Cardiac and liver disease in children

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Cardiac and liver disease in children: implications for management pre and post liver transplantation

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Abstract

There is close interaction between the functions of the liver and heart affecting the presentation, diagnosis and outcome of acute and chronic cardiac and liver disease. Conditions affecting both organ systems should be considered when proposing transplantation as the interaction between cardiac and liver disease has implications for diagnosis, management, selection for transplantation and ultimately long-term outcome post-liver transplantation. The combination of cardiac and liver disease is well recognised in adults but less appreciated in paediatrics. The focus of this review is to describe conditions affecting both liver and heart and how they affect selection and management of liver transplantation in the paediatric population.

Glossary (alphabetical order)

ALT	Alanine transaminase
ALP	Alkaline phosphatase
AS	Alagille syndrome
ASD	Atrial-septal defect
AST	Aspartate Aminotransferase
BA	Biliary atresia
CCM	Cirrhotic cardiomyopathy
CHD	Congenital heart disease
CLHT	Combined liver-heart transplantation
CO	cardiac output
CT	Computerised tomography
DSMRI	Dobutamine stress Magnetic Resonance Imagining
ECG	Electrography
FALD	Fontan-associated liver disease
FFA	Fumarylacetoacetase
FNH	Fibronodular hyperplasia
GGT	Gamma Glutamyl transferase
GSD	Glycogen Storage Disease
HCC	Hepatocellular carcinoma
HT	Heart transplant
HV	Hepatic vein
HVWP	Hepatic venous wedge pressure
IVC	Inferior vena cava
LT	Liver transplantation

LVH	Left Ventricular hyperplasia
LVIDd	Left ventricular end-diastolic diameter
LVMI	Left Ventricular Mass Index
MMA	Methylmalonic acidemia
MDT	Multidisciplinary team
NTBC	Nitisinone
PA	Propionic acidemia
PT	Prothrombin time
RT	renal transplantation
SPLIT	Studies of Pediatric Liver Transplantation
VSD	Ventricular septal defect
WD	Wilson's Disease

Introduction

Cardiac disease is an accepted co-morbidity in adult patients with end-stage liver disease [1] and a recognised component of multi-organ disease in children with congenital disorders or metabolic disease (table 1). As survival improves in paediatric patients with liver disease, particularly following successful liver transplantation (LT), cardiac complications are important determinants of morbidity and mortality pre and post LT, and so cardiac evaluation is an essential part of the transplant work-up [2].

Hepatic disorder	**Hepatic features**	**Cardiac features**	**Implication for transplant**
Biliary atresia	Cholestasis Hepatomegaly Obstructive jaundice	Dextrocardia, ASD, VSD, Cardiomyopathy [3] [4]	Cardiac surgery pre-transplant Transplant may be contraindicated if surgery is not possible
Alagille's syndrome	Cholestasis, pruritis	Branch pulmonary artery stenosis, Tetralogy of Fallot	Cardiac catheter may be required. Pulmonary artery stenosis may be distal and less amenable to surgery [5] pre-transplant Balloon dilatation +/- intravascular stenting for severe stenosis Surgical repair for Tetralogy of Fallot Percutaneous valvuloplasty [6] [7]
Fulminant or subacute liver failure	Encephalopathy, coagulopathy, jaundice	Bounding pulses High cardiac output	Echocardiogram, Electrocardiogram
Mitochondrial cytopathy,	High lactate, coagulopathy [8]	Cardiomyopathy [9]	Transplant contraindicated
Tyrosinemia type 1	Coagulopathy, jaundice	Hypertrophic cardiomyopathy [10]	Transplant curative

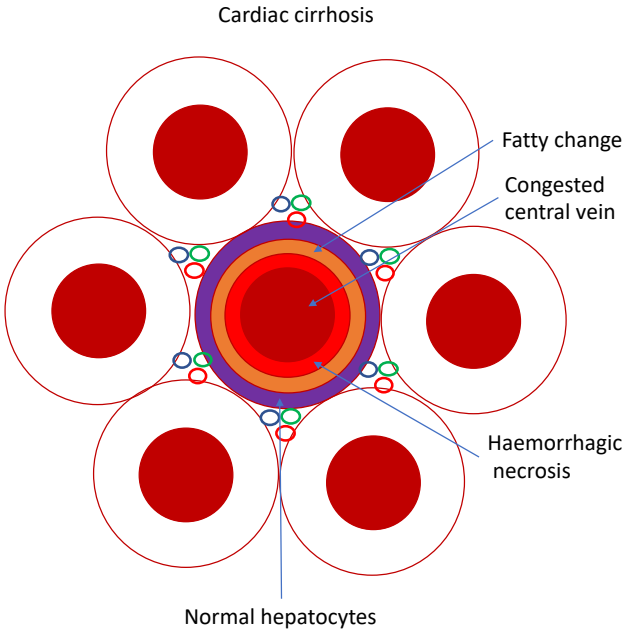
Table 1. The cardiac and hepatic features of common paediatric liver disease. Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD)

Conditions affecting both organ systems may be classified into three groups: (1) Congenital heart disease and the liver (e.g. structural defects); (2) Inherited Metabolic disease and (3) End-stage liver disease and the heart. We review emerging data in this field.

