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Evaluation of cardiac manifestations in pediatric liver transplant candidates

Madan N, Arnon R, Arnon R. Evaluation of cardiac manifestations in pediatric liver transplant candidates.

Abstract: Knowledge concerning the involvement of the cardiovascular system in children awaiting liver transplant is limited. Therefore, no guidelines have been established on evaluating this group of patients for cardiac disease. This review examines the diverse cardiovascular manifestations of liver disease in children. We also discuss the available testing and its applicability in screening for cardiac disease in this vulnerable population.

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Presence of cirrhotic cardiomyopathy and ischemic heart disease is well recognized in adult patients with end-stage liver disease. These cardiac complications are important determinants of morbidity and mortality following a liver transplant (1–3). Thus, guidelines have been developed recently to improve screening of these individuals for cardiac involvement (2). In children, however, the applicability of these guidelines is limited as ischemic heart disease is virtually non-existent. Also, the spectrum of disorders, which result in end-stage liver disease and necessitate a liver transplant in childhood, is different from adults, and many of these disorders are associated with specific congenital heart defects. In the following sections, we will first discuss the broad cardiac manifestations of end-stage liver disease in children followed by description of specific involvement of the cardiovascular system with various disorders (Table 1). Recommended cardiac evaluations for these manifestations are discussed alongside.

Abbreviations: AGS, Alagille syndrome; CF, cystic fibrosis; EKG, electrocardiogram; GSD, glycogen storage diseases; HPS, hepatopulmonary syndrome; LV, left ventricular; PPHTN, portopulmonary hypertension; TOF, tetralogy of Fallot; 2-DE, 2-dimensional echocardiography.

Cardiac manifestations of end-stage liver disease in the pediatric population

End-stage liver disease can be associated with several cardiovascular abnormalities including cardiomyopathy, hyperdynamic circulation, HPS, cardiac conduction abnormalities, and PPHTN.

Cirrhotic cardiomyopathy

In adults, cardiac dysfunction in cirrhosis has been termed as cirrhotic cardiomyopathy. It is characterized by baseline increased cardiac output because of increased cardiac contractility and peripheral vasodilatation, impaired diastolic relaxation, myocardial hypertrophy, repolarization abnormalities, and attenuated response of the heart to direct beta stimulation in the absence of obvious signs and symptoms of congestive heart failure (3, 4). The physiologic response to exercise and other stressors is blunted, and abrupt increases in blood flow to the heart can unmask frank congestive heart failure with pulmonary edema. Not unexpectedly, 7–15% of deaths in the post-operative period following a liver transplant have been attributed to cardiac causes (1, 4, 5). Whether similar findings occur in children with cirrhosis has not been widely reported. A study comparing

Table 1. Cardiac manifestations in pediatric liver transplant candidates

Disease	Cardiac manifestations
End-stage liver disease or cirrhosis	Cirrhotic cardiomyopathy, hepatopulmonary syndrome, prolongation of the QTc interval, and portopulmonary hypertension
Biliary atresia splenic malformation	Interrupted inferior vena cava, wide spectrum of congenital heart defects most commonly atrial septal defects, ventricular septal defects, and tetralogy of Fallot
Alagille syndrome	Branch pulmonary artery stenosis, tetralogy of Fallot, tetralogy of Fallot with pulmonary atresia, and pulmonary valve stenosis
Cystic fibrosis	Pulmonary hypertension, chronic right heart failure
Wilson disease	Cardiac hypertrophy, autonomic dysfunction
Tyrosinemia type I	Cardiac hypertrophy
Glycogen storage disease IIIa	Cardiac hypertrophy, rarely sudden deaths, cardiac failure necessitating a heart transplant, and ventricular arrhythmia
Glycogen storage disease IV	Dilated cardiomyopathy
Primary hyperoxaluria	Abnormalities of the cardiac conduction system, arrhythmias, valvular abnormalities, and cardiac hypertrophy
Propionic acidemia	Cardiac repolarization abnormality and dilated cardiomyopathy
Fatty acid oxidation defects	Dilated cardiomyopathy and cardiac hypertrophy
Infantile hepatic hemangioendotheliomas	Congestive heart failure
Immunosuppression with Tacrolimus	Cardiac hypertrophy

