Chapter 6
Cardiac, Aortic, and Pulmonary Vascular Involvement in Alagille Syndrome

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Spectrum and Frequency of Congenital Cardiovascular Disease Associated with Alagille Syndrome

The earliest descriptions of Alagille syndrome recognized pulmonary arterial hypoplasia or stenosis, occasionally associated with cardiovascular malformations, as one of the five consistent elements in this familial disease [1, 2]. In fact, the alternative descriptive names for the syndrome, such as "arteriohepatic dysplasia," acknowledge the reliable vascular involvement [1]. Although the pulmonary arteries are most frequently involved, many other regional vessels can be affected in approximately 10% of patients, including the intracranial vessels, aorta, renal, celiac, superior mesenteric, and subclavian arteries. Arterial abnormalities can include hypoplasia, stenosis, and aneurysms, as well as aortic coarctation, with related vascular accidents accounting for approximately one-third of mortality in this cohort [3].

In the largest evaluation of patients with Alagille syndrome and/or a JAG1 mutation, congenital heart disease was common, occurring in 75–94% of patients who were referred to a specialty program at the Children's Hospital of Philadelphia (Table 6.1) [4]. Abnormalities of the branch pulmonary artery tree may be present in two-thirds to three-quarters of children with this disease, which is isolated half of the time and in the remainder associated with other forms of congenital heart disease, including tetralogy of Fallot in more than 10% (Table 6.2, Figs. 6.1, 6.2, 6.3, and 6.4) [4, 5]. A study of 15 patients with Alagille syndrome and involvement of

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Table 6.1 Cardiovascular anomalies among 200 patients with a JAG1 mutation and/or Alagille syndrome

Primary cardiovascular anomaly	Total (%) (n = 200)
Cardiovascular anomalies as defined by imaging modalities	150 (75%)
Right-sided anomalies	110 (55%)
Tetralogy of Fallot	23 (12%)
Valvar pulmonary stenosis	15 (8%)
Branch PA stenosis	70 (35%)
Pulmonary atresia, intact ventricular septum	1 (1%)
Truncus arteriosus	1 (1%)
Left-sided anomalies	13 (7%)
Valvar aortic stenosis	4 (2%)
Bicuspid aortic valve without stenosis	2 (1%)
Supravalvar aortic stenosis	2 (1%)
Coarctation of the aorta	4 (2%)
Sinus of Valsalva aneurysm	1 (1%)
Other anomalies	27 (14%)
Ventricular septal defect	10 (5%)
Atrial septal defect	10 (5%)
Unbalanced atrioventricular septal defect	1 (1%)
Patent ductus arteriosus	2 (1%)
Left SVC, absent right SVC	1 (1%)
Right aortic arch	1 (1%)
Anomalous left coronary artery from the PA	1 (1%)
Pulmonary vein stenosis	1 (1%)
Normal or no cardiovascular imaging	50 (25%)
PPS murmur without documented anomalies	37 (19%)
Normal echocardiogram	26 (13%)
No cardiovascular imaging	11 (6%)
No PPS murmur with normal or no imaging	13 (7%)

Adapted from McElhinney et al. [4]
PA pulmonary artery, *PPS* peripheral pulmonary stenosis, *SVC* superior vena cava

the branch pulmonary arteries who were imaged with computed tomography angiography demonstrated a common pattern of involvement consisting of severe proximal left pulmonary artery stenosis, heavy involvement of the lobar and segmental branches (more commonly the right than the left), with greater involvement of the upper lobes. A quarter of these patients had moderate or greater stenosis of the lobar and segmental branches [6].