1. Congenital heart disease and the liver

Liver disease in children with congenital cardiac disease may arise as the direct result of cardiac dysfunction (ie.cardiac cirrhosis), or as part of a genetic disorder (eg, Alagille syndrome). The liver receives around 25% of the cardiac output and is extremely sensitive to a reduction in flow. In addition, there are no valves between the hepatic vein (HV) and the inferior vena cava (IVC) so that any elevation in venous pressure is transmitted directly into the liver sinusoidal bed. It is inevitable that liver involvement occurs in conditions that significantly reduce cardiac output or oxygen delivery leading to impaired liver perfusion, or increased systemic venous pressure predisposing to hepatic congestion and centrilobular necrosis (fig 1).

(a)



(b)

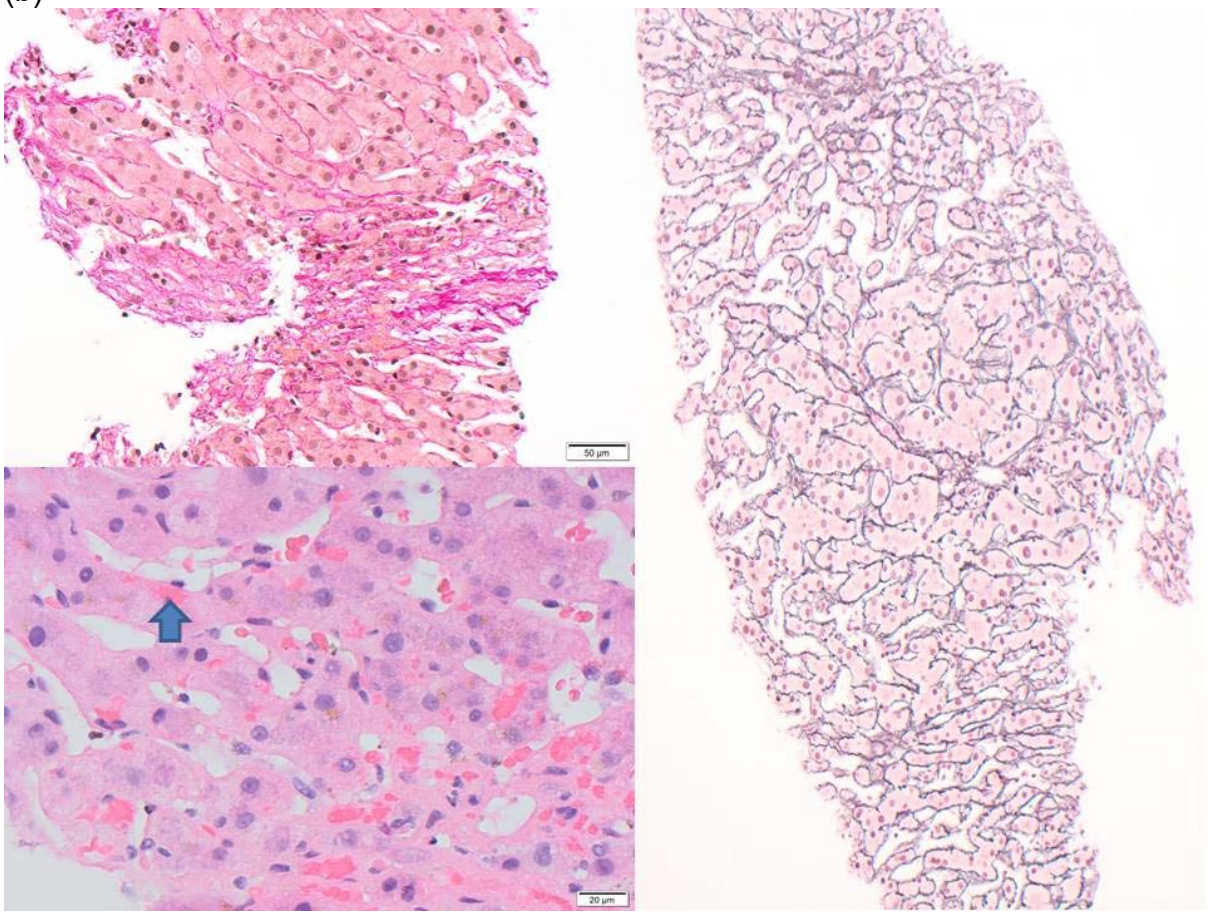


Fig. 1: (a) Schematic representation of changes seen in cardiac cirrhosis. Dilated and congested hepatic venules with centrilobular hemorrhagic necrosis of hepatocytes. Periphery shows fatty change in hepatocytes. Hepatocytes adjacent to portal triad are normal. (b) Histological changes seen (right panel) reticulin staining outlining a nodule

with circumferential plate atrophy (nodular regenerative hyperplasia; (upper left panel) hematoxylin van Gieson demonstrating perisinusoidal fibrosis; (lower left panel) hematoxylin and eosin, there is vascular congestion and in places red blood cells are pushed into the space of Disse (arrow) an indicator of venous outflow obstruction

Reduced cardiac output: In the acute setting, cardiovascular collapse due to closure of the arterial duct in a duct-dependent systemic circulation, results in an acute ischaemic hepatitis with a rise in hepatic transaminases due to hepatic necrosis, unless flow is rapidly restored, with prostaglandin infusion [11]. A similar situation arises after cardiac surgery with a prolonged period of cardiopulmonary bypass or circulatory arrest if the liver becomes ischaemic [12]. Depending on the duration and severity, hepatitis, cholestasis, fibrosis, cardiac cirrhosis/hepatopathy and portal hypertension may develop.