2-DE parameters between 22 children with biopsy proven cirrhosis and 22 age–sex-matched controls showed no significant difference in LV ejection fraction, LV shortening fraction, and LV diastolic dimension. Systolic LV posterior wall thickness was significantly higher in the patient group (6). Increased systolic LV posterior wall thickness does not qualify for the definition of LV hypertrophy that is diagnosed by the presence of end-diastolic LV posterior wall thickness or septal wall thickness above 2 *Z* scores for age and body surface area. A recent study evaluating the cardiovascular status of 40 children with biliary atresia listed for liver transplantation showed abnormal 2-DE parameters in 70% of patients compared with well-matched controls. These included increased LV diastolic wall thickness, LV mass index, and LV shortening fraction. No difference was noted in 2-DE parameters between seven children who died pre-transplant and 33 children who survived to a liver transplant. Post-liver transplant pediatric intensive care unit stay and the hospital length of stay were significantly longer in the patients with abnormal 2-DE (median six days vs. four days and median 21 days vs. 11 days, respectively). In univariate analysis using clinical and 2-DE parameters, LV mass index correlated with the hospital length of stay (7). On the basis of the present knowledge, cardiovascular screening of children with cirrhosis, if available, is indicated. How the presence of abnormal 2-DE findings will alter patient management is unclear. In parallel with observation in adults, significant intravascular volume fluxes, metabolic derangements, and blood loss in the perioperative period following a liver transplant in children with abnormal 2-DE parameters are likely to be detrimental and should, therefore, be judiciously managed.

Hepatopulmonary syndrome

HPS is a triad of liver disease, pulmonary vascular dilation, and impaired oxygenation resulting from a right-to-left shunt. The prevalence of HPS in children with chronic liver disease ranges from 4.6% to 19% (8–10). This wide range in prevalence can be partly attributed to the inconsistency in the cutoffs used to define HPS. A uniform approach to the diagnosis as suggested by the European Respiratory Society task force is recommended (11). There are no clinical hallmarks of HPS, but common signs and symptoms include cyanosis, exertional dyspnea, platypnea, orthodeoxia (deoxygenation accentuated in upright position), and digital clubbing. The onset of cyanosis is variable, can occur in infancy, and is progressive (8). In a prospective adult study, the presence of HPS was shown to be an independent predictor of survival besides age, Child–Pugh class, and blood urea nitrogen (12). Liver transplant is the best treatment option for both children and adults (9, 13–15). Preoperative arterial pO_2 of ≤ 50 mmHg in adults is a predictor of poor post-transplant outcome establishing the need for timely diagnosis and intervention (16). For above reasons, children with features suggestive of HPS should be evaluated by a cardiologist who will perform a contrast-enhanced transthoracic 2-DE using agitated saline injection. The opacification of the left atrium within 3–6 cardiac cycles following opacification of the right side is a positive test result for HPS. The presence of an intracardiac shunt should be carefully excluded, and if necessary, a transesophageal contrast-enhanced echocardiography should be carried out. Both transthoracic and transesophageal imaging cannot discern between pulmonary vasodilation and pulmonary arteriovenous malformations, which occur rarely with HPS. Clinically, arteriovenous malformations produce more hypoxemia and are poorly responsive to 100% oxygen administration.

Pulmonary angiography in the cardiac catheterization lab is confirmatory and can help determine the achievability of coil embolization. Presence of HPS can also be confirmed by technetium-99 m-labeled macroaggregated albumin lung scan.