Right-sided congenital heart disease (excluding isolated abnormalities of the branch pulmonary arteries), whether tetralogy of Fallot (Table 6.3, Fig. 6.5), pulmonary valve stenosis, or pulmonary atresia, has been documented in up to 22% of patients with Alagille syndrome and/or a JAG1 mutation in several large studies [4, 7]. In a screening study of patients with right-sided congenital heart disease without

Table 6.2 Branch pulmonary artery anatomy

Anatomic feature	Total (%) (n = 200)
Branch PA anomalies identified by imaging	111 (56%)
Isolated PA anomalies	55 (50%)
Extent of PA stenosis/hypoplasia	
Discrete	46 (84%)
Diffuse	9 (16%)
Discontinuous branch PAs	0 (0%)
Severity of PA stenosis/hypoplasia	
Mild	27 (49%)
Moderate to severe	28 (51%)
Sidedness of PA stenosis/hypoplasia	
Bilateral	44 (80%)
Unilateral	11 (20%)
Left PA stenosis only	10 (91%)
Right PA stenosis only	1 (9%)
Associated cardiovascular anomalies[a]	56 (50%)
Extent of PA stenosis/hypoplasia	
Discrete	28 (50%)
Diffuse	24 (43%)
Discontinuous branch PA	4 (7%)
Severity of PA stenosis/hypoplasia	
Mild	13 (23%)
Moderate to severe	43 (77%)
Sidedness of PA stenosis/hypoplasia	
Bilateral	51 (91%)
Unilateral	5 (9%)
Left PA stenosis only	5 (100%)
Right PA stenosis only	0 (0%)
Branch PA anomalies suspected from PPS murmur without imaging	41 (21%)

Adapted from McElhinney et al. [4]
PA pulmonary artery, *PPS* peripheral pulmonary stenosis
[a]Includes patients with tetralogy of Fallot

a known diagnosis of Alagille syndrome, a JAG1 mutation was found in 2% of patients with tetralogy of Fallot and 4% of patients with valvar or branch pulmonary stenosis or pulmonary valve atresia, suggesting that all patients with right-sided congenital heart disease should be carefully screened for features of Alagille syndrome or a family history of cardiac defects and clinical features which may suggest the presence of a JAG1 mutation [8]. Similar findings have been reported in other studies, supporting the consideration of JAG1 abnormalities in patients without full-fledged Alagille syndrome [9, 10].

Left-sided congenital heart disease, mostly commonly aortic valve stenosis, followed by supravalvar stenosis and aortic coarctation, was reported in 11% of

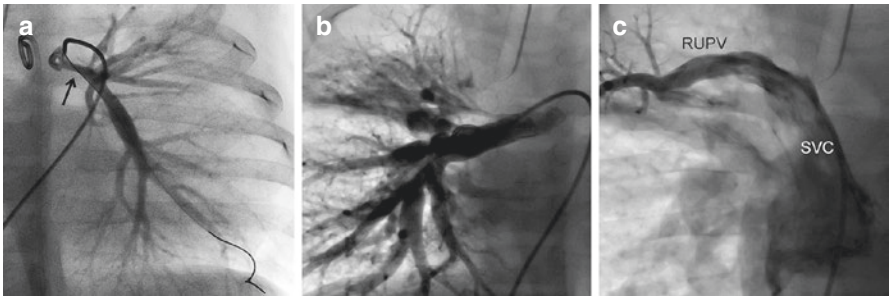

Fig. 6.1 These angiograms illustrate asymmetric branch pulmonary artery stenosis associated with Alagille syndrome. (**a**) There is focal, severe stenosis of the proximal left pulmonary artery, with relatively normal lobar and segmental branches, which appear small due to hypoperfusion. (**b**) The right pulmonary artery, in contrast, is receiving the majority of pulmonary blood flow and is generally larger than the left, although there are multiple lobar and segmental stenoses. This patient also had (**c**) anomalous drainage of the right upper pulmonary vein (RUPV) into the superior vena cava (SVC) and (not shown) a ventricular septal defect

patients in one large study [4]. One of the unique and unusual findings in patients with Alagille syndrome is the frequent coexistence of left- and right-sided congenital heart disease, which was reported to be the case in 6% of patients in that cohort [4, 7].

