Alagille Syndrome and Liver Transplantation

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ABSTRACT

Alagille syndrome is a multisystem disorder in which progressive liver disease with persistent cholestasis and dramatic pruritus often warrant consideration for liver transplantation. The most important part of the transplant assessment is evaluation of the cardiac and renal involvement. Preoperatively, cardiac performance often must be tested with dynamic stress tests, mimicking hemodynamic changes during liver transplant. Many aspects of the syndrome including cholestasis, pruritus, and hypercholesterolemia improve posttransplant, but short stature is rarely significantly affected. One- and 5-year patient and graft survival after liver transplant is comparable to other elective indications, but effects of long-term immunosuppressants on evolution of other components of the syndrome, including vascular, bone, and renal disease, remain largely unknown.

Key Words: alagille syndrome, cholestasis, hypercholesterolemia, pruritus

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Alagille syndrome (AGS) is a highly variable, autosomal dominant disorder that affects the liver, heart, eyes, and skeleton with recognizable facial dysmorphic features including triangular facies, prominent quadrangular forehead, pointed chin, and hypertelorism (1–3). AGS has traditionally been diagnosed in the presence of intrahepatic bile duct paucity on liver biopsy in association with at least 3 of the 5 major clinical features: chronic cholestasis, cardiac disease (typically right-sided lesions and most often peripheral pulmonary stenosis), skeletal abnormalities (usually butterfly vertebrae), ocular abnormalities (most commonly posterior embryotoxon), and characteristic facial features (4). AGS is also associated with short stature and anomalies of the teeth. The kidneys, pancreas, and vascular system are involved in many cases, although these are not defining criteria (4,5). There is a significant variability in the extent to which each of these systems is affected in an individual, if at all (6–8). The prevalence of AGS has been reported as 1 in 70,000 live births, although the advent of molecular testing and the subsequent identification of mildly affected individuals suggest that this is likely an underestimate (8).

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AGS is caused by mutations in Jagged1 (*JAG1*), a ligand in the Notch signaling pathway (9,10). This pathway is evolutionarily conserved and is involved in cell fate determination. *JAG1* mutations are identified in >90% of clinically diagnosed probands (11). Recently, mutations in *NOTCH2* have also been demonstrated in a few patients with AGS who do not have *JAG1* mutations (12). To date, >430 *JAG1* mutations have been identified in patients with AGS, and the frequency of sporadic mutations (ie, new in the proband) is approximately 60% (6,13). Despite the advances made in understanding the genetics of this condition, little of this information has affected the clinical care of the patients because almost no genotype-phenotype correlations have been detected.

AGS engenders controversy at many levels. The condition has been alternately named Watson-Miller syndrome and arteriohepatic dysplasia. The traditional clinical criteria have been challenged with the advent of molecular screening that has identified individuals carrying a mutation in *JAG1*, but with minimal or atypical clinical manifestations, suggesting that AGS represents the tip of the iceberg of *JAG1* mutation–associated disease (8). It has been proposed that the name AGS remain in use for individuals with liver involvement, whereas the broader term, *JAG1* disease, could be reserved for all of the carriers of the mutations, in whom clinical hepatic manifestations may not necessarily be present.

The management of this multisystem condition continues to generate discussion. The main difficulty in optimizing hepatic care in AGS is the unique evolving natural history of the liver disease. Although cholestasis is commonly profound in infancy and early childhood, in some children it resolves with little residual liver disease (14). There are no early clinical, laboratory, or radiological predictors of hepatic outcome in AGS. Furthermore, there are no described genotype-phenotype correlations that could herald the development of end-stage liver disease. This poses a unique management challenge in AGS because severe cholestasis in early childhood may still be associated with well-compensated chronic liver disease and good hepatic outcome in later life. Finally, the multisystem nature of this condition, in particular the association with cardiac disease, lends another level of complexity to long-term management, specifically including organ replacement options. Together, these issues confer particular difficulty in considering the necessity and timing of liver transplantation (LT) in AGS. The general medical care of these children is outlined elsewhere, whereas the purpose of the present review is to address clinical issues to be considered when LT is contemplated in a child with AGS.