Cardiac repolarization abnormalities

Children with chronic liver disease can develop cardiac repolarization abnormalities noted as prolongation of the QTc interval on EKG. A study on 38 pediatric patients awaiting liver transplant showed prolonged QTc in seven (18%) patients (17). None of the patients developed ventricular arrhythmia and QTc normalized in survivors of liver transplant. Studies in both children and adults have shown correlation between prolongation of QTc and PELD scores/Child-Pugh scores, higher mortality in the pre-liver transplant group with prolonged QTc but only PELD scores/Child-Pugh scores have emerged as independent predictors of survival, and no effect of QTc on post-transplant survival (18, 19). Despite these findings, clinicians should exercise caution in managing children with chronic liver disease and a prolonged QTc interval. Efforts should be made to maintain normal electrolytes and avoid use of medications that further prolong the QTc in these patients. Chronic beta-blockade in adults with cirrhosis has shown to be effective in reducing QTc interval (20). Similar data are lacking in children, and consideration for treatment of prolonged QTc interval with beta-blockers will need to be individualized.

Portopulmonary hypertension

PPHTN is a potentially lethal complication observed in 5–10% of adult patients presenting for a liver transplant evaluation (21). Prevalence of PPHTN in children is not well known. A pediatric autopsy study showed 5.2% incidence of pulmonary hypertension in patients with portal hypertension (22). Whitworth et al. (23), in their prospective review of 33 children with stable cirrhosis or extrahepatic portal hypertension, identified no subject with PPHTN. Condino et al. (24) describe the largest experience in seven children with PPHTN who had presented with a new murmur, dyspnea, and/or syncope. Four patients died in their study, and autopsies showed plexiform lesions and pulmonary arteriopathy. PPHTN in adults is progressive and has very poor outcomes (25). Liver transplantation in adults with moderate to severe PPHTN has previously been contraindicated because of high mortality rates in the perioperative period (26). This has changed with increasing evidence demonstrating the use of intravenous epoprostenol as a successful bridge to liver transplant in both children and adults with moderate-to-severe pulmonary hypertension (27–29). Whether liver transplantation cures PPHTN in children or adults is unclear. Some reports have shown resolution, and others have shown persistence or worsening of PPHTN following a liver transplant (28, 30–32). Future studies will delineate this further. In addition, evidence-based screening recommendations in children need to be established. Presently, we follow the European Respiratory Task Force recommended screening of all patients before liver transplantation with 2-DE echocardiography to detect PPHTN (11). A confirmatory cardiac catheterization is performed as needed.

In summary, children with end-stage liver disease can have frequent involvement of the cardiovascular system. At our institute, all children awaiting a liver transplant undergo a complete cardiac evaluation. This includes a thorough history and physical examination with pulse oximetry, an EKG, and 2-DE. Cardiologists then determine whether further testing is necessary.

In the following section, we discuss the specific cardiovascular manifestations of common diseases that warrant a liver transplant in childhood.

Biliary atresia

Biliary atresia is a progressive inflammatory obliterative cholangiopathy with a reported incidence of about 1 in 15 000–20 000 live births (33, 34). Even though bile flow can be re-established in a good proportion of affected infants by timely excision of the extrahepatic biliary tract and biliary reconstruction (Kasai portoenterostomy), biliary atresia still accounts for the most common indication for liver transplantation in childhood (35). This disorder is an isolated finding in 80–90% of infants and occurs in association with other congenital abnormalities in up to 20% of all cases. In the latter group, developmental abnormalities of the spleen are the most prevalent. The term biliary atresia splenic malformation syndrome has been proposed for these, emphasizing the important clinical association with polysplenia as well as other splenic anomalies. Conversely, studies in children with polysplenia have reported a 10% incidence of biliary atresia (36).