Accordingly, patients with tetralogy of Fallot or pulmonary arterial abnormalities along with congenital aortic or aortic valve disease should be considered for evaluation of a JAG1 mutation. The septal structures are affected in a substantial number of patients, with approximately 15% having an atrial or ventricular septal defect (not including septal defects in patients with tetralogy of Fallot), either in isolation or, more commonly, associated with the aforementioned defects [4]. The common occurrence of these various forms of congenital heart disease has been clarified through elucidation of the JAG1 protein and associated Notch signaling pathway, which are involved in ventricular and atrioventricular septation, as well as outflow tract and arterial development [11, 12]. As expected, the presence of intracardiac heart disease is associated with a higher risk of mortality and is important to identify, especially prior to potential liver transplantation [13], with patients that have combined severe liver and heart disease having the poorest survival [5]. Although cardiovascular abnormalities, such as peripheral pulmonary stenosis, are not an absolute contraindication to liver transplantation [14], it may be prudent to precede transplant with the appropriate cardiovascular interventional procedure and/or corrective surgery, as cardiovascular manifestations clearly affect transplantation outcomes [15, 16]. If transcatheter or surgical intervention is not warranted, appropriate consideration of the cardiovascular anomalies should be taken during anesthetic management surrounding liver transplantation, in the context of the resulting hemodynamic derangement.

The inconsistent phenotypic expression resulting from mutations in the JAG1 gene, a ligand in the Notch signaling pathway, is not fully understood. Although

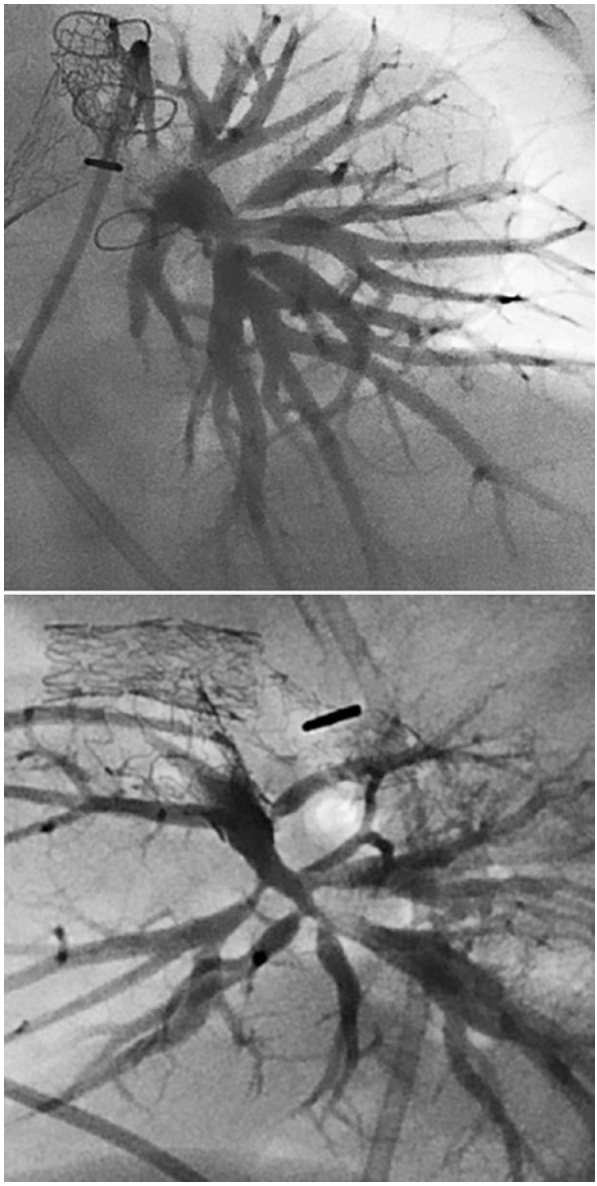

Fig. 6.2 These angiographic images of the left pulmonary artery system from anteroposterior caudal (top) and lateral (bottom) projections illustrate diffuse lobar and segmental stenoses without hypoplasia of the distal vessels. This patient also had previously treated proximal pulmonary artery stenosis, but had no intracardiac abnormalities