ALAGILLE SYNDROME AS A MULTISYSTEM DISORDER: IMPACT ON LIVER TRANSPLANTATION

Comorbidities in AGS resulting from multiorgan involvement have a significant impact on the effects of LT. Structural cardiac disease is the single most important contributor to mortality in AGS (4,15). Meticulous evaluation of cardiac involvement is vital to the LT assessment process to determine the suitability of the

candidate. Combined liver and heart transplantation has been performed in AGS, although only in selected cases (16).

Renal disease in AGS has been described in 40% of the individuals ranging from renal tubular acidosis to structural defects such as unilateral or horseshoe kidney (4). Preexisting renal disease or susceptibility to renal impairment should also be actively sought as part of the liver transplant evaluation in AGS. Microscopic evaluation of the urine, renal ultrasound, blood pressure measurement, chromium ethylenediaminetetraacetic acid glomerular filtration rate, and blood gas measurement are baseline tests required to assess renal involvement in AGS. Recently, serum cystatin C has been described as a simple marker for assessing and monitoring renal impairment in LT patients (17). Consequently, when significant renal impairment is documented, renal-sparing immunosuppressive protocols, including low serum target levels of calcineurin inhibitors and early introduction of mycophenolate mofetil or sirolimus, should be followed.

Vascular involvement in AGS has recently been recognized as a frequent and potentially devastating feature of the condition. There is a significant body of evidence implicating the Notch signaling pathway in vascular development, and it has been suggested that there is a generalized vasculopathy in AGS (15). Intracranial bleeding is reported in approximately 15% of individuals (4,5). Some of these hemorrhagic events have occurred in the peritransplant period. Some, but not all, are associated with documented structural vessel anomalies. Clearly, the presence of such an anomaly would have prognostic implications, and this suggests the need for vascular imaging of the head and neck as part of pre-LT evaluation. This issue has not been systematically evaluated and is not, as yet, a formal recommendation. Generalized vascular involvement is also widely reported (15). Anomalies of the intraabdominal vasculature (15,18–20) may affect technical aspects of LT. Contrast computed tomography (CT) or magnetic resonance angiography is increasingly becoming an important part of routine pre-LT evaluation, but in AGS it should be considered even more important and, arguably, compulsory.

PUBLISHED SERIES ON LIVER TRANSPLANTATION FOR ALAGILLE SYNDROME

LT is a well-established therapy in AGS and is estimated to be required in 21% to 31% of patients with AGS (4,5). Available published information is presented in Table 1.

Conventional indications for LT in chronic liver disease of childhood, such as decompensation of synthetic function, uncontrolled portal hypertension, or chronic encephalopathy, are rare in AGS. In the majority of cases the indications for LT in AGS comprise the complications of profound cholestasis. A principal clinical management problem in AGS is intractable pruritus, which often dramatically affects quality of life of the patient and disrupts family routines. This can be a clinical issue despite maximal medical management with antipruritic agents and even following an attempt to control the symptoms (unpublished observation). Some children have reportedly benefited from external diversion of bile flow (21,22) or from ileal exclusion (23), but this has not been observed universally. In addition to pruritus and poor quality of life, published series on LT in AGS also refer to failure to thrive, severe hypercholesterolemia, and osteodystrophy as less common transplant indications. AGS represents approximately 5% of overall indications for LT in children with reported median age at the operation ranging from 3.5 to 7.8 years (Table 1).

Histological injury in AGS is rarely associated with fibrotic or cirrhotic changes. If progressive portal hypertension is observed after years of stable chronic cholestasis, this usually heralds rapid

TABLE 1. Published series on LT for AGS

References	No. and % for LT	Median age at LT, y	Range, y	Early deaths	Growth change	1-y patient survival, %	Follow–up, y	Previous KPE	Other
Tzakis (26)	23, NR	5	0.5–17.5	Nil	NR	57	4.4	10	5% of all LT
Hoffenberg (5)	8/26, 30.7	6.5	4–21	Nil	NR	100	4.7	2	
Cardona (38)	12, NR	7.8	3.3–17.9	1	Yes	91.7	3.3	2	
Quiros-Tejeira (27)	20/43, 46.5	4	1.3–15.4	2	NR	75	5.9	5	1 patient renal transplant
Emerick (4)	19/92, 20.6	6	0.7–23	Nil	NR	79	4.2	7	Multicenter study
Lykavieris (14)	44/163, 26.9	6.7	2.7–28	10	Yes	77	>20	9	1 HCC
Ovaert (33)	17, NR	3.5	1.2–13	5	Yes	71	5	NR	
Kasahara (35)	20, NR	5	0.6–12.9	1	No	87.7	5.2	8	Living-related series
Englert (29)	24/37, 64.8	3.6	0.6–13.3	1	11 no, 13 yes	91.7	NR	NR	5.3% of all LT

