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Outcome of Alagille Syndrome Patients Who Had Previously Received Kasai Operation during Infancy: A Single Center Study

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Purpose: Infants with Alagille syndrome (AGS) are occasionally misdiagnosed as biliary atresia and subsequently undergo Kasai operation. The purpose of this study was to investigate the outcome of patients with AGS who had previously received Kasai operation during infancy.
Methods: This retrospective study was conducted at the Department of Pediatrics, Samsung Medical Center. We compared the prognosis and mortality between those who had undergone Kasai operation during infancy (Kasai group) and those who had not (non-Kasai group).
Results: Among the 15 children with AGS, five had received Kasai operation, while 10 had not. All subjects in the Kasai group revealed neonatal cholestasis, while 70% of the non-Kasai group showed neonatal cholestasis. Liver transplantation was performed in 100% (5/5) among the Kasai group, and 20.0% (2/10) among the non-Kasai group (p=0.007). Mortality was observed in 60.0% (3/5) among the Kasai group, and 10.0% (1/10) among the non-Kasai group (p=0.077).
Conclusion: Although overall mortality rate did not significantly differ between the two groups, the proportion of patients receiving liver transplantation was significantly higher in the non-Kasai group. The relatively worse outcome in AGS patients who had received Kasai operation may be due to the unfavorable influences of Kasai operation on the clinical course of AGS, or maybe due to neonatal cholestasis, irrespective of the Kasai operation.

Key Words: Alagille syndrome, Kasai operation, Cholestasis, Liver transplantation

INTRODUCTION

Alagille syndrome (AGS) is a complex autosomal dominant disorder due to defects in the Notch sig-naling pathway, and is characterized by paucity of the intrahepatic bile ducts, cholestasis, congenital heart defects, dysmorphic facies, and skeletal and eye anomalies [1]. The clinical diagnosis of AGS has

been based on the classic criteria established by Alagille et al. [2], which requires a minimum of 3 out of 5 major clinical features; chronic cholestasis due to bile duct paucity, congenital heart disease (most commonly peripheral pulmonary artery stenosis), vertebral anomalies (butterfly vertebrae), ocular anomalies (posterior embryotoxon), and the abnormal facies (recognizable dysmorphic features).

The most common initial presenting sign of AGS in infancy is conjugated hyperbilirubinemia, which can be difficult to distinguish from other causes of obstructive cholestasis, especially biliary atresia [3]. A liver biopsy, no longer mandatory if cholestasis is present, typically shows paucity of the intrahepatic bile ducts. However, in infancy ductal proliferation may occasionally be seen, usually with portal inflammation, which may lead to a misdiagnosis of biliary atresia and subsequently receive Kasai operation [4]. Kasai operation in AGS results in significant hepatic morbidity due to profound cholestasis and is an important indication for liver transplantation [3].

The aim of this study was to evaluate the clinical features and outcomes of patients with AGS who had previously received Kasai operation during infancy by comparison with those who had not.

MATERIALS AND METHODS

The medical records of 15 patients diagnosed with AGS and followed at the Department of Pediatrics, Samsung Medical Center (Seoul, Korea) between 1999 and 2014 were retrospectively reviewed. The diagnosis of AGS required at least three of the five major clinical features; chronic cholestasis, congenital heart disease, "butterfly-like" vertebrae, posterior embryotoxon, and peculiar faces, or *JAG1* gene mutation. Complex intracardiac disease was defined as a need for intervention or the critical condition having heart failure, hypoxemia, or hemodynamic instability [4].

Patients were divided into two groups according to whether they had received Kasai operation during infancy. Patients who had received Kasai operation

during infancy were included in the "Kasai group", and those who had not received Kasai operation were included in the "non-Kasai group". We compared the clinical features, prognosis, and mortality of the patients in the two groups. Comparison between the two groups was conducted by the Fisher's exact test using the IBM SPSS Statistics ver. 22.0 for Windows (IBM Co., Armonk, NY, USA). This study was approved by the institutional review board of Samsung Medical Center (2015-01-060-001).

RESULTS

Fifteen patients were diagnosed with AGS (Table 1). Kasai operation had been conducted in five patients (33.3%). *JAG1* gene analysis was performed in eight subjects, and gene mutations were detected in seven of them (87.5%).