JAG1 mutations are commonly reported to be present in at least three-quarters of patients with Alagille syndrome [4, 17–19], with a higher incidence of mutations in patients with multisystem involvement [20], it may be present in all patients but difficult to confirm due to the challenges in fully assessing this large gene [4, 17–19]. Specifically regarding phenotypic expression and cardiovascular abnormalities in Alagille syndrome, it is interesting that members in the same family with the

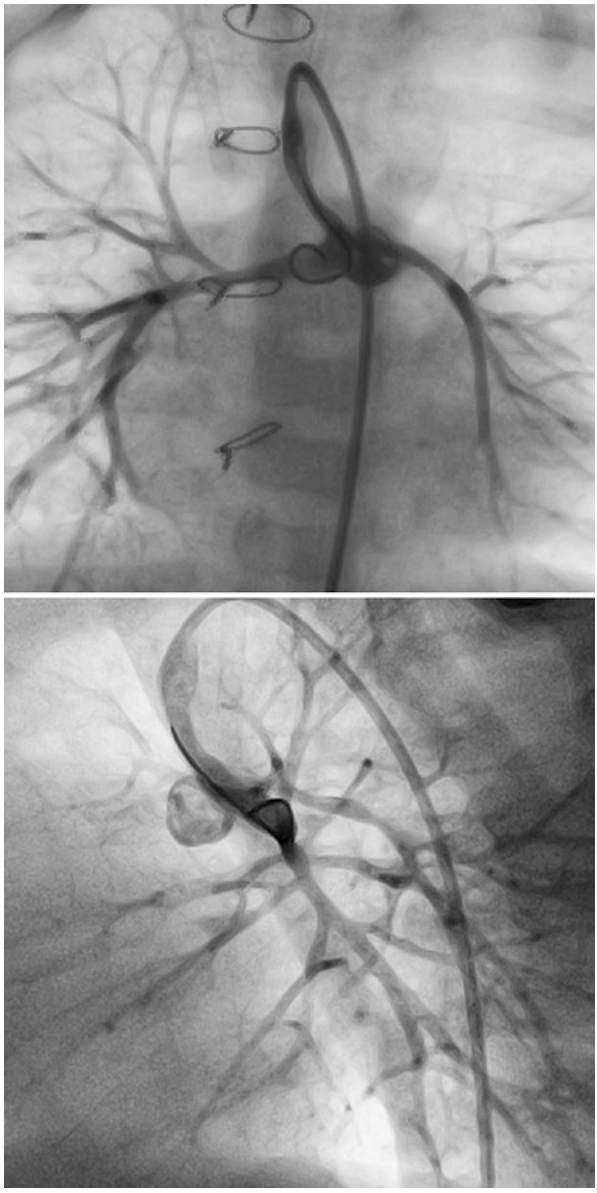

Fig. 6.3 These anteroposterior (top) and lateral (bottom) projection angiograms demonstrate diffuse, severe bilateral pulmonary arterial hypoplasia in a patient with Alagille syndrome who had tetralogy of Fallot with pulmonary atresia but no major aortopulmonary collateral arteries. The patient had previously undergone placement of a systemic-to-pulmonary arterial shunt, but no augmentation of the pulmonary arteries

same JAG1 mutation can manifest completely different forms and severities of heart disease, suggesting other modifiers outside the JAG1 gene. Limited accounts also suggest that the cardiovascular system may be more sensitive than the liver to decreased levels of functional JAG1 protein, evident in reports of patients with a JAG1 mutation who present with cardiovascular abnormalities but no liver involvement [21]. Further understanding in this interplay of genotypic-phenotypic expres-

