Atypical Alagille Syndrome Diagnosed by Genomic Analysis

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Abstract

Alagille Syndrome (ALGS) is an autosomal dominant disease presented by multi-system disorders including liver, heart, eyes, vertebrae, and face. Traditionally, the diagnosis of ALGS is based on a combination of liver biopsy with at least three of the major clinical features. However, this may cause misdiagnosis of atypical or mild ALGS. Here we reported a 12-year-old boy with chief complaint about recurrent mild transaminase elevation and hepatosplenomegaly over 11 years. There were no jaundice and other system disorders. He also had liver biopsy which didn’t present paucity of intrahepatic bile duct. The genome testing demonstrated a heterozygous mutation on exon12 of JAG1 gene. The boy was finally diagnosed as ALGS and treated by ursodeoxycholic acid as well as fat-soluble vitamins. For patients with chronic and progressive liver damage, ALGS should be taken into consideration. Molecular diagnosis is particularly useful for patients with atypical or mild Alagille syndrome who do not meet classic diagnostic criteria.

Abbreviations

ALGS: Alagille Syndrome; RL: Right Lobe; LL: Left Lobe; CL: Caudate Lobe; G: Gallbladder; PV: Portal Vein; TB: Total Bilirubin; DB: Direct Bilirubin; ALB: Albumin; ALT: Alanine Aminotrans; AST: Aspartate Aminotransferase; AKP: Alkaline Phosphatase; GGT: γ-GlutamylTranspeptidase; LDH: Lactate Dehydrogenase; BA: Bile Acid

Introduction

Alagille Syndrome (ALGS) is an autosomal dominant disease presented by multi-system disorders including liver, heart, eyes, vertebrae, and face [1]. ALGS is caused by mutations in or deletions of either the JAGGED1 (JAG1) or NOTCH2 gene [2,3]. Traditionally, the diagnosis of ALGS is based on a combination of the presence of intrahepatic bile duct paucity on liver biopsy with at least three of the major clinical features including liver disease (cholestasis), congenital heart defects, vertebral abnormalities, ocular anomalies and characteristic facial features [4]. However, this may cause misdiagnosis with atypical or mild ALGS. Here we reported a 12-year-old male patient presented by recurrent transaminase elevation and hepatosplenomegaly over 11 years. There were no jaundice and other system disorders. Liver biopsy showed the patient had liver fibrosis but not the paucity of intrahepatic bile duct. The genome sequencing demonstrated a heterozygous mutation of JAG1 gene. The patient was finally diagnosed as ALGS and treated by ursodeoxycholic acid as well as fat-soluble vitamins. For patients with chronic and progressive liver damage, ALGS should be taken into consideration. Molecular diagnosis is particularly useful for patients with atypical or mild Alagille syndrome who do not meet classic diagnostic criteria.

Patient Information

A 12-year-old male patient was charged into hospital with chief complaint about recurrent transaminase elevation and hepatosplenomegaly over 11 years, which was the third time of his hospitalization. 11 years ago, the patient was found anorexia, abdominal distention, and mass on the left upper abdominal. There weren’t obvious jaundice, fever, vomits and clay stool. The patient’s liver function showed a mild elevation of transaminase while the CT scanning showed hepatosplenomegaly accompanied with loss of normal ratio of hepatic lobes. The patient also received gastroscopy examination which indicated mild esophageal varix. Finally, the patient was diagnosed with liver cirrhosis. His parents rejected further treatment and only treated with Chinese herbal medicine (no details of the herbal medicine). 5 years ago, the patient admitted to hospital again with poor appetite and pale complexion. Likewise, the patient didn’t have other symptoms.
The liver function still presented with a mild transaminase elevation. The patient received liver biopsy this time which showed swelling, ballooning degeneration of hepatocyte, focal necrosis and lymphocyte infiltration around portal tract. Neither fibrous hyperplasia nor bile ducts paucity were found. The patient was treated with injected reduced glutathione for a week and then changed into oral formula. The patient’s liver function fluctuated continuously afterward and hospitalized for the third time.

The patient was G2P2 and the birth weight is 3.8 Kg. The patient had delayed clearance of jaundice which lasted nearly 6 months after birth. There was neither growth nor mental retardation of the patient. The patient was an elder brother who was health. There was slight elevation of liver transaminase, other blood tests including Alpha-Fetoprotein (AFP), ceruloplasmin, cholesterol, and triglyceride level, coagulation function test, blood ammonia, Tandem mass spectrometry were normal. The HBsAg, anti-HCV, and autoantibody were all negative. CT scan indicated loss of normal ratio among liver lobes, with lessen of right lobe and enlargement of left and caudate lobe (Figure 1). The portal vein was on the upper limit. Other Imaging examinations including chest X-ray and cardiac ultrasonic were normal. Liver biopsy demonstrated less swelling, ballooning degeneration, focal necrosis of liver cells, however, there was mild proliferation of collagen and bile canaliculus around portal areas. The gene analysis found the boy had a heterozygous mutation of JAG1 gene on exon12 with the deletion of cytosine on p1563-1564, which caused frame shift mutation.