A spectrum of congenital heart defects occurs in children with biliary atresia splenic

malformation with a reported incidence of 45%. The major anomalies include TOF, hypoplastic left heart syndrome, aortic arch anomalies, and complex cardiac defects (37–39). Additional anomalies, like, atrial septal defect, ventricular septal defect, patent ductus arteriosus, patent foramen ovale, pulmonary artery stenosis, and dextrocardia with situs inversus, have also been reported. Interrupted inferior vena cava with azygous continuation occurs commonly with an incidence of 65% in children with polysplenia (40). Although the functional significance of this anomaly is minimal, it is important information if a liver transplant is contemplated. Children with biliary atresia splenic malformation also have a higher incidence and earlier development of significant HPS (8, 41, 42). Hence, a complete cardiac evaluation is prudent for children with biliary atresia and splenic anomalies. In addition, those presenting with cyanosis and/or dyspnea merit a contrast echocardiogram. A corrective surgery for hemodynamically significant cardiac abnormalities is indicated prior to surgical palliation for biliary atresia itself.

Alagille syndrome

AGS is an autosomal dominant disorder characterized by intrahepatic bile duct paucity, ocular abnormalities, facial dysmorphism, vertebral anomalies, renal anomalies, hematologic abnormalities, vascular anomalies, and congenital heart defects. Point mutations in the *JAG1* gene as well as large deletions or rearrangements of 20p12, which include *JAG1,* are pathogenic for this disorder. *JAG1* mutations can be identified in 94% of individuals with AGS (43).

Children with AGS constitute 4–5.3% of those requiring a liver transplant (44, 45). A substantial proportion (>90%) of these children have involvement of the cardiovascular system. The most common pathology is branch pulmonary artery stenosis, and other right-sided heart defects including TOF, TOF with pulmonary atresia, and pulmonary valve stenosis are observed frequently. Left-sided lesions (aortic stenosis, coarctation of the aorta) and septal defects (atrial septal defect, ventricular septal defect, and atrioventricular septal defects) are seen less commonly. In a study of 92 patients with AGS, Emerick et al. showed that the presence of intracardiac heart disease is predictive of mortality. The survival of patients with TOF (66%) and TOF with pulmonary atresia (25%) in this study was significantly less than the estimated 10-yr survival in non-AGS patients (46). In another study analyzing the cardiovascular phenotype of 200 subjects with *JAG1* mutation or AGS, 10 of the 23 (43%) subjects with TOF died from cardiovascular causes. Six of these patients had TOF with pulmonary atresia (75% of 8). Notably, none of the 55 subjects with branch pulmonary artery stenosis (not including those with TOF) developed a substantial increase in the severity of stenosis over time. Forty-six of the 200 (23%) subjects required at least one cardiac intervention (cardiac catheterization or surgery), and during follow-up, an overall 7% mortality was reported from cardiovascular causes (47). Hence, all children with AGS should be evaluated by a pediatric cardiologist, especially if liver transplantation is being considered. A complete pre-operative cardiovascular evaluation is key to successful anesthetic management of these children (48).

Metabolic diseases

Metabolic diseases in aggregate constitute the second commonest indication for liver transplant in children. Amid 2997 children enrolled in the Studies of Pediatric Liver Transplantation registry between the year 1995 and 2008, 446 (14.9%) underwent liver transplant for metabolic diseases (49). The spectrum of metabolic diseases with their respective frequencies is listed in Table 2. In the following section, we focus on the specific cardiovascular manifestations of some of these diseases individually.

Table 2. Spectrum of metabolic and non-metabolic liver diseases as primary diagnosis in the SPLIT registry

	N	%
Metabolic disease (N = 446)		
Urea cycle defects	114	25.6
Alpha 1 antitrypsin deficiency	88	19.7
Cystic fibrosis	48	10.8
Wilson disease	34	7.6
Maple syrup urine disease	29	6.5
Tyrosinemia	33	7.4
Glycogen storage disease	23	5.2
Crigler–Najjar	21	4.7
Neonatal hemochromatosis	18	4.0
Primary hyperoxaluria	9	2.0
Inborn error in bile acid metabolism	3	0.7
Other metabolic disease	26	5.8
Non-metabolic disease (N = 2551)		
Biliary atresia	1214	47.6
Fulminant liver failure	421	16.5
Other cholestatic	386	15.1
Tumor	212	8.3
Other	318	12.5

Arnon et al. (49). Reprinted with permission from John Wiley and Sons.