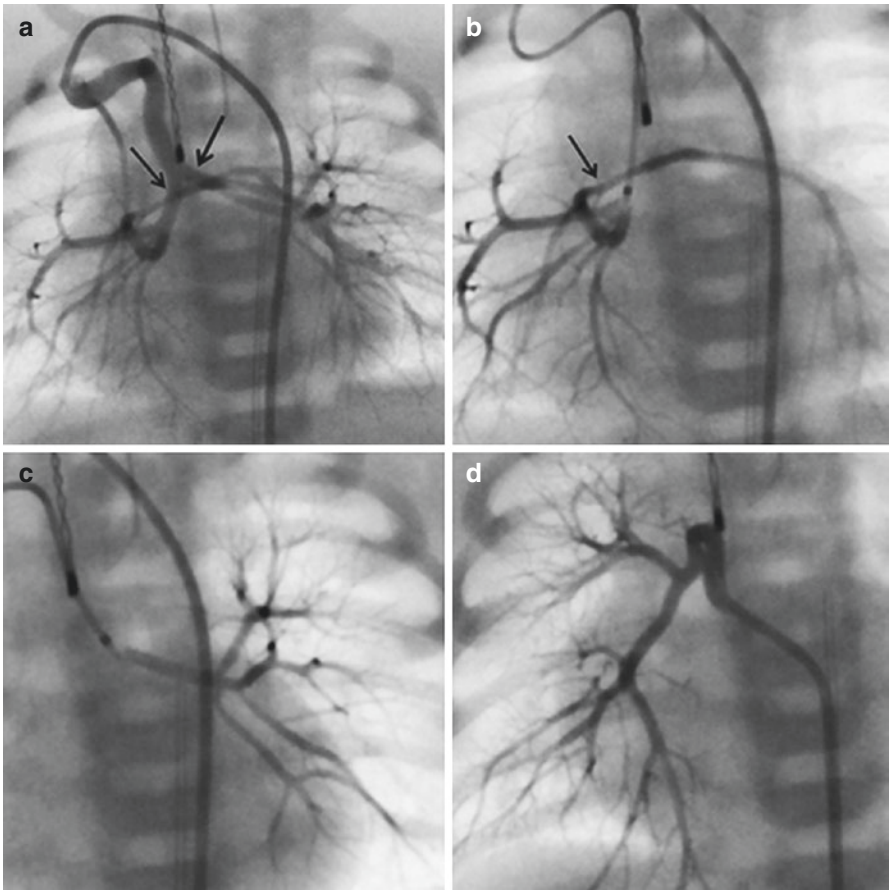

Fig. 6.4 These angiograms are from a patient with tetralogy of Fallot, pulmonary atresia, and major aortopulmonary collateral arteries. The intraparenchymal pulmonary arteries are supplied by two major collateral arteries (**a**, **d**). The collateral in (**a**) arises from the right subclavian artery and then divides into two branches (arrows) to the left and right lungs. (**b**) The right lung branch supplies hypoplastic and stenotic lobar and segmental branches to portion of the right lung, and connects (arrow) to a hypoplastic central pulmonary arterial system, which feeds a portion of the left lung. (**c**) The leftward branch of this collateral supplies hypoplastic and stenotic branches to the remainder of the left lung. (**d**) A collateral from the descending aorta supplies the remaining segments of the right lung

sion is necessary to appreciate fully the variability in aberrant cardiovascular development.

Dyslipidemia as a result of cholestasis and liver dysfunction is prevalent in patients with Alagille syndrome. Whether this dyslipidemia leads to the early development of atherosclerotic disease is not fully known [22, 23]. This concern, however, was supported in a reported case of a young child with Alagille syndrome and tetralogy of Fallot with pulmonary atresia and major aortopulmonary collateral

Table 6.3 Anatomic features of subjects with tetralogy of Fallot

Anatomic feature	Total (%) $n = 23$
Pulmonary valve	
Stenosis	14 (61%)
Atresia	8 (35%)
Absent	1 (4%)
Pulmonary blood supply[a]	
Diffuse pulmonary artery hypoplasia	15 (65%)
Discontinuous branch pulmonary arteries	4 (17%)
MAPCAs	8 (35%)
Aberrant right subclavian artery	2 (12%)
Valvar aortic stenosis	3 (13%)

Adapted from McElhinney et al. [4]
MAPCAs major aortopulmonary collateral arteries
[a]These categories are not mutually exclusive: all individuals with discontinuous branch pulmonary arteries had MAPCAs and diffuse pulmonary artery hypoplasia