On the other hand, chronic heart failure with reduced systemic blood flow, such as with a left-to-right intra-cardiac (eg. VSD) or extra-cardiac (eg. patent arterial duct) shunt, or a pressure gradient across the aortic arch (eg. coarctation of the aorta) may affect liver function. In children with a chronic right-to-left shunt, cyanosis will reduce oxygen delivery to the tissues despite normal flow and may result in chronic liver hypoxaemia [13]. Treatment is directed towards repair of the primary congenital heart defect to correct the physiological sequelae. Although early cirrhosis likely can regress, the heavily cross-linked collagen and elastin of late cirrhosis may be resistant to remodelling.

Increased systemic venous pressure: Any right-sided cardiac lesion that increases right atrial pressure or volume leads to elevated pressure in the IVC and hepatic venous congestion. *Cardiac hepatopathy* is caused by defects downstream of the right

atrium such as pulmonary arterial hypertension (either primary or secondary to left-sided heart disease), pulmonary stenosis, right ventricular outflow tract obstruction, a VSD (with left-to-right shunt), right ventricular hypertrophy or failure, or tricuspid regurgitation (including Ebstein's anomaly). Patients with hepatic congestion are usually asymptomatic but have mild unconjugated jaundice and abnormal hepatic transaminases. Bridging fibrosis or cardiac cirrhosis result from prolonged haemodynamic abnormalities, leading to impaired hepatic function with coagulopathy, hypoalbuminemia, and alteration in the metabolism of several cardiovascular drugs, with unwanted toxicity [14]. The hepatic venous wedge pressure (HVWP) is normal in contrast to the elevated portal/systemic venous pressure gradient in hepatic cirrhosis due to chronic liver disease, explaining why varices very rarely develop in the setting of congestive hepatopathy [11] [15].

Congenital cardiac disease. Children with congenital cardiac disease may have no obvious signs of liver congestion but many develop jaundice, dependent oedema, ascites and hepatomegaly. Laboratory investigations reveal a cholestatic picture with raised Gamma Glutamyl Transferase (GGT), alkaline phosphatase (ALP) and conjugated bilirubin, while hepatic transaminases (ALT, AST) remain normal. The degree of cholestasis is directly proportional to the degree of systemic venous pressure elevation. Cardiac cirrhosis, which resembles micronodular cirrhosis, is found in up to 50% of patients with congestive heart failure [16]. As fibrosis or cirrhosis may regress if the initial insult is neutralized [17], [18] [19], it is possible that cardiac cirrhosis may regress following successful cardiac surgery or a heart transplant (HT), but as irreversible hepatic cirrhosis greatly increases the risks of HT, it is an absolute

contraindication for HT and a Combined Heart and Liver Transplant (CHLT) is indicated.

Fontan circulation: Children with a single ventricle heart condition who go on to have Fontan completion all have chronic hepatic congestion. Often from birth, they undergo a variety of initial surgical palliations, converging at around 3-4 years of age with a Fontan procedure [20]. In this operation, the functioning ventricle is used to support the systemic circulation with passive, non-pulsatile blood flow in series from the caval veins directly to the lungs. The loss of the ventricular pump to drive pulmonary blood flow leads to an immediate and sustained rise in systemic venous pressure to overcome the transpulmonary gradient to the left atrium, usually around 20-25mmHg, leading to chronic hepatic congestion and associated cardiac cirrhosis [21]. Hepatic perfusion pressure may also be reduced due to decreased cardiac output, with chronic hypoxemia secondary to shunting via a Fontan pathway fenestration, if present. The chronically elevated hepatic venous pressure leads to mechanical transduction of hepatic stellate cells, transformation into myofibroblasts which produce collagen deposition in both centrilobular and portal venous patterns. In addition, the chronic venous pressure elevation on the gut may lead to protein-losing enteropathy, characterised by loss of serum protein into the intestine and hypoproteinaemia, leading to peripheral oedema, ascites, pleural effusions and malnutrition further complicating the liver disease [22].

Hepatomegaly and abnormal liver function have been reported in up to 50% of patients post Fontan [23] (table 2) but liver synthetic function is initially only mildly affected. However, most children develop chronic hepatic congestion, with progressive hepatic fibrosis known as Fontan-associated liver disease (FALD) [24] [25].

