A Case of Infantile Alagille Syndrome With Severe Dyslipidemia: New Insight into Lipid Metabolism and Therapeutics

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Abstract

Alagille syndrome (AGS) is an autosomal dominant genetic disorder characterized by congenital heart disease, hepatic cholestasis, dyslipidemia, and characteristic facies since infancy. Cholestatic hypercholesterolemia in patients diagnosed with AGS is occasionally refractory and resistant to conventional treatments. We report the case of a 4-month-old boy diagnosed with AGS and refractory dyslipidemia due to cholestatic liver disease. He had repeated episodes of cyanosis due to pulmonary artery atresia since birth and underwent a Blalock-Taussig shunt procedure at age 3 months. At age 4 months, a laboratory test revealed severe dyslipidemia (serum total cholesterol, 1796 mg/dL; serum triglycerides [TGs], 635 mg/dL), and the presence of xanthomas. A pathogenic variant of the JAG1 gene (c.1326G > A, p.Trp442X) was detected through genetic testing. Oral ursodeoxycholate normalized hyperbilirubinemia with a subtle improvement in dyslipidemia. Combination therapy with pravastatin and fenofibrate did not successfully improve dyslipidemia. At age 20 months, altering pravastatin to atorvastatin was effective in normalizing serum cholesterol and TGs with no adverse events.

Combination therapy with atorvastatin and fenofibrate was successful in improving refractory dyslipidemia in a child with AGS. Atorvastatin is a well-known statin that can lower serum cholesterol, and fenofibrate can lower serum TG levels. We propose that atorvastatin be taken into consideration for the treatment of persistent hyperlipidemia in patients diagnosed with AGS, because atorvastatin upregulates bile acid synthesis and lipoprotein scavenging, and inhibits intrinsic cholesterol production.

Key Words: Alagille syndrome, cholestatic dyslipidemia, atorvastatin, lipid metabolism

Abbreviations: AGS, Alagille syndrome; ApoA-V, apoprotein A-V; CYP7A1, cholesterol 7α-hydroxylase; HDL-C, high-density lipoprotein cholesterol; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; HTGL, hepatic triglyceride lipase; IDL, intermediate-density lipoprotein; JAG, jagged canonical notch ligand; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LPL, lipoprotein lipase; mRNA, messenger RNA; NGS, next-generation sequencing; PPARα, peroxisome proliferator-activated receptor-α; SHP, small heterodimer partner; SREBP2, sterol regulatory element-binding protein 2; TC, total cholesterol; TGs, triglycerides; UDCA, ursodeoxycholic acid; VLDL, very low-density lipoprotein.

Alagille syndrome (AGS, OMIM No. 118450) is an autosomal dominant genetic disorder that is usually characterized by congenital heart disease, cholestasis, eye involvement, kidney defects, vertebral anomalies, and deafness [1, 2]. In addition, patients diagnosed with AGS commonly have cholestatic hypercholesterolemia/dyslipidemia since infancy or early childhood. The paucity of the intrahepatic bile duct primarily contributes to the mechanism of dyslipidemia in patients with AGS [1]. Cholestatic dyslipidemia in AGS is occasionally refractory to established therapies for cholestatic dyslipidemia, such as ursodeoxycholic acid (UDCA) [3] and cholestyramine [4]. If cholestatic dyslipidemia in patients with AGS becomes uncontrollable, liver transplantation is the only known treatment [3].

Mutation or haploinsufficiency of the JAG1 gene, which is located on chromosome 20p, is the leading cause of AGS (> 90%), whereas mutations in the NOTCH2 gene are responsible for a small number of cases, accounting for less than 1% of the total [5]. JAG1 protein plays a crucial role in NOTCH signaling for the excretion of bile juice in the liver. In terms of embryonal development, JAG1-knockout mice showed that the role of JAG1 is necessary for the development of the bile duct. Mice with portal vein–specific JAG1 deletion also demonstrated a paucity of the bile duct. This paucity of the bile duct is crucial in causing cholestatic hypercholesterolemia in patients with AGS.