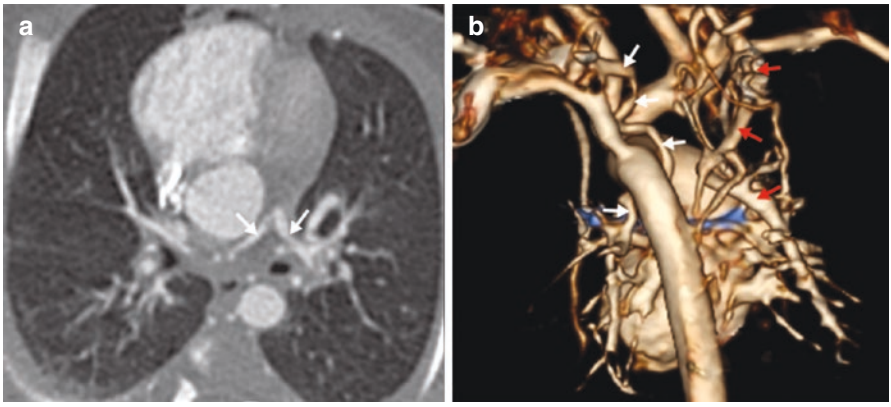

Fig. 6.5 Computed tomographic images from a patient with Alagille syndrome and tetralogy of Fallot with pulmonary atresia and major aortopulmonary collateral arteries (MAPCAs). (**a**) This axial plane image demonstrates the severely hypoplastic but confluent branch pulmonary arteries (white arrows). (**b**) This 3D reconstruction image viewed from the posterior perspective demonstrates a MAPCA from the right subclavian artery coursing rightward of the left-sided aortic arch and then under the arch toward the left lower lung lobe (white arrows). A second MAPCA arises from the left subclavian artery and supplies a segment of the left lower lung lobe (red arrows). The hypoplastic branch pulmonary arteries are colored blue

arteries who had dehiscence of three serially placed central shunts due to diffuse atherosclerosis and significant atherosclerotic plaque at the site of dehiscence [24]. Whether dyslipidemia in these patients in fact leads to accelerated atherosclerosis and the development of coronary artery disease remains unclear, as a small study of five children with Alagille syndrome and dyslipidemia unexpectedly revealed normal intimal-medial wall thickness and wall stiffness when compared to age-matched

controls, potentially related to the beneficial effects of the coexisting elevated levels of high-density lipoprotein also present in these patients [25]. It has been suggested that different lipoprotein metabolism in patients with Alagille syndrome, possibly related to lipoprotein X, may protect against atherosclerosis despite very high cholesterol levels. Dyslipidemia in this population may also have implications for cardiac valve disease. JAG1 and the Notch signaling pathway have been demonstrated in mice models to play an important role not only in valve development and remodeling but also in calcium metabolism. JAG1 mutations resulting in protein deficiency lead to abnormal valve development and also the early development of valve calcification, which can be exacerbated further by dyslipidemia [12]. Nevertheless, at present, there is no clear consensus on recommendations for the monitoring and treatment of hyperlipidemia in Alagille syndrome.

Many patients with Alagille syndrome develop cholestasis and hepatic dysfunction, potentially progressing to end-stage liver disease requiring liver transplantation in up to one-third of patients [13]. These patients with end-stage liver disease are at risk for the complications of hepatic dysfunction, including hepatopulmonary syndrome, portopulmonary hypertension, and cirrhosis, which themselves can lead to acquired cardiovascular aberrations including cirrhotic cardiomyopathy, the effects of pulmonary arterial hypertension, and cardiac repolarization abnormalities [26]. Thus, evaluation and management of acquired cardiovascular complications secondary to liver disease are essential to improve outcomes of these patients, particularly while awaiting liver transplantation [27].