Cystic fibrosis

CF is an autosomal recessive multisystem disorder of children and adults characterized by dysfunction of exocrine glands. It primarily results in chronic lung disease, pancreatic insufficiency, and their associated complications. With improved overall survival of CF patients, hepatic involvement is being increasingly recognized. Current data estimate the prevalence of advanced liver disease in 4–10% of CF patients. Liver transplantation is a viable option in management of these patients. In patients who receive a transplant, pulmonary complications account for the most common cause of mortality. Thus, pre-liver transplant work-up should include evaluation of lung function and pulmonary hypertension, to establish the need for simultaneous lung transplant as well. A study on 245 CF patients (children and adults) from the United Network for Organ Sharing (UNOS) database showed comparable one- and five-yr patient and graft survival rates between the liver lung transplant group vs. liver transplant group alone (50).

Chronic lung disease and hypoxia in CF patients result in vascular changes leading to development of pulmonary hypertension. Cardiac catheterization is a gold standard test for pulmonary hypertension, but 2-DE serves as a sensitive tool in identifying and monitoring patients with this disease. A prospective study with 2-DE data in 37 patients with CF showed a 30% prevalence of pulmonary hypertension using a conservative Tricuspid regurgitation jet velocity of 2.8 m/s (estimated right ventricular systolic pressure of 31 mmHg + right atrial a wave pressure). Patients in the pulmonary hypertension group had significantly lower baseline oxygen saturations and lung function parameters (51). Long standing pulmonary hypertension may result in chronic right-sided heart failure presenting with dyspnea, tense and tender hepatomegaly, pedal edema, increased jugular venous distension, and unusual weight gain. LV function is usually well preserved in CF patients. In patients who develop systolic dysfunction of the LV, a multitude of causes have been postulated including cirrhotic cardiomyopathy and ventricular interdependence in patients with cor pulmonale. In addition, studies using ventriculography and 2-DE strain mapping have shown LV diastolic dysfunction in adult patients with CF (52, 53). The clinical significance of diastolic dysfunction and its implication to patient outcome needs to be established. Considering all the factors listed above, cardiac evaluation is recommended in children with CF awaiting liver transplant to assess for both pulmonary hypertension and irreversible cardiac dysfunction, which may warrant a heart transplant. At present, the role of phosphodiesterase inhibitors in managing CF patients with pulmonary hypertension is unclear with some positive case reports (54). This drug class has become the first line in management of patients with idiopathic pulmonary hypertension. It is likely that future studies will evaluate the role of these drugs in managing pulmonary hypertension in CF patients. Also, there is evidence suggesting that sildenafil, a phosphodiesterase inhibitor, may attenuate inflammatory process within the airway and augment trafficking of CF transmembrane conductance regular protein to apical cell membranes (55), and further studies are underway. Serial cardiac evaluation to assess for pulmonary pressures will be paramount to establish the outcome of these studies.

Wilson disease

Wilson disease is a rare autosomal recessive disorder of copper metabolism caused by mutation in the gene *ATP7B* that encodes for a copper-transporting P-type adenosine triphosphatase. The excretion of copper from the liver cells into the bile is impaired and pathologic amounts of copper accumulate in the liver, and other organs especially brain, kidneys, and cornea. Clinical presentations of the disease are variable with hepatic involvement being the most common manifestation in young patients. Forms of hepatic disease include asymptomatic disease, chronic hepatitis, cirrhosis, and uncommonly fulminant hepatic failure. Liver transplantation is a good treatment option for children presenting with fulminant hepatic failure or chronic liver disease unresponsive to medical treatment (56–58).