Atorvastatin is a well-known and strong 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitor. In recent years, the clinical use of atorvastatin in children with hypercholesterolemia has shown excellent outcomes [6-8]. However, clinical trials of atorvastatin in infant and early-childhood cases of hyperlipidemia have rarely been reported. We herein describe the case of a patient with AGS successfully
treated with atorvastatin, as our experience with infants with AGS and refractory dyslipidemia could be informative and beneficial for the discussion on the pathogenicity and treatment of dyslipidemia due to AGS.

**Case Report**

A 2-month-old boy was referred to our university hospital to receive cardiac surgery for the treatment of pulmonary artery atresia. No consanguinity was observed in the family. He was born at gestational age 34 weeks and weighed 1640 g at the time of birth. The Apgar score was estimated to be 8 points at 5 minutes after birth. He developed severe repetitive cyanosis after birth. Angiocardiographic imaging was used to establish a diagnosis of pulmonary artery atresia (Fig. 1A). A Blalock-Taussig procedure was successfully completed at age 3 months. At age 4 months, cholestatic liver disease with jaundice was diagnosed with an elevation of serum total bilirubin (19.9 mg/dL), followed by high levels of serum direct bilirubin (16.6 mg/dL), serum total bile acid (112.3 μmol/L), serum γ glutamyl peptidase (151 IU/L), serum aspartate transaminase (110 U/L) and serum alanine transaminase (75 IU/L) (Table 1). Simultaneously, dyslipidemia was also detected with a serum total cholesterol (TC) of 408 mg/dL; low-density lipoprotein cholesterol (LDL-C), 35 mg/dL; high-density lipoprotein cholesterol (HDL-C), 12 mg/dL; and triglycerides (TGs), 564 mg/dL (see Table 1). Polyacrylamide gel electrophoresis of serum revealed that intermediate-density lipoproteins (IDLs) and very-low-density lipoproteins (VLDLs; normal range, 5%-20%) values of 45% and 25%, respectively. Abdominal magnetic resonance imaging revealed hepatosplenomegaly and a normal gallbladder (Fig. 1B and 1C). Oral UDCA was prescribed for intrahepatic cholestasis with hyperlipidemia along with fat-soluble vitamins.

At age 9 months, oral pravastatin was added at a dose of 1 mg/day, because the levels of serum TC and TGs were markedly increased. This was followed by a remarkable spread of xanthomas around the joints (Fig. 1D and 1E).

At age 11 months, oral fenofibrate treatment was added because oral pravastatin and UDCA were not successful in treating the dyslipidemia. The dyslipidemia worsened after antihyperlipidemic treatment with a combination of pravastatin and fenofibrate following UDCA. At age 12 months, serum TC and TG levels were markedly elevated to 1780 mg/dL and 635 mg/dL, respectively, even though 4 mg/d of pravastatin and 16 mg/d of fenofibrate were administered. We replaced pravastatin with 7.5 mg/d of atorvastatin because the hyperlipidemic condition was refractory to the combination therapy with pravastatin and fenofibrate. Finally, the new treatment regimen improved the dyslipidemia. At age 24 months, serum TC and TG levels were approximately within the normal range (see Table 1).

The roentgenogram showed no vertebral abnormalities, and the patient’s facial appearance was not in accordance with the characteristic phenotype of AGS.

To confirm a diagnosis of cholestatic dyslipidemia, we performed genetic testing on the patient and his parents after informed consent was obtained from the parents. Genomic DNA was extracted from peripheral blood using the QIAmp Blood Midi Kit (Qiagen). The genes responsible for hereditary intrahepatic cholestasis, including JAG1, NOTCH2, ABCCX2, SLC25A13, ATP8B1, ABCB11, ABCB4, TJP2, HSDB7, AKR1D1, CYPIA1, BAAT, EPAT1, SLC10A1, ABCB1, SLC4A2, and SLCO1A2, were analyzed by next-generation sequencing (NGS) with targeted sequencing [9]. Genetic testing revealed that the patient had a heterozygous mutation in the JAG1 gene: NM_000214.3:c.1326G > A, p.Trp442X. This variant was not found in either of the parents. This de novo variant of the JAG1 gene has been reported to be pathogenic in AGS [10, 11].

