Respiratory problems associated with liver disease in children

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Shareable abstract (@ERSpublications)
From post-liver transplant complications to respiratory manifestations of liver disease, it is important for paediatric hepatologists to recognise when a referral to a paediatric respiratory medicine specialist is warranted https://bit.ly/3T64jdM

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Abstract

Respiratory manifestations of chronic liver disease have a profound impact on patient clinical outcomes. Certain conditions within paediatric liver disease have an associated respiratory pathology. This overlap between liver and respiratory manifestations can result in complex challenges when managing patients and requires clinicians to be able to recognise when referral to specialists is required. While liver transplantation is at the centre of treatment, it opens up further potential for respiratory complications. It is established that these complications place patients at risk of longer stays in hospital and reduced survival. Additionally, late post-transplant complications can occur, including post-transplant lymphoproliferative disease and immunosuppression-induced interstitial lung disease. Although rare, it is important for clinicians to recognise these conditions to allow for prompt management. Finally, as liver disease progresses in children, respiratory complications can occur. Hepatopulmonary syndrome can occur in the context of portal hypertension, resulting in increased mortality and poorer quality of life for patients. Another consequence is portopulmonary hypertension, which can be associated with poor survival. Failure to recognise these complications in children may result in poorer outcomes and therefore it is vital that clinicians can establish when referral to a paediatric respiratory medicine specialist is required.

Educational aims

- To explore general respiratory complications within paediatric chronic liver disease.
- To outline the disease-specific causes of chronic liver disease and associated respiratory pathology.
- To highlight early and late respiratory complications post-liver transplant in children.

Introduction

Chronic liver disease (CLD) is associated with a variety of adverse outcomes for patients. It is well established that as liver disease progresses, the involvement of other organ systems becomes more pronounced, resulting in further opportunity for complications [1]. Pulmonary manifestations and complications are known to occur in patients with CLD or portal hypertension (PHT) and have a profound impact on patient survival and clinical outcomes [2]. Most of the existing reviews are based on adult liver pathology and pulmonary manifestations after liver transplant (LT). This review aims to include paediatric liver pathologies, such as metabolic liver conditions, and the most up to date indications for LT in patients with inherited metabolic diseases and potentially associated respiratory issues. Furthermore, this review outlines the pulmonary manifestations of paediatric liver disease, as well as exploring the risks and outcomes associated with respiratory complications after LT.

Pre-transplant: CLD and respiratory complications

CLD and general respiratory complications

Hepatopulmonary syndrome

Hepatopulmonary syndrome (HPS) is defined as the triad of CLD, arterial hypoxaemia and abnormal intrapulmonary shunting [1, 3]. Hypoxaemia is a significant consequence of HPS and is typically due to intrapulmonary shunting of blood from intrapulmonary vascular dilatations [4]. HPS can occur as a result of CLD and is independent of aetiology [5]. HPS can also occur in the context of PHT, but patients will often have stable and compensated liver disease [5]. While the incidence of HPS is not widely reported, retrospective studies have suggested a prevalence of 9–20% and 0.5% in children with biliary atresia and extra-hepatic portal vein obstruction, respectively [6, 7]. HPS can be challenging to recognise, especially in the early stages when the patient can be asymptomatic [8]. However, as HPS progresses patients may experience dyspnoea, hypoxaemia and cyanosis [8].

Platypnoea, defined as shortness of breath relieved by lying down, is considered an important indicator to suspect and screen patients for HPS [1]. Furthermore, orthodeoxia is deemed to be a specific sign of HPS although importantly it does not occur in all patients [1]. Instead, patients may report symptoms such as breathlessness during activity and during mobilisation [3].

When there is clinical suspicion of HPS, it is important to carry out documentation of arterial hypoxaemia [1, 9]. Although it allows more reliable measurement of hypoxaemia, gaining an arterial oxygen value in paediatrics can be challenging due to the invasive nature of arterial blood gases [3]. However, pulse oximetry can be used as a screening tool to detect hypoxaemia and has been shown to have high sensitivity and specificity [1]. Pulse oximetry should not be used in isolation since it is insufficient in diagnosing HPS alone; instead it should be used in conjunction with other measures to raise the clinical suspicion of HPS [10]. It is important to mention that children with subclinical HPS may have an oxygen saturation measured by pulse oximetry of >98% and therefore HPS may be harder to recognise [3]. Serial haemoglobin levels have been suggested as a tool to raise an index of suspicion in these patients [3]. Therefore, clinicians should remain cautious about the potential of HPS in children with liver disease.