HCC = hepatocellular carcinoma; KPE = Kasai portoenterostomy; LT = liver transplantation; NR = not reported.

decompensation and indicates that consideration for LT should follow soon. Similarly, detection of new focal change within liver should prompt immediate contrast CT scanning and serum α-fetoprotein testing because hepatocellular carcinoma has been described in AGS (14).

Hypercholesterolemia per se should not be regarded as an indication for LT. It was known for many years that children with AGS have no major macroscopic vascular changes or indeed major cardiovascular incidents due to the development of atherosclerosis in the short term, in contrast to, for example, children with familial hypercholesterolemia. A recent study (24) has shown that the profile of dyslipidemia in syndromes of progressive familial cholestasis, namely familial intrahepatic cholestasis type 1 disease and bile salt export pump deficiency, is actually more atherogenic than that in AGS. However, statins could be considered for disfiguring xanthomata in AGS.

As mentioned earlier, an estimated 25% of the children with AGS studied in major pediatric hepatology centers will require liver replacement during childhood (4,5), but there are no data yet about what proportion of AGS patients would need LT after entering adulthood when factors such as alcohol abuse, pregnancies, or diabetes mellitus may further affect their condition. Ranking individuals with AGS within objective scoring systems developed to predict 3-month mortality on the LT waiting list, such as model for end-stage liver disease or pediatric end-stage liver disease score, is not easy (25). Their most common indications for the operation such as pruritus or impaired quality of life are not part of the pediatric end-stage liver disease model, whereas failure to thrive, included in the scoring system, may partially reflect severity of their ''syndrome'' rather than of their chronic liver disease. Therefore, debate about fair assessment and ranking, including consideration of granting exceptional status for children with AGS when they compete with others for elective LT, needs to continue.

RESULTS OF LIVER TRANSPLANTATION FOR ALAGILLE SYNDROME

The median survival rate from all of the published series on LT for AGS is 79% (Table 1). With the exception of 1 early series (26), reporting 1-year survival of only 57%, more contemporary series describe 1-year survival ranging between 71% and 100%.

An extremely important determinant of success of LT in AGS is the severity of an associated cardiac anomaly (see below). Cardiac defects in AGS vary from classical asymptomatic peripheral pulmonary stenosis to midline defects and more complicated complex defects including tetralogy of Fallot. Pretransplant cardiac assessment should be carefully planned and conducted to assess functional ability of the cardiovascular system to cope with increased demands during LT and postoperatively.

WHEN TO CONSIDER LIVER TRANSPLANTATION?

When assessing a patient with AGS for LT, this procedure must be considered in light of systemic disease in which liver replacement may be successful but other organ involvement will remain. Some extrahepatic disease may become aggravated by long-term use of antirejection therapy such as calcineurin inhibitors (nephrotoxicity), steroids (bone changes), or sirolimus (dyslipidemia/atherosclerosis). In that sense LT in AGS should be regarded as beneficial, but not an always curative surgicomedical procedure. LT undoubtedly has the potential to significantly improve and remove some (eg, cholestasis, pruritus, hypercholesterolemia) but not all clinical problems, similar to, for example, LT in cystic fibrosis or familial intrahepatic cholestasis type 1 disease. AGS is a prime example in which careful balancing of potential benefits and undoubted risks cannot be overemphasized during consideration of LT.

The majority of retrospective studies report that growth problems do not improve after successful LT in AGS (14,27). Escape from the disability of chronic cholestatic liver disease will likely lead to a more active lifestyle, improved appetite, cured fat-soluble vitamin deficiencies, and loss of xanthomas and result in improved general nutritional condition and some catch-up growth (28,29). However, the final height in AGS usually remains unaffected by LT, strongly supporting multifactorial and ultimately genetic reasons for short stature in this syndrome.