**Discussion**

We encountered an infantile case of AGS presenting with severe dyslipidemia. Our case showed extreme hypercholesterolemia and hypertriglyceridemia, associated with high levels of IDL and VLDL and low levels of LDL-C and HDL-C.

![Figure 1.](https://academic.oup.com/jes/article/6/3/bvac005/6511002/2)

**Figure 1.** A, Roentgenogram shows the hypoplasia of peripheral pulmonary artery branches associated with pulmonary atresia on the catheterized examination. B and C, Abdominal magnetic resonance imaging shows liver enlargement, mild splenomegaly, and a normal gallbladder. D and E, Yellow arrows indicate xanthomas identified around multiple joints.
HDL-C. Reportedly, patients with AGS have abnormal lipoprotein patterns, which differ depending on the degree of hyperbilirubinemia [12]. The lipid profile of patients with AGS and mild hyperbilirubinemia shows high levels of LDL-C and HDL-C, with increased levels of serum apoprotein A-I and apoprotein A-II. However, patients diagnosed with AGS who have severe hyperbilirubinemia show dyslipidemia with lower levels of LDL-C and HDL-C, which is associated with low levels of apoprotein A-I and apoprotein A-II [12]. LDL and HDL are cholesterol-rich lipoproteins. One of the pivotal functions of the hepatic triglyceride lipase (HTGL) is to convert IDL to LDL, and the main function of lipoprotein lipase (LPL) is to convert VLDL to IDL. IDL and VLDL are TG-rich lipoproteins. Thus, HTGL plays an important role in TG level regulation in the blood by maintaining steady levels of IDL, HDL, and LDL. In that context, our patient’s condition theoretically indicated that LPL activity and/or HTGL activity might have decreased, depending on the severity of cholestasis.

In contrast, a previous report documented that the SRB1 gene, the gene of the HDL receptor, was upregulated in the liver of patients with AGS [13]. Upregulated SRB1 messenger RNA (mRNA) in the liver is helpful in scavenging HDL-C converted from IDL and VLDL with cholesteryl ester transfer protein, which is a compensatory mechanism in patients with AGS that might be protective against atherosclerosis [14]. However, our case suggests the possibility that premature HDL can accumulate because of a decrease in HTGL activity and/or a mass due to cholestatic liver damage, thus indicating that mature HDL levels could be decreased by decreased HDL metabolism in the present patient [15].

This was the first reported case of the therapeutic use of atorvastatin for infants with AGS and cholestatic dyslipidemia. A similar case in terms of severity was previously described by Hannoush et al [16]. They reported that cholestatic dyslipidemia was successfully treated with UDCA [16]. The case reported by Hannoush and colleagues [16] might have been a case of spontaneous recovery of dyslipidemia. However, the index case was refractory to UDCA therapy, pravastatin, and fenofibrate therapy. We emphasize that atorvastatin therapy was effective and safe in terms of lowering serum TC and TG levels in refractory cases, with no adverse effects. Atorvastatin is widely used as a statin in the treatment of hypercholesterolemia and has proven beneficial in hyperlipidemic patients. Atorvastatin is well known as a statin with great effectiveness in lowering circulating LDL-C levels. Statins upregulate the expression of hepatic LDL receptors at the transcriptional level by activating sterol regulatory element-binding protein 2 (SREBP2), whereas it reduces intrinsic cholesterol production by the inhibition of HMG-CoA reductase, the rate-limiting enzyme of cholesterol synthesis. LDL (remnant VLDL) is also captured by the apoprotein B receptor and LDL receptor in the liver. Therapeutic uses of atorvastatin in infants have not been reported in the literature, although the efficacy and safety of atorvastatin treatment in adolescents and children with familial hypercholesterolemia have been reported [6]. Its safety and efficacy in infants with AGS should be verified in future clinical studies.