Cardiac involvement with Wilson disease in the pediatric population has not been well studied. Most adults with this disease are asymptomatic from the cardiovascular standpoint. In a prospective study of 53 patients with Wilson disease, EKG abnormalities were found in 18 subjects (34%). Two cardiac deaths were reported. The first patient developed a sudden collapse, was found to be in ventricular fibrillation, and could not be resuscitated. Autopsy showed a normal heart and coronaries with a below-normal copper level in the myocardium. The second patient had dilated cardiomyopathy and died of worsening heart failure. An autopsy was not performed (59). Pathologic and 2-DE

studies in adults with Wilson disease have shown cardiac hypertrophy in some patients. There is no correlation of cardiac hypertrophy with tissue levels of copper, presence of cirrhosis or duration, and type of therapy used for treatment (60, 61). Autonomic dysfunction has also been described in adults with Wilson disease. However, symptomatic orthostatic hypotension is rare in these patients (59, 62). On the basis of the current knowledge, cardiac involvement with Wilson disease appears to be mild. The progression of cardiac disease or its influence on the prognosis of patients with Wilson disease is not well established. Cardiac involvement, akin to other organ system injury, is postulated to be because of oxidative injury and, with improved medical management, might become even less significant. In the absence of pediatric studies, screening EKG and 2-DE, if available, can be performed. Further follow-up should be individualized for each patient.

Tyrosinemia Type I

Tyrosinemia type I is the most common disorder of tyrosine metabolism caused by mutation in the gene for enzyme fumarylacetoacetase. The disease commonly manifests in infancy with progressive liver damage and liver failure with a high risk of hepatocellular carcinoma. Renal tubular dysfunction and hypophosphatemic rickets are other common manifestations. Introduction of nitisinone therapy since 1992 has transformed the management of this disease. Nitisinone inhibits the second step in tyrosine metabolism and prevents the formation of toxic metabolites like fumarylacetoacetate and maleylacetoacetate. Liver transplantation is a curative option and is indicated for non-responsiveness to nitisinone therapy, risk of malignancy, and poor quality of life related to dietary restriction (63). Cardiomyopathy in tyrosinemia type I has been reported since 1987 (64). A retrospective study in 20 children with tyrosinemia showed a 30% incidence of cardiomyopathy. Both symmetric and asymmetric hypertrophy was reported. All of the six patients with cardiomyopathy were asymptomatic from the cardiovascular standpoint. After a median interval of 3.6 yr, cardiomyopathy resolved in five of the six children and significantly improved in the remaining one patient. The frequency of cardiomyopathy was significantly less in children on nitisinone therapy (65). This substantiates other reports suggesting resolution of severe cardiac hypertrophy after initiation of nitisinone therapy (66). Overall, cardiomyopathy is frequent in tyrosinemia type 1, but usually asymptomatic and severe cases have been shown to improve both with nitisinone therapy and liver transplantation (63).

GSD or glycogenoses

Glycogenoses are rare inherited disorders affecting glycogen metabolism. More than 12 forms of GSD have been recognized of which seven forms principally affect the liver. GSD type I, III, and IV can result in significant hepatic metabolic disease requiring a liver transplant. Other forms of hepatic GSD are usually mild disorders (67, 68).