The family of a child with AGS facing LT should be given frank and realistic expectations following eventual success of this procedure, reminding them that many of the clinical problems inherent to this syndrome could be ameliorated, but some, such as nutritional difficulties or short stature, may not be significantly affected. Other organ involvement is likely to remain or even deteriorate on long-term immunosuppression.

Two factors have emerged as potential markers suggestive of requirement for LT in AGS: earlier age at presentation with prolonged conjugated jaundice and history of performed Kasai portoenterostomy. The latter observation could be interpreted either by more severe phenotype, clinically difficult to distinguish from biliary atresia, or by negative impact of the corrective biliary surgery on already suboptimal bile flow in AGS. The series observing that Kasai portoenterostomy had been performed in children with AGS illustrate difficulties in clinical and histological diagnosis of AGS in early infancy when classical dysmorphic features may not be obvious, and when histological features may demonstrate early bile duct proliferation rather than classical picture of portal tract hypoplasia and bile duct paucity (30).

PRETRANSPLANT CARDIAC ASSESSMENT

A critical element of post-LT outcome in AGS is severity of cardiac disease. Potential pathophysiological problems with cardiac function in AGS during LT are predominantly related to inadequate cardiac reserve associated with established right ventricular hypertrophy (RVH) complicating peripheral pulmonary stenosis. To provide information about right ventricular pressure, many transplant centers would rely on noninvasive cardiac tests including electrocardiography, chest x-ray, and Doppler echocardiography. The presence of tricuspid regurgitation on echocardiography would indicate more advanced RVH. However, echocardiography has been criticized because of a lack of specificity and limited ability to assess descending aorta and peripheral branches of pulmonary arteries, often affected in AGS (31). It was suggested that cardiac pre-LT assessment should include formal evaluation of the dynamic vascular pressure changes during induced cardiac stress monitored via cardiac catheterization (31).

In the immediate post-LT period the main pathophysiological concerns are the ability of the right ventricle to increase output to cope with the fluids required to maintain adequate perfusion of the liver graft. Clamping of the inferior vena cava during LT leads to increased intraoperative fluid requirements, which could result in right ventricular overload and acute heart failure. Most children with end-stage chronic liver disease already have chronic peripheral vasodilatation, which can worsen after graft reperfusion. This could become particularly problematic in patients with AGS who tend to have established RVH. They are often unable to raise the cardiac output to the level sufficient to maintain adequate perfusion of the liver graft. Furthermore, increase in pulmonary vascular resistance after reperfusion could add to the poor graft perfusion and early graft dysfunction post-LT.

This pathophysiological scenario may be worsened in the presence of sepsis.

The Brussels group has studied hemodynamic changes in 16 children with AGS with echocardiographically documented peripheral pulmonary stenosis (16/16) and established RVH (15/16) during LT (32). They observed that caval clamping led to mean decreases in systolic, pulmonary artery, and central venous pressure of 15 mmHg, 5 mmHg, and 4 mmHg, respectively. At unclamping, systolic blood pressure further reduced by a mean of 16 mmHg, whereas pulmonary artery and central venous pressures increased by a mean of 3 mmHg and 1 mmHg, respectively. They also reported that use of venovenous bypass appeared to alleviate the hemodynamic changes during LT (32).

There are, however, some reported experiences in which severe pulmonary stenosis and RVH did not contraindicate or cause intraoperative problems during LT (33,34). Ovaert et al (33) performed pre-LT cardiac catheterization in 10 of 17 patients with AGS, who had been estimated to have elevated right ventricular pressure on electrocardiography and Doppler echocardiography, and found that the mean right ventricular pressure was 55 mmHg, with 6 patients having a ratio between right ventricular and systemic pressure >0.5. Although there was no perioperative mortality, Ovaert et al report 1-year survival around 70%, with no deaths attributed to cardiac causes (33).