Interestingly, atorvastatin upregulates cholesterol 7 alpha-hydroxylase (CYP7A1) by downregulating the small heterodimeric partner (SHP) gene in the rodent liver. CYP7A1 is the first rate-limiting enzyme in the bile acid synthesis pathway in the liver [17]. Reportedly, atorvastatin has a stronger effect on fecal excretion of bile acids than rosuvastatin and lovastatin [18]. In this context, atorvastatin has a unique effect of lowering circulating cholesterol by cholesterol excretion into the intestine by increasing hepatic bile acid pro-

### Table 1. Therapeutic management and laboratory findings for cholestatic dyslipidemia of the index patient

| Patient age, mo | Alteration of antihyperlipidemic drugs | Biochemical examination of serum | 4 | 9 | 11 | 12 | 20 | 22 | 24 |
|----------------|---------------------------------------|---------------------------------|---|---|---|---|---|---|---|
|                | Initiating with UDCA | Adding pravastatin | Adding fenofibrate | Increasing dosage of pravastatin and fenofibrate | Adding atorvastatin and ceasing pravastatin | Increasing dosage of atorvastatin | Increasing dosage of atorvastatin |
| UDCA/d         | 80 mg | 80 mg | 80 mg | 80 mg | 80 mg | 80 mg | 80 mg |
| Pravastatin/d  | –     | 1-2 mg | 3 mg | 4 mg | –     | –     | –     |
| Fenofibrate/d  | –     | –     | 8 mg | 16 mg | 16 mg | 16 mg | 16 mg |
| Atorvastatin/d | –     | –     | –     | –     | 2.5 mg | 5.0 mg | 7.5 mg |
| Normal range   | Total cholesterol, mg/dL | 125-220 | 408 | 843 | 961 | 1796 | 957 | 519 | 234 |
|                | LDL cholesterol, mg/dL | 70-139 | 35 | n.d. | 184 | 137 | 170 | 115 | 79 |
|                | HDL cholesterol, mg/dL | 40-90 | 12 | n.d. | 10 | 3 | 15 | 9 | 37 |
|                | Triglycerides, mg/dL | 50-149 | 564 | 635 | 496 | 635 | 467 | 378 | 237 |
|                | Total bilirubin, mg/dL | 0.2-1.2 | 19.9 | 6.62 | 3.85 | 3.28 | 1.15 | 1.03 | 0.8 |
|                | Direct bilirubin, mg/dL | < 0.4 | 16.6 | 4.77 | 2.46 | 1.93 | 0.67 | 0.51 | 0.35 |
|                | AST, U/L | 12-35 | 110 | 156 | 238 | 110 | 171 | 132 | 92 |
|                | ALT, U/L | 6-33 | 75 | 151 | 258 | 126 | 150 | 83 | 56 |
|                | γGT, U/L | 3-54 | 151 | 1298 | ND | 1001 | ND | 436 | 284 |
|                | Total bile acid, μmol/L | < 14.4 | 112.3 | 174.8 | ND | 288.4 | n.d. | n.d. | 38.6 |

Abbreviations: γGT, γ glutamyl transpeptidase; ALT, alanine transaminase; AST, aspartate transaminase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; n.d., not done; UDCA, ursodeoxycholic acid.
duction. Reportedly, hepatic mRNA of CYP7A1 was statistically significantly reduced in AGS patients, indicating that a reduction in the cholesterol-to-bile acid conversion contributed to the high cholesterol content in the liver of patients with AGS [13]. The major upregulated proteins in hepatic cholesterol production, including farnesoid X receptor, SHP, and liver X receptor α, might be increased in patients with AGS, indicating that impairment of the negative feedback mechanism accelerates hepatic cholesterol accumulation [13]. In this context, we expect that atorvastatin could have desirable effects against hyperlipidemia in patients with AGS by upregulating hepatic CYP7A1 mRNA through SHP downregulation at the transcriptional level, in addition to enzymatic inhibition of HMG-CoA reductase, compared with pravastatin.