	Early	Late
Hepatic function	Bilirubin normal Transaminases normal or mildly elevated	Mildly elevated unconjugated hyperbilirubinemia Transaminases (esp GGT) elevated
Serum albumin	Normal Can be reduced due to protein losing enteropathy	
Coagulation	Normal (unless on warfarin)	PT abnormal (deficiency of Protein C,S, Factors II,V,VII,IX and X, Antithrombin III and plasminogen)
Full blood count	Normal	Thromobocytopenia (marker of portal hypertension)

Table 2: Early and late hepatic laboratory investigations in patients following Fontan surgery (GGT, gamma-glutamyltransferase; PT, Prothrombin Time)

In addition, survivors of the Fontan procedure may develop liver nodules similar to those seen in Budd-Chiari syndrome and Fibronodular hyperplasia (FNH) resulting from arterialisation of hepatic blood supply. It is important to differentiate these nodules from hepatocellular carcinoma (HCC). A recent review found 33/2470 patients (1.3%) developed biopsy proven HCC at a median age of 30 years (IQR 12-53), 22 years (2-36 years) after Fontan completion [26]. Surgical management of these tumours is complicated by the high systemic venous pressure required to sustain adequate preload and cardiac output, which predisposes to bleeding during hepatectomy. Non-surgical treatments for locoregional control may therefore be preferable such as transarterial chemoembolization or radiofrequency ablation [27] [28].

In patients who develop either cardiac or liver failure consideration for either LT or HT transplantation may become necessary. Chronic Liver Disease post-Fontan may be a contraindication to isolated HT or require CLHT [29]. In a recent study, 7 (41%) of 17 children with a failing Fontan and progressive liver disease underwent successful CLHT, with no perioperative mortality and minimal short term morbidity [30]. Although preliminary in its nature this is the first reported evidence for better outcome in children

with combined liver and heart transplant on failing Fontan. The hepatic and gut pathology may be reversed by a successful heart transplant as 35% of patients undergoing HT for a failing Fontan had resolution of protein losing enteropathy or oesophageal varices [31].

There is no current consensus about how best to evaluate or predict progression of cardiac and liver disease in these patients. At present cardiac function is established by echocardiography with or without cardiac catheterisation, while assessment of synthetic liver function with abdominal ultrasound or computerised tomography (CT) scans to determine liver vascular anatomy is usual.

Congenital heart disease in other syndromes:

Liver disease and cardiac disease coexist in a number of childhood diseases, notably Alagille syndrome (AS) and Biliary atresia (BA). Patients with Congenital heart disease (CHD) and end stage liver disease need careful assessment and management including timing of cardiac procedures and LT.

Alagille Syndrome (AS). AS is a multi-system autosomal dominant disease due to defects in the *JAG 1* or *NOTCH 2* genes occurring at a frequency of approximately 1:30,000, characterised by variable clinical features and penetrance. CHD and liver disease are the most common clinical manifestation of AS, affecting up to 90% of patients [32]. Branch pulmonary artery stenosis is the most common cardiovascular feature and may be associated with Tetralogy of Fallot (Table 1). Cardiovascular disease is the leading cause of death in AS in infancy, whereas liver disease accounts for the majority of deaths in later childhood and adolescence. The incidence of vascular anomalies such as intracerebral anomalies, aortic aneurysms, and rarely aortic coarctation are now recognised as a significant cause of morbidity and mortality

[33]. Routine echocardiography should be used to assess cardiac lesions, with a low threshold for cardiac catheterisation to determine the need for catheter intervention or surgery, as required (Table 1).

LT is indicated in 21–33% of patients with AS because of impaired quality of life with metabolic bone disease or growth failure secondary to severe cholestasis, xanthomatosis, refractory pruritus and rarely progressive liver disease with portal hypertension. However, eligibility may be hindered by the severity of cardiac disease because of adverse hemodynamic effects before, during or following transplantation [34] [32] or the identification of vascular anomalies. LT is associated with significant intraoperative haemodynamic instability particularly during the reperfusion phase, which results in reduced mean arterial pressure, increased pulmonary artery pressure, increased pulmonary artery wedge pressure and increased central venous pressure. Cardiac arrhythmias may also occur during episodes of instability. Careful patient selection and management during surgery is essential. Survival after LT in AS may be as low as 57% [35] with nearly a third of deaths attributed to cardiovascular complications. In a recent multicentre review, survival was significantly lower for patients with AS versus children with biliary atresia [36] 87% versus 96% at 1-year, respectively. No pre-transplant risk factors for decreased survival were identified, however death in the AS group was associated with vascular, biliary, renal, and CNS complications in the first 6 months after transplantation and re-transplantation. The multisystem involvement of AS and the burden of associated comorbidities may explain this survival difference, although patients were selected at least partly on the basis of no significant cardiac disease, as evidenced by the lower prevalence of complex cardiac anomalies in this cohort versus larger series [7].