GSD-III, also called Cori-Forbes disease, is the hepatic GSD with which involvement of the cardiovascular system has been well described. The lack of debranching enzyme activity in this disease results in accumulation of an abnormal form of glycogen, limit dextrin, in affected tissues. Liver and muscle involvement occurs in more than 80% of patients (GSD-IIIa), and the liver is exclusively involved in 15% of patients (GSD-IIIb). In infancy and childhood, liver involvement with hepatomegaly, elevation of hepatocellular enzymes, and fibrosis is common, but usually improves with age and resolves after puberty (69). Liver transplantation has been performed rarely for cirrhotic liver disease and risk of hepatic malignancy (67). Skeletal myopathy with severe limitations by the fourth decade of life, cardiomyopathy, and poor growth are other manifestations of the disease. LV hypertrophy has been indentified in patients with GSD-III since the early descriptions of the disease. Two-dimensional echocardiography studies have shown increased LV wall thickness and LV mass in 30–80% of patients, especially those with GSD-IIIa (70, 71). A progressive increase in the LV dimensions over time has also been reported (71). Indices of LV systolic function and diastolic function are normal in most of the patients. Clinical manifestations of LV hypertrophy in this patient population are much more subtle compared with similar finding in patients with hypertrophic cardiomyopathy. Patients with GSD-III and significant LV hypertrophy are predominantly asymptomatic, have normal cardiac response to exercise and stress thallium scintigraphy, and demonstrate minimal abnormalities on 24-h ambulatory electrocardiographic monitoring (72). These patients also do not develop valvular disease, and endomyocardial biopsies are negative for myocardial disarray, a feature pathognomonic of hypertrophic cardiomyopathy. Yet, case reports of sudden deaths,

cardiac failure necessitating a heart transplant, and ventricular arrhythmia in patients with GSD-III and cardiomyopathy exist in the literature (71, 73–75). Indicators predicting a worse cardiac outcome are unidentified, and no correlation with creatine kinase activity or severity of myopathy has been noted. The American College of Medical Genetics has recommended baseline cardiac screening with 2-DE and follow-up every 12–24 months for patients with GSD-IIIa (76). GSD-IV, also known as Andersen disease, resulting from deficiency of the branching enzyme, has been reported to cause dilated cardiomyopathy in different age groups (77, 78).

Primary hyperoxaluria

Primary hyperoxaluria is a rare genetic disorder in which large amounts of oxalates accumulate in the body. Type I primary hyperoxaluria is the most common form (~80%) caused by deficiency of hepatic alanine glyoxylate aminotransferase resulting in inadequate conversion of glyoxylate to glycine. Consequently, there is marked increase in conversion of glyoxylate to oxalate. Age of presentation is variable, but more than 50% of patients have symptoms within the first decade of life (79). Symptoms are related to renal stones and nephrocalcinosis followed by progression to renal insufficiency. Systemic oxalosis then occurs predominantly involving the cardiovascular, musculoskeletal, and peripheral nervous systems. Renal transplantation in these patients has been unsatisfactory with a high incidence of recurrent renal oxalosis. Combined liver and kidney transplant recipients have shown better outcomes (80).

Myocardial calcium oxalate deposition can result in abnormalities of the cardiac conduction system, arrhythmias, valvular abnormalities, and cardiomyopathy presenting in adulthood (81–83). In a study evaluating cardiac abnormalities in 93 patients with primary hyperoxaluria, the mean age at the time of cardiac manifestations was 40 yr. Symptoms included dyspnea, chest pain, palpitations, and syncope. EKG and/or 2-DE were performed in 38 patients. Seven of the 33 patients who had an EKG showed abnormalities including LV hypertrophy, bundle branch block, and atrioventricular block. The predominant 2-DE abnormalities included increased LV mass index, left atrial enlargement, pulmonary hypertension, and diastolic dysfunction. The presence of cardiac abnormalities correlated with the severity of renal dysfunction and plasma oxalate levels (84). Combined liver and kidney transplant may reverse the cardiac manifestations (85).

Propionic acidemia

Propionic acidemia is a rare inherited disorder of branched chain amino acid metabolism arising from deficiency of propionyl coenzymeA carboxylase enzyme. Liver transplant reduces the risk of metabolic decompensation, neurologic sequelae and improves the quality of life (86). Children with this disease frequently develop prolongation of QTc interval and dilated cardiomyopathy meriting cardiac evaluation and close follow-up (87). Cardiomyopathy is reversible following liver transplantation (88).