A valuable recommendation about pre-LT cardiac assessment of children with AGS has been provided by the King's College group (31). They proposed a protocol, based on retrospective analysis of their data, in which prospective LT recipients undergo dynamic stress test with dobutamine, an inotropic vasodilatator, simulating perioperative conditions. The continuing infusion rate during the study would initially be $10\,\mu g \cdot kg^{-1} \cdot min^{-1}$ and then would be increased to $20\,\mu g \cdot kg^{-1} \cdot min^{-1}$. Cardiac performance, measured as cardiac index (ratio between cardiac output and body surface area), systemic vascular resistance, and pulmonary vascular resistance index are monitored during cardiac catheterization, and if the patient achieved >40% increase in the cardiac output, then his cardiac reserve was deemed adequate for LT. The authors found no correlation between baseline right ventricle pressure and cardiac index during the stress test. Since publication, this empiric approach has stood the test of time (unpublished observation). The only other pretransplant protocol was suggested by the Brussels group, who performed cardiac catheterization only in selected patients with AGS in whom echocardiography had indicated increased transstenotic gradient and right ventricular pressure of >50% of systemic (33).

Should the cardiac assessment indicate that there is a potential to improve cardiac performance (significant pulmonary artery gradient, inadequate increase in the cardiac index), interventional procedures such as balloon dilatation with stenting or formal corrective cardiac surgery should be considered and performed before LT. The feasibility of children with AGS with more complex congenital heart defects for LT should be assessed on an individual basis in close collaboration with experienced pediatric cardiology teams.

LIVING-RELATED LIVER TRANSPLANT IN ALAGILLE SYNDROME

Colleagues in Japan have recently published their experience on living-related LT in AGS, which has an additional value given the possibility that some of the parent donors may be affected by *JAG1* disease in the absence of clinical features of AGS (35). Their results from 20 transplanted children (median age at LT 5 years) with 1-year survival rate of 80% are comparable to the overall results from cadaveric LT series (35). They conclude that potential donors and recipients should have comprehensive radiological vascular assessment (with CT or magnetic resonance angiography), because life-threatening complications including fatal abdominal bleeding secondary to severe hypoplasia of abdominal aorta (mid-aortic syndrome) have been observed in the early postoperative period (29,35). They also argue that pre-LT assessment of prospective family donors should include a liver biopsy to minimize surprising intra- or postoperative discoveries of bile duct hypoplasia in the donated liver grafts from asymptomatic parents (35), the finding observed by another case report (36). In an era of chronic organ shortage, living-related LT for AGS will remain a precious backup option but it is hoped with increased awareness of subclinical cases of *JAG1* disease by the donor assessment team (typically led by an independent adult hepatologist). In the future one may consider *JAG1* mutation screening of potential living-related donors, where available, although the clinical value of this information remains unclear at present.

Given the fact that the principal indication for LT in AGS is the complications of persistent cholestasis with frequent absence of cirrhosis and portal hypertension, a recently described heterotopic auxiliary LT in AGS makes an interesting discussion topic (37). The authors report a 15-year-old boy who received a liver graft from his mother uneventfully with rapid loss of jaundice and normal liver function after 14 months follow-up (37). It remains to be seen what effect the improved bile flow will have on evolution of his chronic liver disease and whether his symptoms recur. At present, the auxiliary transplant approach due to its more demanding technical aspects should be regarded as experimental.

HOW TO PLAN LIVER TRANSPLANTATION IN ALAGILLE SYNDROME?

Children with severe phenotypes of AGS could benefit from some pre-LT forward planning. In addition to the aggressive nutritional support and fat-soluble vitamin supplementation, which often require nasogastric overnight feeding, gastrostomy, or additional parenteral nutrition, they should receive extended courses of immunizations, such as pneumococcal, varicella zoster, meningitis C, and hepatitis A and B, which may not necessarily constitute the standard local schedule. If the cardiac condition must be corrected, this should be done before the LT. Dental health, which is often problematic in children with AGS, should be optimized to minimize potential foci of infection after LT. Finally, even in the absence of clinical renal involvement, children with AGS should be receiving renal-sparing regimens with low calcineurin inhibitor serum target levels and early introduction of additional immunosuppressants such as mycophenolate mofetil and sirolimus, or everolimus when approved for use in children.

CONCLUSIONS

LT in AGS is a therapeutic option that needs careful consideration because of the multisystem nature of the condition. The best candidates for the operation are children with unremitting cholestasis and resistant pruritus, who have a simple cardiac defect, subclinical renal involvement, and relatively good nutritional state. Short-term prognosis remains comparable to other indications for elective LT in childhood, but effects of long-term immunosuppressive treatment on evolution of renal and vascular disease, which are now well-recognized components of the syndrome, remain uncertain.

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