Biliary atresia. This is the leading indication for LT in children worldwide [37]. About 20% of patients have syndromic biliary atresia (Biliary Atresia Splenic Malformation syndrome) with dextrocardia, ventricular or atrial septal defects, polysplenia and abnormal hepatic vasculature. In infancy, the congenital cardiac disease may dominate the liver disease, delaying the diagnosis. In one recent review, a patient with biliary atresia was deemed too unwell from their underlying cardiac disease to undergo Kasai portoenterostomy, which lead to premature death due to multiple comorbidity, highlighting the difficult decisions about the timing of cardiac surgery and the Kasai portoenterostomy [38]. In contrast, repair of the cardiac condition may stabilise the liver disease and allow a successful Kasai or subsequent liver transplant. When considering LT in these patients, evaluation of underlying cardiac disease as described above in table 1 is important.

In addition to congenital cardiac disease, recent studies have suggested that up to 70% of patients with biliary atresia awaiting LT may develop cirrhotic cardiomyopathy (CCM) with increased left ventricular mass index (LVMI), hyperdynamic contractility, thickened left ventricular free wall and septum [4] [39]. The severity of LVMI was predictive of pre, peri and post-transplant outcomes, with a high incidence of morbidity and mortality. Other authors have demonstrated a prolonged hospital stay but no increase in mortality in children with CCM and all made a complete recovery post successful LT [40] [3] and so further evaluation of the significance of CCM in children is required.

2. Inherited Metabolic Disease

LT is indicated for a number of metabolic disorders in childhood. These conditions involve many systems, including cardiac and liver, so that careful evaluation is necessary to estimate the risks and benefits of transplantation compared to alternative therapies.

Tyrosinemia type I: Tyrosinemia type 1 is an autosomal recessive disorder of tyrosine metabolism which is caused by a mutation in the gene for the enzyme fumarylacetoacetase (FAA). Children affected with this condition present with acute liver failure in the newborn period or chronic liver disease in later childhood, with progressive liver failure and a high risk for development of hepatocellular carcinoma (HCC). Many children with tyrosinemia develop an asymptomatic hypertrophic cardiomyopathy which resolves following successful LT [10]. Since the introduction of Nitisinone (NTBC), which controls the metabolic abnormalities and reverses cardiomyopathy, few children require LT [10] [41] [42] and it is reserved for those who have failed therapy or if HCC is detected.

Wilson disease: Wilson's disease is an autosomal recessive condition due to a mutation in the Wilson disease protein (ATP7B) which leads to copper accumulation in the liver and brain predominantly. The hepatic and neurological manifestations of Wilson disease (WD) are well described, but cardiac involvement is more variable. Cardiac arrhythmias, cardiomyopathy and sudden cardiac death are rare complications but have been reported in children due to myocardial copper accumulation [43]. Echocardiography is a valuable tool for surveillance of patients with WD who, as adults, are at increased risk of heart failure and atrial fibrillation [44] [45].

Therapy includes oral copper chelation therapy or LT for progressive liver failure which may stabilise both cardiac and liver status.

Primary hyperoxaluria type 1 (PH1): This is a rare autosomal recessive multi-system disorder due to mutations in the AGXT gene, in which there is over production and accumulation of calcium oxalate in many tissues. The main clinical features are progressive renal failure and treatment is with pre-emptive LT or combined renal and liver transplant. Oxalate is deposited in the myocardium which predisposes to arrhythmia, heart block, left ventricular hypertrophy (LVH), systolic and diastolic dysfunction, which may preclude LT due to clinical instability to withstand the haemodynamic disturbances during LT. [46]. Ideally LT is performed before advanced renal or cardiac disease has developed but may not be feasible in children with severe phenotypes and cardiac assessment of how well the heart responds to stress is key. There are no proven methods of assessing the heart's response to the potential stress of transplant. Echocardiography and clinical signs, particularly hypotension during dialysis inform management. LVH on echocardiography suggests that there may be haemodynamic issues peri-transplant which may need aggressive management of intravascular filling intraoperatively.

The success of renal/liver transplantation (RT or LT) depends on establishing effective clearance of oxalate from tissues often necessitating perioperative dialysis. Effective RT or LT may improve cardiac function, reduce myocardial oxalate deposits and reduce mortality from end stage cardiomyopathy [47].

Glycogen storage disease (GSD): GSD are autosomal recessive disorders caused by enzyme deficiencies affecting glycogen synthesis, breakdown or glycolysis within muscles and/or liver cells. Twelve forms are reported, only five affect the liver [48] [49]: GSD types I, III, IV, VI and IX [50] [51] [52], of which only types III and IV affect both the heart and liver [53]. Glycogen accumulates in muscles, heart and liver in GSD IIIa. Hepatic disease includes hepatomegaly, transaminitis and hepatic fibrosis. Cardiac involvement includes left ventricular hypertrophy and cardiomyopathy which may require HT. LT is indicated for end stage liver disease or if HCC is identified [54] and reverses the hepatic manifestations of the disease, such as glucose instability, but the outcome on cardiac disease was not determined in this study [55]. There are no reports of co-existing cardiac disease precluding LT In type IV GSD, but evidence of progressive cardiac disease despite LT in a single patient who died at 9 months post LT with cardiac failure and pathological infiltration of amylopectin, despite mild LVH and a normal echocardiogram pre-transplantation [56], suggesting that echocardiogram alone may be insufficient to evaluate cardiac disease in this population and further testing with dynamic studies may be warranted or dobutamine stress test.

