance is low but highly variable (2). It is characterized by variable combinations of hepatic anomalies, characteristic facial features and ocular, skeletal, cardiovascular and renal abnormalities (1). The diagnosis of ALGS is determined by the identification of *JAG1* or *NOTCH2* mutations. It is one of the most common causes of intrahepatic cholestasis in infancy (3) and is almost exclusively diagnosed in children (4). An ALGS diagnosis in adulthood is rare (4,5). Here, we report a case of ALGS associated with a novel *JAG1* mutation that was diagnosed in adulthood without a well-defined familial history.

CASE REPORT

Clinical manifestations

A 28-year-old male with a nine-year history of abnormal liver biochemistry tests presented to our hospital without any symptoms. His medical history was remarkable due to transient neonatal icterus, atrial septal defect with spontaneous closure at seven years of age and bilateral inborn reduction of vision. He denied a history of excessive alcohol consumption and had never taken any recreational drugs or dietary supplements. His family history was not remarkable.

Physical examination showed a peculiar triangular face with a prominent forehead and a pointed chin, and a harsh blowing systolic murmur was heard at the area of the left internal carotid artery. Laboratory investigations were as follows: alanine aminotransferase 291 U/l (normal 9-50); aspartate aminotransferase 145 U/l (normal 15-40); alkaline phosphatase 712 U/l (normal 45-125); gamma-glutamyl transpeptidase 1,010 U/l (normal 10-60); albumin 39.2 g/l (normal 40-55); globulin 37.3 g/l (normal 20-40); total bilirubin 1.9 mg/l (normal 0.2-1.0); direct bilirubin 0.7 mg/l (normal 0-0.4); total bile acid 69.4 µmol/l (normal 0-10); and cholinesterase 5.1

KU/l (normal 5.4-13.2). Serum markers for viral hepatitis A-E were all negative. Anti-mitochondrial antibody (M2) and immunoglobulin M were normal.

Magnetic resonance imaging (MRI) of the liver (Fig. 1A-D) identified multiple nodules in the right lobe that were hyperintense on T1-weighted images and enhanced in the arterial phase. This was followed by a rapid washout and they became almost completely isointense to the liver on the venous and delayed phase, which is typical of benign regenerative nodules. Furthermore, there was no evidence of dilation of the intra- and extra-hepatic bile ducts. Computed tomography (CT) angiograms of the head and neck (Fig. 1E) revealed a narrowing of the left internal carotid artery. Liver histology showed the absence of bile ducts in the portal area, while the hepatic arterioles and portal venules were normal (Fig. 1F). Immunohistochemistry of cytokeratin 7 (CK7) (Fig. 1G) revealed biliary metaplasia of periportal hepatocytes, indicating chronic cholestasis.

Detection of genetic mutations

ALGS was suspected based on the clinical features of the patient. Informed consent was obtained before a blood sample was taken from the patient and his parents for the analysis of ALGS-associated genes. Mutation analysis of ALGS-associated genes was performed by target sequence capture and next generation sequencing. A novel frameshift mutation, c.2087_2088insAAAAATGG (p. W697Kfs*49), in *JAG1* was identified in the patient. This led to a truncated mutant protein of 745 amino acids (Fig. 2). This mutation was not identified in either of his parents.

Follow-up

The patient was treated with oral ursodeoxycholic acid but the liver enzyme profile did not change significantly after one year. The patient should have been followed-up with blood tests for liver function and alfa-fetoprotein and imaging studies of the liver and cerebral vascular vessels. However, we were unable to contact him for follow-up, even though every effort was made.

DISCUSSION

This patient had five clinical features of ALGS, including dysmorphic facial features (peculiar triangular face with a prominent forehead and a pointed chin), an eye abnormality (bilateral inborn reduction of vision), chronic cholestasis with bile duct paucity on liver biopsy, congenital heart disease (atrial defect), and cerebrovascular abnormalities (stenosis of left internal carotid artery). The diagnosis of ALGS was confirmed by the identification of a mutation in *JAG1.*

ALGS is a multisystem autosomal dominant disease that was first reported by Alagille et al. in 1969 and subsequently by Watson and Miller in 1973 (1). ALGS is a heterogeneous genetic disorder caused by variations in the Notch signaling pathway ligand gene, *JAG1* (OMIM#601920) or the gene that codes for its receptor *NOTCH2* (OMIM#600275) (1). The phenotypic findings of ALGS are highly variable, ranging from an apparently normal phenotype to severe cases with liver failure that requires liver transplantation (2). The main clinical features and malformations include chronic cholestasis due to a paucity of intrahepatic bile ducts and congenital heart disease. This is primarily peripheral pulmonary stenosis or tetralogy of Fallot, butterfly vertebrae, characteristic facial features with a broad forehead, posterior embryotoxon and/or anterior segment abnormalities of the eyes and pigmentary retinopathy. Intracranial bleeding may occur as a consequence of a relatively minor head trauma due to the intracranial vascular anomalies (2). In addition, renal defects including functional and structural abnormalities have also been reported (1). Treatment of ALGS usually focuses on the consequences of liver disease and the surgical and medical treatment of congenital heart defects. The prognosis of ALGS depends on the severity of the disease in the worst affected organ system.