Huang et al [19] reported that combination therapy with atorvastatin and fenofibrate reduced the levels of circulating TC and TGs in rats that were fed a high-fructose diet, followed by upregulation of hepatic mRNA of peroxisome proliferator-activated receptor-α (PPARα) better than sole treatment with atorvastatin. The TG-lowering effects of fenofibrate were mediated by upregulation of apoprotein A-V (ApoA-V) by PPARα in the liver, whereas fenofibrate effectively upregulates hepatic PPARα at the transcriptional level. PPARα plays a crucial role in the homeostasis of lipid and lipoprotein metabolism at the transcriptional levels [20]. Activated PPARα induces a reduction in serum TGs and an increase in HDL-C [20]. Activation of PPARα increases the production of LPL and ApoA-V in the liver, while it decreases the circulating apoprotein C-III, which inhibits LPL activity, thereby enhancing the catabolism of TG-rich lipoproteins and reducing serum TG levels [20-22]. PPARα activation also upregulates the expression of genes involved in β-oxidation pathways. Fatty acid levels in the liver are decreased through enhanced β-oxidation and increased expression of hepatic acyl-CoA synthase [23]. Thus, the hepatic production of VLDL particles is attenuated by PPARα activation [24]. In addition, atorvastatin directly upregulates ApoA-V production in the liver. ApoA-V is an important factor in the circulating TG-lowering mechanism [23]. In this context, atorvastatin has an additive TG-lowering effect based on PPARα upregulated by fenofibrate in the liver, although atorvastatin itself is not able to upregulate PPARα effectively [26]. We hypothesized that fenofibrate was necessary to treat the present patient diagnosed with AGS because atorvastatin is less effective than PPARα agonists in terms of lowering TG levels.

We detected a pathogenic variant of the JAG1 gene in a patient with AGS using NGS. Pediatricians usually face difficulties in diagnosing infantile cholestatic liver diseases. In particular, our patient showed an atypical phenotype of AGS, since he neither had vertebral abnormalities nor specific facial characteristics. Biliary atresia is a frequently encountered cholestatic hepatic disease during infancy [27]. The differential diagnosis of AGS and biliary atresia is usually difficult for pediatricians and pediatric surgeons. We suggest using genetic analysis using NGS, a noninvasive and effective tool, for a prompt diagnosis by differentiating infantile cholestatic liver diseases. This diagnostic tool is recommended before exploratory laparotomy as a less invasive method for children with cholestatic liver disease. Diagnosis based on genetic testing also helps determine the proper treatment policy and follow-up plan.

Conclusion
We report a case of infantile AGS successfully treated with atorvastatin, based on the combination of UDCA and fenofibrate. Our experience suggests that add-on atorvastatin therapy could be effective for the improvement of refractory dyslipidemia in patients diagnosed with AGS by accelerating bile acid production and excretion, inhibiting cholesterol production, and upregulating lipoprotein scavenging. We believe that a clinical trial involving treatment with atorvastatin is necessary for infant and early-childhood AGS with severe dyslipidemia. We start in earnest the discussion on strong statin treatment in hyperlipidemic AGS patients with unique lipid metabolism.

Acknowledgments
We are grateful to Dr T. Sugiura and Dr T. Togawa (Department of Neonatology and Pediatrics, Nagoya City University Graduate School of Medical Science) for genetic analysis using targeted NGS. We would like to thank Editage (www.editage.com) for English-language editing.

Financial Support
The authors received no financial support for the research, authorship, and/or publication of this article.

Disclosures
The authors have nothing to disclose.

Data Availability
Some or all data generated or analyzed during this study are included in this published article or in the data repositories listed in “References.”

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