Diagnostic Approach and Surveillance

Two-dimensional echocardiography remains the mainstay of initial diagnosis and for follow-up of congenital heart disease, with increasing utility of three-dimensional echocardiography as technology improves [28, 29]. Given the high prevalence of congenital heart disease, any child suspected of having Alagille syndrome should undergo a full cardiac evaluation by a pediatric cardiologist, including a thorough history and physical examination, a 12-lead electrocardiogram to assess for repolarization abnormalities secondary to hepatic dysfunction, and a transthoracic echocardiogram. Regardless of the diagnosis of Alagille syndrome, the above recommended evaluation holds true in patients with any form of liver disease being considered for liver transplantation [26]. The common finding of proximal branch pulmonary artery hypoplasia and/or stenosis in Alagille syndrome is often visualized on transthoracic echocardiography (Fig. 6.6) and supported by evidence of elevated right ventricular pressures. In the setting of peripheral pulmonary arterial hypoplasia and/or stenosis identified on echocardiogram that is significant enough to warrant intervention, the detailed pulmonary arterial vasculature can be fully defined in the cardiac catheterization laboratory with angiography (Figs. 6.1 and 6.2). A technetium-99 m lung perfusion scan can aid in quantifying the distribution of flow, although the results may be normal in the setting of diffuse or bilaterally symmetric disease. Given the

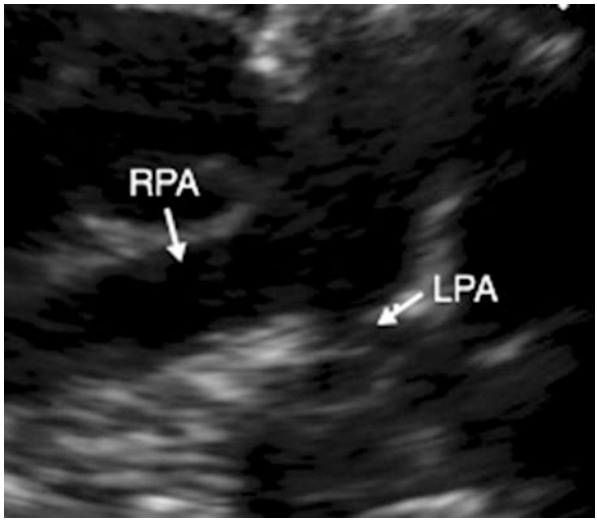

Fig. 6.6 This transthoracic echocardiogram cross-sectional parasternal short-axis plane image demonstrates severe left pulmonary artery hypoplasia. The right pulmonary artery is normal in caliber

high variability of both cardiovascular and hepatic involvement in these patients, follow-up is individualized based on the specific involvement of both systems.

Given the autosomal dominant inheritance of this syndrome and the associated high incidence of congenital heart disease, a prenatal echocardiogram should be performed on any fetus with a parent identified to have Alagille syndrome, or with history of first-degree relatives or offspring identified to be affected, given the variable expressivity of the syndrome. Likewise, genetic testing should be considered in the fetus identified to have forms of congenital heart disease associated with the syndrome, especially in those with other associated extracardiac involvement or family history of Alagille syndrome [30].

Management

As previously mentioned, cardiovascular involvement should be defined fully and potentially treated in the catheterization lab or surgically, especially prior to any consideration for liver transplantation. Regarding the most common cardiovascular abnormality present in Alagille syndrome, peripheral pulmonary stenosis, and/or hypoplasia with no intracardiac abnormalities, the appropriate management strategy remains controversial and institution dependent, whether surgical, transcatheter, or a hybrid approach [31–35]. In patients with mild or focal pulmonary arterial obstruction, there is limited information about time-related evolution or improvement, but it is safe to say that, depending on the degree of involvement and the severity of pulmonary stenosis, the obstruction may remain stable and intervention avoided altogether [4].

Historically, surgical management was typically limited to the central or proximal pulmonary arteries. However, recent reports suggest that a more aggressive and thorough surgical strategy may prove to be the best management approach in these

patients. Surgical arterioplasty is an option not only for proximal branch pulmonary artery stenosis but also for disease that extends into the lobar and segmental branches and is especially appropriate when concurrent intracardiac surgical repair is necessary. The Stanford group has recently reported their experience with an effective surgical approach addressing not only the central branches of the pulmonary arteries but also lobar and segmental branch stenosis [32].