Although hepatocellular carcinoma (HCC) is a rare complication of ALGS, it can develop in ALGS at any age from childhood to the fifth decade of life, with most adult cases occurring at 30-40 years of age (6). Adult patients may develop HCC without cirrhosis and ALGS itself may be a risk factor for the development of HCC (6). There are no recommendations for the surveillance of HCC in ALGS. However, annual screening for HCC in ALGS patients by serum alpha-fetoprotein and ultrasonography is encouraged due to the fact that the development of HCC is unpredictable and the treatment of HCC at an early stage has a relatively good prognosis (6). The patient

described here had several liver nodules. However, unfortunately, we did not have the opportunity to repeat a radiological exam of the liver and further study the nodules histologically. According to the risk of HCC, the patients should be closely monitored by serum alpha-fetoprotein and ultrasonography every six months.

ALGS is one of the most common causes of pediatric chronic liver disease and occurs in one of 70,000 to 100,000 newborns with no sex differentiation (3). However, ALGS diagnosed in adulthood is rare. Several cases of ALGS involving liver disease diagnosed in adulthood have been reported. We searched for cases reported in the literature in English before June 2018, using the terms “Alagille syndrome” OR “arteriohepatic dysplasia” AND “adult”. The search retrieved 171 abstracts from PubMed. Among these, there were six reports of ALGS with hepatic involvement diagnosed in adulthood (Table 1). ALGS is probably underdiagnosed in adult patients as the penetrance of the disorder is low and highly variable. Some adult cases without overt liver disease are almost certainly overlooked and this pediatric disease is largely unknown to adult physicians.

Nearly 500 *JAG1* mutations and ten *NOTCH2* mutations have been identified (HGMD Professional 2018.3) in ALGS. Most *JAG1* mutations are protein-truncating variants (small deletions, small duplications/insertions and nonsense), whereas the majority of *NOTCH2* mutations are missense. A novel frameshift mutation in *JAG1*, c.2087_2088insAAAAATGG (p. W697Kfs*49), was identified in this patient. The mutation is located within exon 16 of *JAG1* and leads to a stop codon 48 amino acids after the p.W697K position and a truncated mutant protein of 745 amino acids. The p.W697Kfs*49 mutation in *JAG1* has not been reported in the HGMD database, thus indicating that it is a pathogenic variant. However, the mutation was not identified in either of his parents. In fact, approximately 60% of mutations in *JAG1* are *de novo* and germline mosaicism may occur at a frequency up to 8% (1). We speculate that this case may be the result of a spontaneous mutation or that germline mosaicism may occur in his family. Thus, the mutation was not identified in the genomic DNA extracted from blood samples of his parents.

To our knowledge, this is the first report of ALGS diagnosed in adulthood in China. Due to the fact that the phenotype of ALGS shows a variable expression that ranges

from mild cholestasis and cirrhosis to acute liver failure, it should be considered as a differential diagnosis for cholestasis in certain cases with a wide variety of clinical manifestations. These include cardiac disease, skeletal abnormalities, ocular abnormalities and characteristic facial features. The detection of a mutation in *JAG1* or *NOTCH2* is very helpful to establish the diagnosis of ALGS (1).

In conclusion, we report the first case of ALGS diagnosed in adulthood in China and a novel frameshift mutation c.2087_2088insAAAAATGG was also identified in this patient.

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Table 1. Reported cases of Alagille syndrome with hepatic involvement diagnosed during adulthood

Author	*Country*	*Age at on-set*	*Initial symptoms*	*Age at diagnosis*	*Presentation*	*Liver biopsy*	*JAG1 mutation*
Bail, 1990 (7)	France	Infancy	Jaundice	48	Enlarged liver with jaundice that spontaneously resolved during adolescence, characteristic facies, HCC	Paucity of bile ducts	ND
Murata, 2000 (5)	Japan	15	Cholestasis	32	Cholestasis, characteristic facies, heart murmur, posterior embryotoxon	Paucity of interlobular bile duct	ND
Jacquet, 2007 (4)	France	NA	Hypertension	31	Cholestasis, butterfly vertebrae, hypertension, solitary kidney, renal failure	Paucity of interlobular bile duct	Negative
Yucel, 2010 (8)	Netherlands	Childhood	Pulmonary valve stenosis, jaundice	38	Cholestasis, peculiar facies, posterior embryotoxon, pulmonary valve stenosis, hypertension, chronic pyelonephritis	ND	ND
Hayashi, 2013 (9)	Japan	NA	Heart murmur	47	Cholestasis, characteristic facies, heart murmur, butterfly vertebrae, hypoplastic and malrotated kidneys	ND	c. 1544delC, p.Thr515MetfsX49
						Paucity of	

HCC: hepatocellular carcinoma; NA: not available; ND: not done.

