The negative impact of Alagille syndrome on survival of infants with pulmonary atresia

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Received for publication Dec 12, 2006; accepted for publication Dec 18, 2006.

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J Thorac Cardiovasc Surg 2007;133:1094-6

0022-5223/\$32.00

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doi:10.1016/j.jtcvs.2006.12.009

Alagille syndrome (AGS) is a complex disorder with multisystemic involvement, including the liver, heart, kidneys, cerebral vasculature, skeleton, eyes, and face.¹ A structural heart defect is one of the diagnostic criteria for AGS. These vary in severity, with peripheral pulmonary arterial stenosis being a common problem. Pulmonary atresia (PA) is a rare presentation in AGS, but we were impressed by the poor outcome of such infants following review of our institutional experience over the last 20 years. The information has particular relevance in this era where prenatal diagnosis of both AGS and PA can be made.

Clinical Summary

A number of information sources including cardiac, genetic, and gastroenterology departmental databases and hospital medical

TABLE 1. Clinical summary, surgical procedures, and outcomes in 5 cases presenting with Alagille syndrome and pulmonary atresia between 1985 and 2005

Patient (gender)	Born/status/age at last follow-up	Cardiac lesions	Alagille-specific features	Genetics/family history
1 (M)	2003/alive/2.5 y	PA/VSD/PAH with minor collaterals	Jaundice, butterfly vertebra, radioulnar synostosis, mild facial dysmorphism	<i>JAG1</i> mutation/mother and maternal aunt have mutation and mild cardiac problems, maternal cousin has CHD
2 (M)	2002/dead/2.5 y	PA/IVS/PAH with MAPCAs	Butterfly vertebra, pointed chin, high forehead, bilateral Axenfeld-Reiger anomaly	<i>JAG1</i> mutation/father has heart murmur, paternal grandfather has had mitral valve replacement, no family gene testing
3 (M)	1995/dead/2.5 y	TOF/PAH	Decreased bile ducts, prominent forehead, pointed chin	No testing/father has TOF, 2 siblings have pulmonary valve stenosis
4 (F)	1987/dead/5.5 y	PA/VSD/PAH with MAPCAs	Paucity of intrahepatic bile ducts, frontal bossing, small mandible, butterfly vertebra, global DD	No testing/no mention of similar conditions in immediate or extended family members
5 (M)	1976/dead/20 y	PA/VSD/PAH with MAPCAs	Thickened portal tracts, butterfly vertebrae, prominent forehead, pointed chin	No testing/no mention of similar conditions in immediate or extended family members

PA, pulmonary atresia; VSD, ventricular septal defect; IVS, intact ventricular septum; PAH, pulmonary artery hypoplasia; TOF, tetralogy of Fallot; MAPCAs, major aortopulmonary collateral arteries; DD, developmental delay; CHD, congenital heart disease; DUA, death under anesthesia; RV, right ventricle.

records were searched and cross-referenced to identify patients with AGS and/or PA between 1985 and 2004. We identified 26 patients with AGS and 505 patients with PA, 5 of whom had both diagnoses. Patients with AGS and only peripheral pulmonary arterial stenoses were excluded. Our institution serves a population of more than 6 million people, performs more than 400 cardiac procedures annually, and has a raw operative mortality of <2%.

Five cases of AGS with PA were identified (see Table 1): 4 with PA and ventricular septal defect (VSD), 1 with PA and intact ventricular septum. Four of 5 patients (80%) have died as a result of cardiac disease, and the remaining individual is receiving palliative management.

The most striking feature is the failure of small pulmonary arteries to grow following systemic-to-pulmonary arterial shunts. In 3 patients, collateral pulmonary blood flow was deemed sufficient to allow delay in initial surgery for more than 6 months. Where pulmonary arteries have been considered to be borderline adequate, establishment of a pulmonary arterial confluence and/or biventricular repair have not been successful.

Discussion

AGS is an autosomal-dominant disorder caused by mutations or deletions in the *JAG1* gene, located on chromosome 20p11.2-20p12. The *JAG1* gene produces a protein, *Jagged1*, which is an important ligand in the *NOTCH* signaling pathway and plays an important role

in early cell determination.² The expression of *Jagged1* within the developing embryo of both mice and humans correlates with cardiovascular disease in AGS.³ Expression is primarily seen in structures destined to become part of the right-sided circulatory system, including the sixth pharyngeal arch, which gives rise to the pulmonary artery, as well as in the pulmonary outflow tract. No clear genotype-phenotype correlations have yet been established to account for the high degree of variability of both the number and the extent to which the various organ systems are involved. In a study of monozygotic twins with an identical splice site mutation in *JAG1*, 1 twin had PA and the other had only mild cardiac disease but more severe hepatic involvement.⁴ Although it is recognized that mutations or deletions in *JAG1* cause AGS, other factors including environmental triggers, modifying genetic loci, and epigenetic factors may contribute to the phenotype of an individual, as is the case in many other forms of structural heart disease.