Organic acidemias: These include: Propionic acidemia (PA) and Methylmalonic acidemia (MMA). Propionic acidemia (PA) is a rare autosomal recessive disorder resulting in abnormal branched chain amino acid metabolism due to deficiency of the enzyme propionyl-coenzyme A carboxylase, a critical component of certain amino acids and lipids. Clinical manifestation is varied and it may present at any time in the patient's life with frequent metabolic crises, neurological damage and the development of cardiomyopathy. Dietary management has been the mainstay of treatment but there

remains a significant risk of cardiac, ophthalmological, renal and neurological disease [57] [58] [58] [57]. Cardiac disease includes dilated cardiomyopathy [59] and electrophysiological changes such as prolonged QT syndrome. LT to restore enzyme activity for patients with PA is a potential treatment modality as the liver is the main site of branched chain amino acid metabolism and propionic acid production. If successful, it reduces the risk of metabolic decompensation, neurologic sequelae, stabilises cardiomyopathy and conduction defects and improves quality of life. Careful cardiac evaluation and management is needed as cardiac complications may occur before or after LT particularly if there is persistent or intermittent acidosis during metabolic crises [60] [57]. Although PA-associated cardiomyopathy is reversible post LT [61] long term survival was affected by a high complication rate leading to a 58% mortality at 5 years in two European centres [60]. 25% of patients in this series had cardiomyopathy on echocardiogram and had cardiac catheterisation pre-operatively, which did not preclude LT in any patient [60].

Cardiac disease has also been described in methylmalonic acidemia (MMA) [62]. There are limited data available about the long-term implications of cardiac disease on LT.. Strict metabolic control appears to improve short-term outcome of cardiac bypass surgery, although has no effect on long-term survival [63].

Mitochondrial disorders:

This rare group of disorders may present with acute liver failure, multiorgan disease and Alpers syndrome. There are many clinical phenotypes with different inheritance:- autosomal recessive, autosomal dominant or transmission through maternal DNA. The pathological effects are secondary to dysfunction of the electron transport chain resulting in cellular ATP deficiency, impaired fat oxidation and the generation of toxic

free radicals. Clinical symptoms are variable depending on the nature of the primary defect but include the nervous system, liver and heart. Cardiac manifestations include hypertrophic and dilated cardiomyopathy, arrhythmias, left ventricular myocardial non-compaction, and heart failure which worsens acutely during a metabolic crisis. Diagnosis is suggested by a persistently elevated plasma lactate and multi-organ involvement and confirmed by genetic analysis for the common mutations in POLG, DGUOK, MPV17 and TRMU [8]. LT is rarely indicated due to the multi system involvement [64] [9] and thus it is important to establish the diagnosis.

3. Chronic liver disease leading to cardiac disease

Cirrhotic cardiomyopathy (CCM) is defined as impaired cardiac function or electrophysiology in patients with end stage liver disease without known primary cardiac disease (table 3). It includes the combination of reduced cardiac contractility with systolic and diastolic dysfunction and conduction defects and has been extensively reported in adults with cirrhosis [65] [69] who have a higher mortality after LT [66] [67] [68] and more recently in some paediatric studies [4].

Cardiac feature	Extracardiac features	Implication for transplant
Reduced cardiac output due to systolic and diastolic dysfunction [69]	Ascites Renal dysfunction (hypernatremia) Hepatorenal syndrome [70]	Increased mortality Inotropic support required peritransplant
Increased cardiac output due to reduced systemic vascular resistance [67]		Inability to maintain CVP peri-transplant – careful fluid management necessary
Rhythm abnormality eg. chronotropic incompetence, prolonged QT interval [3] [71]		Inability to increase heart rate further contributes to an impaired ability to maintain cardiac output.

Table 3: Features of cirrhotic cardiomyopathy and implications for transplantation.

In advanced cirrhosis, the circulation is hyperdynamic with increased cardiac output due to arterial vasodilatation leading to reduced systemic vascular resistance. This reduction in afterload may mask any impairment in systolic function [69]. Systolic dysfunction may lead to a fall in cardiac output, arterial blood pressure, sodium and water retention and ascites formation as well as renal dysfunction and adversely affect long-term survival. Diastolic dysfunction develops due to increased stiffening of the myocardium from myocardial hypertrophy, fibrosis and subendothelial oedema, and is associated with ascites, hepatorenal syndrome and reduced survival [70]. It is most severe in patients with significant hepatic decompensation, who develop myocardial hypertrophy and contractile dysfunction. Often asymptomatic, it may only manifest in response to physiological stress, and thus must be considered in both adults and children assessed for LT.

Chronotropic incompetence characterised by tachycardia is noted in patients with advanced liver disease. The inability to increase the heart rate in response to stress means the patient is unable to maintain cardiac output and is a problem in patients

with hepatorenal syndrome or following large volume ascitic drainage when hypovolaemia suddenly worsens.