All of the patients in the Kasai group had neonatal cholestasis (100%), while seven patients in the non-Kasai group revealed neonatal cholestasis (70.0%). The five patients in the Kasai group had been initially misdiagnosed as biliary atresia. Three of the five subjects (60.0%) had received Kasai operation at other hospitals. They were later referred to our hospital and diagnosed as AGS. The median age

Table 1. Characteristics and Prognosis of Alagille Syndrome Patients

	Kasai group (n=5)	Non-Kasai group (n=10)
Sex (male:female)	2:3	2:3
Neonatal cholestasis	5/5 (100)	7/10 (70.0)
Cardiac anomalies	3/5 (60.0)	10/10 (100)
Abnormal facies	5/5 (100)	10/10 (100)
Vertebral anomalies	5/5 (100)	10/10 (100)
Ocular anomalies	1/5 (20.0)	4/10 (40.0)
Median age at liver biopsy (d)	65 (52-95)	617 (45-1,880)
Histology		
Bile ductular proliferation	5/5 (100)	2/6 (33.3)
Bile duct paucity	2/5 (40.0)	5/6 (83.3)
JAG1 mutation	2/3 (66.6)	5/5 (100)
Liver transplantation	5/5 (100)	2/10 (20.0)
Deaths	3/5 (60.0)	1/10 (10.0)

Values are presented as number only, number (%), or median (range).

at liver biopsy for the Kasai group was 65 days (range, 52-95 days), whereas for the non-Kasai group it was 617 days (range, 45-1,880 days). Histologic findings on liver biopsy specimens revealed bile duct paucity in 2 out of 5 patients (40.0%) in the Kasai group, and in 5 out of 6 patients (83.3%) in the non-Kasai group. Bile ductule proliferation was observed in all of the subjects (100%) in the Kasai group, and in 2 out of 6 subjects (33.3%) of the non-Kasai group. Intraoperative cholangiogram was performed in two patients in the Kasai group, who had received Kasai operation at our hospital due to findings consistent with extrahepatic biliary atresia. Medical records lacked information of the other three patients in whom Kasai operation was conducted at other hospitals. One patient in the non-Kasai group did not proceed to receive Kasai operation as findings on intraoperative cholangiogram were inconsistent with biliary atresia.

The median follow-up duration of all AGS patients was 528 days (range, 94-5,723 days). One patient (20.0%) in the Kasai group and four patients (40.0%) in the non-Kasai group had complex intracardiac diseases (33.3%). The patient in the Kasai group received balloon dilatation due to pulmonary stenosis. Among the non-Kasai group, two patients received closure operation for patent ductus arteriosus, one patient underwent angioplasty due to stenosis of left and right pulmonary arteries, and one patient received coarctoplasty due to coarctation of the aorta. None of the patients with complex intracardiac diseases died during or after cardiac interventions or surgeries. Liver transplantation was performed in 100% (5/5) among the Kasai group, and 20.0% (2/10) among the non-Kasai group ($p=0.007$). Mortality was observed in 60.0% (3/5) among the Kasai group, and 10.0% (1/10) among the non-Kasai group ($p=0.077$). All of the patients in the Kasai group eventually received liver transplantation at the median ages of 12 months (range, 7-29 months). The indications for liver transplantation were refractory pruritus and xanthomas, biliary cirrhosis, somatic growth retardation and development delay. Refractory pruritus and xanthoma were present in all of the

five children (100%), and biliary cirrhosis in two patients (40.0%). Two patients (40.0%) revealed somatic growth retardation and developmental delay. Three (60.0%) died in the Kasai group. Two of the mortalities were due to acute rejection leading to liver failure, the 15 days after cadevouric donor liver transplantation, and 13 days after living related liver transplantation, respectively. One was due to intra-abdominal hemorrhage on the following day of surgery. In the non-Kasai group, two patients (20.0%) underwent liver transplantation due to refractory pruritus and xanthomas at ages of 33-month-old and 10-month-old, respectively. One (10.0%) died of multiorgan failure after the seventh day of surgery. The surviving patients are currently well without serious complications.

DISCUSSION

We have compared the clinical features and outcomes between the patients with and without a history of Kasai operation. The results or our study show that all of the patients with a history of Kasai operation had ultimately received liver transplantation in the future. The percentage of liver transplantation was relatively higher in those who had received Kasai operation in infancy compared to those who had not (100% vs. 20.0%), leading to a relatively higher overall mortality rate (60.0% vs. 10.0%). Our study is the first in Korea to compare the outcome of AGS between patients who had previous received Kasai operation during infancy and those who had not.

According to previous studies, the presence of clinical features in AGS are diverse, showing a bile duct paucity of 75-100%, cholestasis of 83-100%, congenital heart diseases of 85-98%, butterfly vertebrae of 32-87%, peculiar facies of 70-98%, ocular anomalies of 30-88% [2,5-10]. Compared to these previous studies, bile duct paucity was less frequently detected in our study, while the prevalence of vertebral and facial anomalies was relatively higher in our study. The relatively lower frequency of bile duct paucity in our study may have been due to those in

the Kasai group because liver biopsy was performed in early infant period, leading to a misdiagnosis of biliary atresia.