Cardiac disease significantly impacts on the life expectancy of patients with AGS and accounts for 34% of mortality.¹ PA alone, with or without a VSD, is a serious condition; however, with contemporary surgical techniques, most patients survive infancy, with an increasing number expected to achieve biventricular repair.¹ It is not clear why the patients with AGS who received systemic-to-pulmonary shunts did not show evidence of pulmonary arterial growth. In the 3 who had generous collateral flow, initial palliation was deferred, but in the current

TABLE 1. Continued

1st surgery age/ description	2nd surgery age/description	3rd surgery age/description	4th surgery age/description	Comments
9 d/central shunt (4 mm)	4 mo/augment central shunt (5 mm) utilizing cardiopulmonary bypass	1 y 1 mo/modified right Blalock shunt (4 mm)	1 y 10 mo/modified left Blalock shunt (5 mm)	Failure of pulmonary arteries to grow despite augmentation of pulmonary blood flow
27 d/pulmonary valve balloon dilation	3 mo/modified right Blalock shunt (4 mm)	—	—	Extremely hypoplastic pulmonary arteries despite shunt; no further surgery undertaken
6 mo 19 d/central shunt (4 mm)	6 mo 20 d/left Blalock shunt (5 mm)	2 y 3 mo/attempted biventricular repair with RV-PA conduit	—	Initial shunt blocked; following repair, high RV pressures, VSD patch fenestrated; DUA
9 mo/left Blalock shunt (5 mm)	1 y 8 mo/recruitment MAPCAs and right Blalock shunt (5 mm)	5 y 7 mo/attempted establishment of pulmonary arterial continuity	—	Difficulty establishing satisfactory pulmonary artery confluence; attempted bilateral systemic- pulmonary shunt without RV to pulmonary artery conduit; DUA
6 y 3 mo/right Blalock shunt (5 mm)	14 y 7 mo/recruitment of MAPCAs, left Blalock shunt (6 mm)	14 y 8 mo/pericardial drainage	—	Difficulties recruiting MAPCAs, coagulopathy from liver disease and aortic incompetence; further surgery not offered

era we would aim to augment pulmonary blood flow as soon as possible to achieve what pulmonary arterial growth is possible. Unfortunately, even when this approach was aggressively employed (case 1), satisfactory pulmonary vascular development has not been achieved.

Our study expands on a theme identified by McElhinney and colleagues,² who noted that patients with a *JAG1* mutation and PA/VSD had a poor outcome, with 6 of 8 patients (75%) not surviving treatment in infancy. The survival rate in their patient group mirrors that of our cohort and highlights the severity of the condition. These results have implications for clinical decision making and management of PA in the context of AGS and allow us to calibrate expectations for those requiring surgery.

We acknowledge the contributions of Prof Tim Cartmill, Dr David Johnson, Dr Graham Nunn, Dr Ian Nicholson, and Dr Stephen Cooper, who were involved in the clinical management of these patients.

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Infant arch reconstruction during total system perfusion

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Currently, neonatal arch reconstruction requires the use of circulatory arrest or, predominantly, regional cerebral perfusion techniques.¹ With regional perfusion, the question remains as to the adequacy of brain perfusion.^{2,3} Recent clinical and experimental evidence suggests that, with all techniques, systemic perfusion is sacrificed and unwanted effects of deep hypothermia remain. With the use of the INVOS cerebral oximeter (Somanetics, Troy, Mich), changes in the regional cerebral oxygen saturation are now noninvasively and continuously monitored, allowing for the comparison of different techniques. We present a case of successful aortic arch reconstruction in an infant using a novel technique that allows total cerebral as well as systemic perfusion during arch reconstruction.

Clinical Summary

A 6-month-old infant with Shone's anomaly, who had undergone a previous repair of coarctation of aorta and total anomalous

pulmonary venous return, developed a new arch that narrowed between the innominate artery and left carotid takeoff. Because of worsening left ventricular hypertrophy, increased left ventricular end diastolic pressure, and a mild increase in right-sided pressures, reintervention was recommended.

Figure 1. Positioning of Pruitt-Inahara shunt for aortic arch repair. CPB, cardiopulmonary bypass.

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Received for publication Oct 25, 2006; accepted for publication Oct 30, 2006.

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J Thorac Cardiovasc Surg 2007;133:1096-8

0022-5223/\$32.00

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doi:10.1016/j.jtcvs.2006.10.072