Prolongation of the QT interval on ECG is found in > 60% of adults with advanced cirrhosis [72]. The pathophysiology of QT prolongation has not been defined but may be related to baseline sympathetic nervous system hyperactivity. A sudden increase in activity, during an acute gastrointestinal bleed, for instance may further lengthen the QT interval with adverse outcomes. [71]. One adult study noted that prolongation of QT-interval was associated with a 3.66 fold increase in mortality [3], although the QT interval normalised in 63.8% of patients following LT, suggesting interval prolongation is directly related to end-stage liver disease and cirrhosis. In most patients, cirrhotic cardiomyopathy resolves after successful LT [73] [74]. Many drugs used in the peri- and post-transplant periods will also affect QT interval including tacrolimus, erythromycin and domperidone which should be considered, and further cardiac evaluation in the form of an ECG may be required.

CCM has recently been reported in children. A Turkish study evaluated CCM in children with cirrhotic portal hypertension, non-cirrhotic portal hypertension and in healthy children. Only 20% of the cirrhotic children had CCM and only one was symptomatic [68]. In a more comprehensive study, Junge et al evaluated cardiac changes associated with CCM by echocardiography and 12-lead electrocardiogram in 198 paediatric patients before and 12 months after LT [40]. They found a correlation with the stage of liver fibrosis and cholestasis before transplantation. Left ventricular end-diastolic diameter (LVIDd) and left ventricular mass were significantly higher in children with cirrhosis compared with those with non-cirrhotic liver disease at both baseline and also at follow-up 12 months later (-0.10 versus 0.98, $P < 0.001$; -1.55 versus -0.42, $P = 0.001$; 78.99 versus 125.64 g/m2, $P = 0.001$). Importantly, all

observed cardiac changes were reversible one year after LT. LVIDd was strongly correlated with intensive care unit (ICU) stay (9.6 days versus 17.1 days, respectively, P = 0.002) but not with patient survival pre-LT or post-LT. They concluded that CCM-associated cardiac changes in paediatric patients with cirrhotic liver disease are frequent, mild, associated with cholestasis, and reversible after LT but may impact peri-transplant care and post-transplant hospitalization time. This is in contrast to the study by Gorgis et al which documented an increased morbidity and mortality in children with CCM [4].

Management of cardiac and hepatic disease:

Management of liver and cardiac disease requires a multidisciplinary (MDT) approach (fig. 2) to manage the individual organ disease and to consider whether it affects selection for transplantation. Specific therapies may be recommended based on the underlying disease, such as:

(1) Cardiac catheter intervention and/or surgery for children with congenital cardiac disease although the timing may be crucial eg in relation to Kasai portoenterostomy or LT in a child with biliary atresia

(2) Specific therapy for liver disease may also resolve cardiac disease e.g copper chelation in WD, NTBC in tyrosinemia type 1

Haemodynamic alterations during liver transplantation

Anaesthesia has effects on many organ systems, most importantly the respiratory and cardiovascular systems. In particular, there are significant haemodynamic changes due to haemorrhage, impaired venous return, from caval manipulation or clamping and the reperfusion syndrome which can be hugely challenging

perioperatively. Rapid fluid replacement, electrolyte and acid–base disturbances are also important factors.

During reperfusion of a liver graft, the cardiac output increases up to 50% above baseline value, which is often higher than normal in patients with chronic liver disease. Mean arterial pressure drops due to a fall in systemic vascular resistance and there may be a concomitant rise in pulmonary vascular resistance [75]. Failure to achieve an adequate cardiac output due to pre-existing cardiomyopathy, oxalate deposits in cardiac muscle or to CCM will risk graft failure due to hypoperfusion .

Furthermore, the circulation in chronic liver disease is a high output, low resistance state and is therefore vulnerable to volume depletion due to impaired vasoconstriction. Residual congenital heart disease such as a right-to-left shunt leading to evolving pulmonary hypertension may further complicate transplantation, in which large fluid shifts are inevitable leading to fluid overload, increased pulmonary vascular pressures and difficulties managing pulmonary oedema and ventilation.

Selection for transplantation

Careful management and patient selection are essential in liver transplantation for children with combined cardiac and liver disease, but particularly those with Primary Hyperoxaluria, organic acidemias and AS.

When considering a patient with both liver and cardiac disease for LT there are a number of important considerations. These include:

1. Assessment of the severity of cardiac disease
2. Does the cardiac disease require cardiac catheter intervention or surgery pre/post LT?
3. Does the cardiac disease preclude transplant?

4. Is any specific therapy required peri-transplant e.g. vasopressors such as norepinephrine, epinephrine, dopamine or dobutamine.

5. Does the patient need a combined liver/lung/heart transplant?

A recent study from the Studies of Pediatric Liver Transplantation (SPLIT) registry reported that patients with significant cardiac disease have a relative contraindication to LT [76] and so assessment for liver transplantation should include a formal cardiac evaluation to include echocardiogram and electrocardiogram, with ultrasound assessment of neck vasculature as well as consideration of CT angiography of abdomen and brain.