**Therapeutic Intervention**

The patients were diagnosed with Alagille Syndrome (ALGS) and treated with ursodesoxycholic acid and fat soluble vitamins. The patient was asked to follow-up regularly.

**Discussion**

In this case, hepatic disorder (Table 1) and facial feature were two main manifestations of the patient. No positive found on other systems. There wasn’t obvious jaundice except for prolonged neonatal jaundice. Liver biopsies didn’t show paucity of bile ducts, there was mild proliferation of bile canaliculus around portal areas instead (Figure 2). This result indicated that the liver histology of ALGS could be varied. Some patients may not present as paucity of bile duct in histology. In fact, it has been realized that a liver biopsy is no longer considered mandatory to make a diagnosis of ALGS, and the presence of cholestasis is acceptable to fulfill this criterion. The γ-Glutamyl transpeptidase and bile acid level of the patient were kept abnormal, BA was mild proliferation of collagen and bile canaliculus around portal areas. The γ-Glutamyl transpeptidase level, however, there was no positive found on other systems. The γ-Glutamyl transpeptidase and bile acid level of the patient were kept abnormal, BA was mild proliferation of collagen and bile canaliculus around portal areas. The γ-Glutamyl transpeptidase level, however, there was no positive found on other systems. BA was mild proliferation of collagen and bile canaliculus around portal areas. The γ-Glutamyl transpeptidase level, however, there was no positive found on other systems. BA was mild proliferation of collagen and bile canaliculus around portal areas. The γ-Glutamyl transpeptidase level, however, there was no positive found on other systems. BA was mild proliferation of collagen and bile canaliculus around portal areas. The gene analysis found the boy had a heterozygous mutation of JAG1 gene on exon12 with the deletion of cytosine on p1563-1564, which caused frame shift mutation.

**Diagnostic Assessment**

There was slight elevation of liver transaminase, other blood

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<th>22/07/05</th>
<th>8/11/12</th>
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<td>N/A</td>
<td>N/A</td>
<td>43.8</td>
<td>30.5</td>
</tr>
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</table>

**Abbreviations:** TB: Total Bilirubin; DB: Direct Bilirubin; ALB: Albumin; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; AKP: Alkaline Phosphatase; GGT: γ-GlutamylTransferase; LDH: Lactate Dehydrogenase; BA: Bile Acid

**Clinical Findings**

The patient had peculiar facial features with prominent forehead, bulbous nose, and pointed chin (supplementary data 1). There were no jaundice, pedal edema, purpura, spider nevi, cardiac murmur and lung rale. Abdomen examination revealed enlargement of liver and spleen. The liver was firm in texture and the span was 4.5 cm along the right mid-clavicular line while the spleen was 4 cm below the left costal margin with firm texture.

**Figure 1:** Enhanced abdomen CT scan of the patient. There was loss of normal ratio among liver lobes, with lessen of right lobe and enlargement of left and caudate lobe. The portal vein was on the upper limit.

**Figure 2:** Liver histology results of the patient. a,b: liver histology by hematoxylin and eosin staining 5 years ago; c,d: latest liver histology by hematoxylin and eosin staining; e: Ki67 staining of bile duct.

**Abbreviations:** RL: Right Lobe; LL: Left Lobe; CL: Caudate Lobe; G: Gallbladder
diagnosed. The result proved that his parents didn’t carry the same mutation. The patient had a de novo mutation. Supportive treatment is the main therapy for liver damage caused by Alagille syndrome. Ursodeoxycholic acid is recommended for cholestasis. It has been reported that liver transplantation for ALGS has an 80% 5-year survival rate, and results in some catch-up growth in 90% of affected individuals [5].

**Conclusions**

Alagille syndrome has complicated clinical manifestations varies from sub-clinical to multisystem disorders. For patients with chronic and progressive liver damage in his early life, ALGS should be taken into consideration. Molecular diagnosis is particularly useful for patients with atypical or mild Alagille syndrome who do not meet classic diagnostic criteria.

**Informed Consent**

Written informed consent was obtained from the patient’s legal guardians for publication of this case report and any accompanying images.

**References**