Fatty acid oxidation defects

Fatty acid oxidation defects are rare recessively inherited disorders of lipid metabolism. They constitute a small proportion of metabolic diseases warranting a liver transplant in childhood (49). Dilated cardiomyopathy and cardiac hypertrophy have been reported with various forms of fatty acid oxidation defects including medium-chain-acyl-CoA dehydrogenase deficiency (89–92). Depending on the specific metabolic defect, dietary modifications, micronutrient, and essential fatty acid supplementation may improve the cardiac manifestations (92, 93).

No specific cardiac manifestations have been reported with urea cycle defects, alpha 1 antitrypsin deficiency, Crigler–Najjar disease, or maple syrup urine disease.

Infantile hepatic hemangioendothelioma

Hepatic tumors are uncommon in the neonatal period, and of those infantile hepatic hemangioendotheliomas are the most frequently occurring primary hepatic lesions (94). These lesions present most commonly in young infants <6 months of age. Common presenting signs and symptoms include massive hepatomegaly, high-output heart failure, skin hemangiomas, anemia, and hyperbilirubinemia. Consumptive hypothyroidism because of the expression of deiodinase enzyme in the tumor cells has been described (95, 96). In addition, *in utero* and early postnatal decompensation may occur because of rapidly progressive liver failure, heart failure, tumor rupture, consumptive coagulopathy, and Kasabach–Merritt syndrome. Congestive heart failure occurs in 15–45% of patients and is a strong predictor of mortality and poor outcome meriting aggressive treatment (97, 98). Hypothyroidism can further worsen symptoms of heart failure because of the direct stimulating effects of thyroid hormone on cardiac contractility (99). Medical management should focus on cardiac

stabilization with inotropic support, decongestive therapy, and thyroid hormone replacement as necessary. Medications that help reduce the tumor burden and result in symptomatic improvement include intravenous steroids (98), interferon alpha (100, 101), cyclophosphamide (102), and more recently propranolol (103–106). Patients unresponsive to medical therapy may benefit from interventional procedures with embolization of the vascular supply, surgical ligation of the hepatic artery, or surgical resection of the tumor (98, 107–110). In patients who fail these management strategies, a liver transplant may be contemplated as a life saving option (98, 111, 112).

Cardiac effects of immunosuppression

Failure of primary liver transplant may require retransplantation. Also liver transplantation may be needed in children already on immunosuppression for prior renal or small bowel transplants. Most of these children will be on tacrolimus that is used as a primary immunosuppressive agent following solid organ transplants. It is important to recognize that cardiac toxicity in the form of cardiac hypertrophy can occur rarely in these children. This toxic effect occurs almost exclusively in the pediatric population (113). Both symmetric cardiac hypertrophy or asymmetric interventricular septal hypertrophy have been reported (114, 115). The onset of hypertrophy following initiation of therapy has varied between reports, ranging from as early as three wk to as late as five yr (115, 116). The risk of development of cardiac hypertrophy has been linked to the serum levels of the drug (113, 114). Case reports have suggested reversal of this pathologic process on discontinuation of therapy and use of cyclosporine or sirolimus instead (115–118). Thus, development of symptoms related to the cardiovascular system or presence of a new murmur on physical examination in a child on this therapy should trigger an evaluation with a pediatric cardiologist. Prospective studies systematically evaluating the cardiovascular function in children on tacrolimus over long term are necessary to estimate the true incidence of this pathology and to establish guidelines for cardiac evaluation and follow-up of such patients.

Conclusion

In summary, cardiac disease is not an uncommon occurrence in pediatric liver transplant candidates. The spectrum of cardiac disease in this population is much wider than in adults. The information presented here will enhance the awareness of clinicians on this topic and provides them with future research directions. Also, it should facilitate the effective utilization of available tests to screen for cardiac disease. Finally, it may help improve perioperative management and outcomes following liver transplant in children.

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