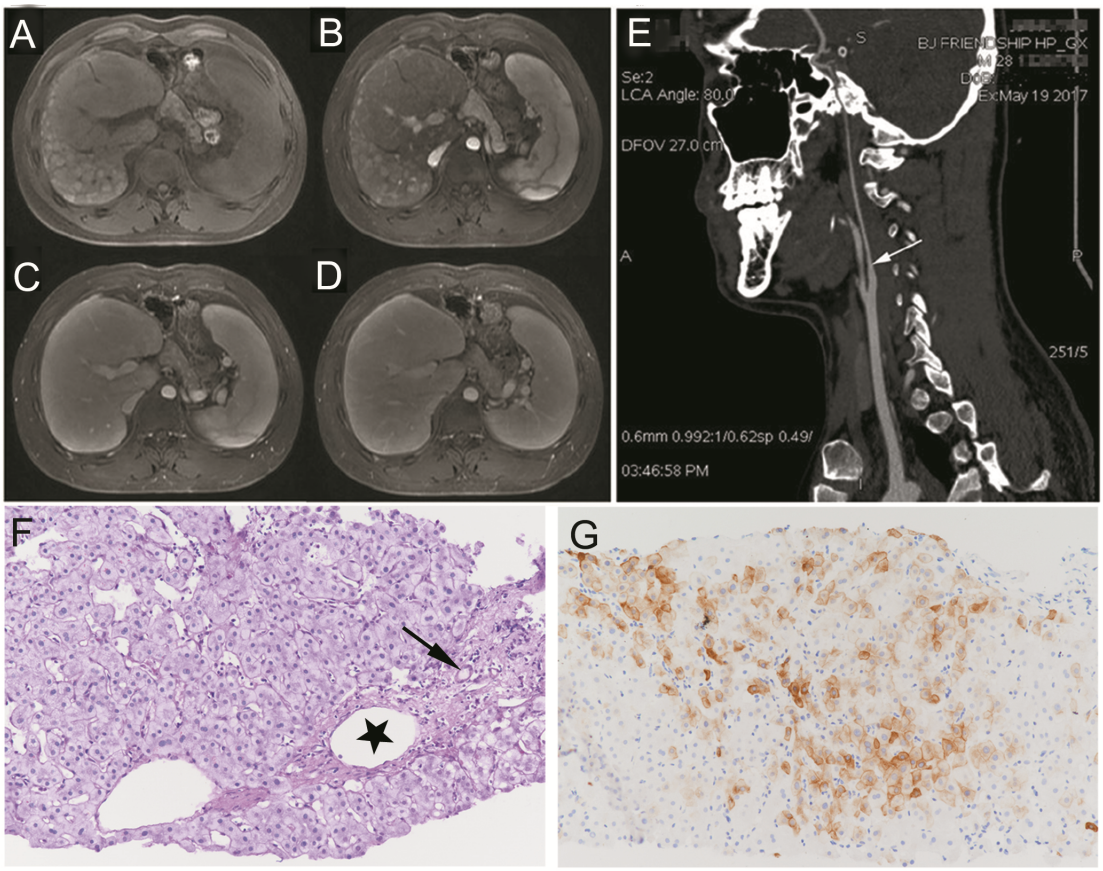

Fig. 1. Contrast-enhanced MRI of the liver showing multiple nodules in the right lobe that are hyperintense on T1-weighted images (A) and enhanced in the arterial phase (B). This is followed by a rapid washout and they become almost completely isointense to the liver on the venous (C) and delayed phase (D), which is typical of benign regenerative nodules. CT angiograms of the head and neck (E) revealed narrowing of the left internal carotid artery (arrow). Liver biopsy histology (F and G) showed the absence of bile ducts in the portal area, while the hepatic arterioles (arrow) and portal venules (star) were normal (HE, 400×). Periportal hepatocytes positive for CK7 indicated cholestasis (CK7 staining, 400×).

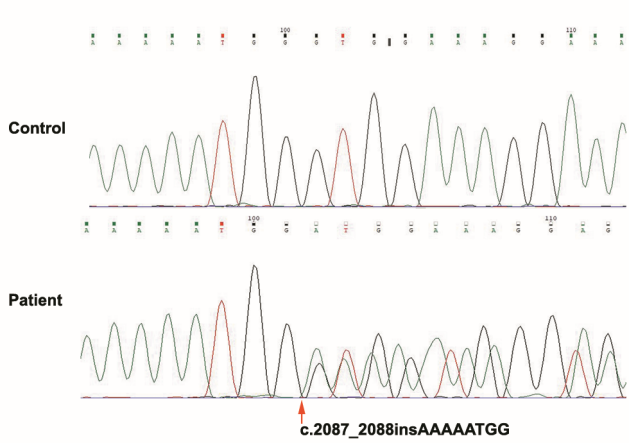

Fig. 2. Sequence analysis of the *JAG1* gene showing the heterozygous frameshift mutation, c.2087_2088insAAAAATGG.