The cardiac output (CO) response to dobutamine has been suggested as a way to identify patients at higher risk of cardiovascular complications during liver transplantation [65] [77] [78]. A recent study modelled three different simulated scenarios using data from a 6 year old child with AS undergoing catheter/dobutamine stress MRI (DSMRI) and concluded that there was impaired coronary flow reserve which was undetected by DSMRI resulting in myocardial ischemia [79]. It is possible that using computational data, this novel approach to risk stratification could be useful to predict morbidity and mortality post-LT in children with congenital cardiac disease or cirrhotic cardiomyopathy [80] [81].

Cardiac surgery in children with end stage liver disease prior to liver transplantation is associated with significant mortality [35] a small retrospective study in 5 infants with end stage liver disease and congenital cardiac defects (VSD, ASD and tetralogy of Fallot as cardiac diagnoses) demonstrated that it was possible to improve outcomes with cardiac surgery pre transplant in 4/5 infants [82]. A formal cardiology review is required to assess the severity of cardiac disease with ECG and echocardiography to

assess ventricular and valvular function. Pulmonary artery pressure and right ventricular function should also be evaluated and an assessment made for the need for cardiac catheterisation or intervention (table 4). Assessment of cardiac reserve pre-LT may be performed with a dobutamine stress test (to date mainly in adults), and cardiac catheterisation (table 4).

Investigation	**Patient group**	**Associated findings**	**Implication for transplantation**
ECG	All patients	Arrhythmia, prolonged QT interval	May need rhythm stabilising medication e.g. amiodarone, propranolol. Cardioprotective medications, (ACE inhibitors, beta-blockers) avoid medications which could prolong QT interval (erythromycin, domperidone, tacrolimus).
Echocardiogram	All patients	Valvular or septal defects, cardiomyopathy, anomalous vascular changes Pulmonary hypertension	Consider cardiac catheterisation, surgical repair pre LT
Cardiac catheterisation	All patients with large septal defects or valvular anomalies detected on echocardiogram	Vascular anomalies 4 chamber pressure measurements,	Assess: Valve incompetence/ stenosis Need for intervention (valvoplasty/ angioplasty/balloon dilatation) Severe PH precludes LT
Cardiac stress test Dobutamine;- Not standard in children	Patients with haemodynamically significant lesions or cardiomyopathy	Assess response to increasing workload as would be experienced intraoperatively/post-operatively.	May preclude transplant if significant cardiomyopathy or consider combined transplant
CT angiography of abdominal vessels, chest	Patients with significant vascular anomaly demonstrated on echocardiogram, high risk patients (e.g. post-Fontan, Alagille syndrome)		Allows assessment of abdominal vessels, vascular access

Table 4: Cardiac assessment in patients being considered for liver transplantation

Post-transplant outcomes

In general, with careful pre-transplant planning and selection most children undergoing LT with cardiac disease have a good outcome, although some with CCM, for instance may have a prolonged Intensive Care (ICU) stay. Successful transplantation reverses many of the acquired cardiac problems outlined above, particularly cardiomyopathy in tyrosinemia type 1 and in most children with CCM. Exceptions include those children with organic acidemias who have a high rate of post-transplant complications including new onset cardiac failure, particularly if there are metabolic complications or graft dysfunction [57]. Children with severe cardiac oxalate deposits may also have a difficult post–transplant course with continued cardiac instability due to the delay in oxalate removal from the tissues, particularly if they have renal dysfunction as oxalate is poorly removed by dialysis [83].

Thus even with careful pre-transplant planning, patients with both cardiac and liver disease may have an increase in morbidity and ICU stay but the long-term outlook is good with most patients achieving resolution of cardiac complications.

Conclusions

Cardiac and liver disorders are common in the paediatric population. The success of cardiac surgery for congenital heart disease has improved long term survival in many of these children, but the implications of cardiac hepatopathy with the development of focal nodular hyperplasia, cirrhosis and HCC are now becoming apparent, particularly in children who have survived the Fontan procedure who require combined cardiac and hepatic follow up.

In addition, congenital cardiac defects may be part of a syndrome affecting both organs, as in biliary atresia or Alagille's syndrome. Cardiomyopathy, both dilated and

hypertrophic is a common finding in metabolic disease and may develop secondary to tyrosinemia type I and the organic acidemias. Cirrhotic cardiomyopathy has now been identified in children with significant liver disease and in a cohort with biliary atresia, which is the most common indication for LT in the paediatric population.

Underlying structural congenital heart disease may delay or preclude listing for LT unless cardiac surgical repair is feasible pre LT. Cardiac catheterisation may be necessary to determine whether cardiac function is adequate to withstand the haemodynamic changes associated with LT and careful pre-LT evaluation is paramount.

Liver transplantation is contra-indicated in those children with severe cardiac defects which are not amenable to surgery pre-transplant, or who cannot be supported haemodynamically during the operation.

This review highlights the need for a careful multi-disciplinary team approach to assessing the LT candidate with careful consideration around timing of LT and the need for cardiac evaluation and intervention in order to improve morbidity and mortality.

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