It has been suggested that, given the common morphological subtype of peripheral pulmonary stenosis in Alagille syndrome, with diffuse peripheral involvement, as well as the high rate of restenosis following both transcatheter and contemporary surgical approaches (up to 60%), a transcatheter approach with serial interventions (balloon dilation and/or stenting) may be appropriate [31]. A study of nine patients with Alagille syndrome who were followed for a median of 11 months following transcatheter intervention for pulmonary artery stenosis concluded that both balloon angioplasty and stenting are acutely safe and effective [36]. However, it is our impression that patients with Alagille syndrome may be more prone to pulmonary hemorrhage related to interventions or even wire-related injury than patients without Alagille syndrome who have pulmonary artery stenosis (unpublished data). Longer-term results with transcatheter intervention have been less promising, with in-stent stenosis following pulmonary artery stenting in nearly two-thirds of patients with Alagille syndrome [37]. Other investigators have suggested a combined approach, with serial transcatheter ballooning of the peripheral pulmonary arterial stenosis and surgical repair of the proximal obstruction [35]. Unfortunately, few studies have focused on the subset of patients with Alagille syndrome, and there is currently no evidence to support one management strategy over the other for peripheral pulmonary stenosis in Alagille syndrome. In light of the current limited evidence, we support a more aggressive surgical approach in Alagille syndrome patients with severe branch pulmonary artery stenosis requiring treatment, as described by the Stanford group.

The surgical management of tetralogy of Fallot with major aortopulmonary collateral arteries has evolved to support an early complete repair with unifocalization of lung segments supplied by major aortopulmonary collateral arteries, incorporating these segments into the major branch pulmonary arteries, with additional extensive lobar and segmental pulmonary artery reconstruction when necessary. Similar to the management of branch pulmonary artery stenosis, the Stanford group has led the way in this surgical approach. A recent review of their 15-year experience highlighted the excellent results with their approach. Interestingly, the presence of Alagille syndrome was one of the two factors associated with worse survival in their experience, again emphasizing the increased general risk in these patients, likely related in part to their multisystem involvement [38].

Outcomes

Cardiovascular involvement clearly affects outcomes in patients with Alagille syndrome [3, 13]. Additionally, when comparing patients with either unrepaired or repaired congenital heart disease and Alagille syndrome to non-syndromic patients

with similar cardiac conditions, survival is significantly worse. This higher mortality in patients with Alagille syndrome may be related to the associated systemic manifestations, as well as the increased association of pulmonary vascular hypoplasia or stenosis with structural heart disease [38, 39]. Likewise, patients with peripheral pulmonary arterial abnormalities and Alagille syndrome may have poorer outcomes when compared to non-syndromic patients with the same vascular abnormalities, which may additionally be related to their tendency for a more diffuse involvement of the pulmonary vascular tree [31].

Likewise, patients with Alagille syndrome who undergo liver transplantation have poorer survival than children undergoing liver transplantation with other conditions. Again, the multisystem involvement, including vascular involvement with a higher incidence of vascular complications (namely, hepatic artery thrombosis and portal vein thrombosis), likely contributes to this disparity in outcomes. Vascular complications are likely related to the underlying vasculopathy. Less clear is the effect of right ventricular hypertension secondary to peripheral pulmonary stenosis on outcomes, especially surrounding liver transplantation. It is common practice to address the peripheral pulmonary stenosis when right ventricular pressure is elevated above approximately 50% systemic pressure, although limited reports demonstrate no relationship between transplant outcomes and right ventricular pressure [40, 41]. The appropriate strategy in patients with Alagille syndrome and peripheral pulmonary stenosis is clearly in need of more robust evidence to guide management.

Conclusion

Cardiovascular involvement is common in Alagille syndrome, adding to the mortality risk of this multisystem disease. A thorough cardiovascular assessment is necessary in these patients to identify possible associated abnormalities, including the common occurrence of peripheral pulmonary arterial stenosis and/or hypoplasia. Interventional and/or surgical management is often necessary, although at present, evidence is limited regarding the appropriate timing and strategy.

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