Bile duct paucity is not present on initial biopsy in patients with AGS in early infant period, and initial findings may actually reveal bile duct proliferation leading to a misdiagnosis of biliary atresia [4]. One study that investigated serial liver biopsies in AGS patients demonstrated that bile duct paucity is more common in older infants and children rather than those of younger age [7]. Emerick et al. [7] found that bile duct paucity was present in only 60% of 48 AGS infants under 6 months of age, while it was observed in 95% of 40 patients who underwent biopsy after 6 months of age. Meanwhile, Kaye et al. [3] reported that bile duct proliferation was more frequently detected in children with AGS who had received Kasai operation, while bile duct paucity was more prevalent among AGS patients who had not received Kasai operation, which correlates with the findings of our study. Explorative laparotomy with intraoperative cholangiography should be undertaken by an experienced surgeon and careful interpretation of an intraoperative cholangiography is necessary before proceeding with a Kasai operation.

The correlation of Kasai operation and prognosis in AGS has been investigated in several studies [3,6]. Kaye et al. [3] reported that compared to AGS children who had not received Kasai operation, those who had demonstrated a significantly higher rate of liver transplantation (47.3% vs. 13.9%) and higher mortality (31.6% vs. 2.8%) in the future. Hoffenberg et al. [6] reported that the liver transplantation rate in AGS patients who had previously undergone Kasai operation was higher than that of non-Kasai patients (75% vs. 23%).Our results are consistent with these previous reports, in which suggests that Kasai operation does not benefit but rather worsens the clinical course of AGS patients. This may be due to exposure to intestinal contents and/or ascending cholangitis via the portoenterostomy deteriorating the status of formerly abnormal bile ducts, or the procedure itself may exert direct detrimental effects on the disease [3]. Emerick et al. [7] reported that

approximately 15% of AGS patients required liver transplantation due to progressive liver diseases, cirrhosis, and failure. The most common indications for liver transplantation in the AGS population were persistent cholestasis leading to severe pruritus and xanthomata, recurrent and poorly healing bone fractures, end-stage liver disease, and portal hypertension with gastrointestinal bleeding [6,7]. Liver transplantation is known as a good treatment option for AGS patients with progressive cholestasis and end-stage liver diseases [11]. The 5-year survival rate following transplantation has been reported to improve up to 80% [12]. Therefore, AGS patients with neonatal cholestasis may rather benefit from liver transplantation in the future when their disease status progresses to biliary cirrhosis and end-stage liver diseases, instead of Kasai operation during infancy. Parental mosaicism of *JAG1* mutations in families with AGS has been reported and may produce bile duct paucity in donor candidates [12]. It may be helpful to conduct genetic analysis for *JAG1* mutation in donors of family members of AGS, who reveal a normal phenotype.

Neonatal cholestatic jaundice has been reported as an independent prognostic factor in AGS [13]. According to the study of Lykavieris et al. [13], multivariate analysis of prognostic factors of 10 year survival with native liver in AGS patients revealed that neonatal cholestatic jaundice was the only independent prognostic factor (relative risk [RR], 2.52; 95% confidence interval [CI], 1.25-5.88; $p=0.012$), while a history of no Kasai operation was not (RR, 0.65; 95% CI, 0.35-1.21; not significant). These results suggest that the presence of neonatal cholestasis itself may negatively affect the course in AGS, irrespective of the history of Kasai operation. The presence of complex intracardiac disease, which has been defined as a need for intervention or the critical condition having heart failure, hypoxemia, or hemodynamic instability has been suggested as the most significant indicator of early mortality [4,7,10]. However, we were unable to observe this subgroup of poor outcome due to cardiac origin in our study.

There are several limitations of this study. First,

there is the possibility that patients in the Kasai group reflect a subgroup of AGS patients with neonatal cholestatic jaundice predestinated to progress to an end-stage liver disease, regardless of the Kasai operation they had received. The presence of neonatal cholestatic jaundice itself may have led to unfavorable courses in the Kasai group. In the neonatal period, AGS patients are likely to not present with all clinical features of AGS. This may lead to the misdiagnosis of biliary atresia instead of AGS. The difficulty of diagnosing AGS at early infancy lies in the variable expression of clinical features at this period. Moreover, genetic analysis itself is insufficient for determining the diagnosis as *JAG1* mutation gene analysis is incapable of diagnosing all cases of AGS. Second, there are limitations in concluding that Kasai operation during infancy leads to a harmful clinical course in AGS patients, due to the small number of subjects in our study. Further large-scale prospective studies are required in the future.

In summary, our study shows the future outcomes of AGS patients who had received Kasai operation during infancy. The results of our study highlight the importance of differentiating AGS from other causes of neonatal cholestasis, especially biliary atresia, as inappropriate surgical intervention may worsen the outcome. Thorough medical investigation with particular consideration of AGS is essential for the pediatrician to identify subclinical features in patients with conjugated hyperbilirubinemia in the early infantile period.

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