Technetium-99m-labelled macroaggregated albumin (^{99m}Tc-MAA) lung perfusion scans are used in the diagnosis of HPS, allowing for the detection of intrapulmonary shunting and intrapulmonary vascular dilatation (IPVD) [3, 10]. However, its low sensitivity, especially in patients with mild-to-moderate HPS, and invasive nature open up the opportunity for other measures to be used [10, 11]. One method described is the use of an oxyhaemoglobin dissociation curve as a noninvasive measure of oxygen abnormalities [11]. This method can be used to establish ventilation/perfusion mismatch as well as a right-to-left shunt in children with CLD, acting as a tool for screening and monitoring HPS in these patients [11]. Such methods may have an important role in clinical practice due to their noninvasive nature compared with ^{99m}Tc-MAA lung perfusion scans, as well as their potential to allow for early diagnosis of HPS in children with CLD [11]. Contrast enhanced echocardiography, using agitated saline with microbubbles, can also be used to confirm the presence of IPVD and differentiate intracardiac shunting from intrapulmonary shunting [1]. The presence of agitated saline bubbles in the left atrium on echocardiography, typically after 3–5 cardiac cycles is suggestive of intrapulmonary shunting and HPS [1].

While there is a greater understanding of outcomes of HPS in adults, previous studies have highlighted higher mortality and poorer quality of life in patients with CLD and HPS compared to those without HPS [3]. Outcomes post-LT are of particular importance since LT is the only treatment for HPS [1]. Furthermore, failure to recognise HPS in a patient may delay appropriate treatment, which has implications such as progressive polycythaemia and home oxygen requirements [3]. A small study highlighted that patients with pre-transplant polycythaemia required longer stays in intensive care and had a higher requirement for oxygen therapy [3]. These adverse outcomes from delayed treatment highlight the requirement for timely diagnosis of HPS, which may be challenging in asymptomatic children. Screening for HPS could be enforced to increase the chances of timely diagnosis and treatment of HPS to improve outcomes for these children.

Portopulmonary hypertension

Another consequence of CLD is portopulmonary hypertension (PoPH). The hallmarks of PoPH include raised pulmonary arterial pressure, increased pulmonary vascular resistance with pulmonary arterial occlusion, or a left-ventricular end-diastolic pressure of <15 mmHg [9]. The mechanisms *via* which PoPH occurs as a consequence of PHT is not known, although several hypotheses have been proposed. Almost all patients who have PoPH have a hyperdynamic circulation and high cardiac output resulting in increased stress of the pulmonary circulation [9]. As a consequence of the increased resistance, remodelling of the

pulmonary vasculature is undertaken, which can result in pulmonary hypertension. Common presentations include dyspnoea on exertion, fatigue and syncope, with the latter being less common [12].

PoPH is associated with poor survival, especially when patients do not receive treatment or undergo a LT [13]. However, transplantation does not ensure regression of symptoms, with many patients still requiring treatment after LT [13].

Disease-specific causes of CLD and associated respiratory pathology

Cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive condition characterised by mutations in the cystic fibrosis transmembrane conductance regulator *(CFTR)* gene [14]. Since the CFTR protein is found in the liver as well as other organs within the body, the condition is not limited to respiratory manifestations. In fact, liver manifestations are well described in CF. Cystic fibrosis liver disease (CFLD) usually presents in childhood, with a reported prevalence ranging from 5% to 68% [14]. Not all children with CF have clinically significant liver disease, but those with significant liver disease may experience both short- and long-term adverse outcomes [14].

The clinical features of CFLD form a spectrum, ranging from elevation of aminotransferases to PHT and reduced synthetic function [14]. In those with severe manifestations of liver disease, LT may be appropriate in order to improve survival [14]. Indications for such treatment include hepatic dysfunction and the presence of complications including HPS, PoPH and hepatorenal syndrome. Importantly, LT does not offer long-term improvement of pulmonary function, with most pulmonary function improvement returning to that pre-transplant by 3 years post-transplant [14, 15]. Furthermore, although it is known that LT plays a vital role in managing patients with CFLD, there is a lack of guidance outlining the appropriate timeline for providing LT in patients with CFLD [15]. Additionally, post-LT fungal, bacterial and viral infections inevitably have a huge impact on the patient, manifesting as a significant cause of morbidity and mortality for these patients [15]. Therefore, it is vital that those with CFLD are managed by a multidisciplinary team with the appropriate expertise from both respiratory and hepatology clinicians. The use of new treatment modalities, such as a combination of CFTR modulators or potentiators pre- and post-LT, seems to have a favourable impact on lung involvement although with reported derangement in liver function tests [16].

Metabolic diseases

Inherited metabolic disorders are systemic and so multiple organ systems can be affected [17]. Several metabolic conditions present with respiratory manifestations and often present as either restrictive or obstructive respiratory disease.

Alpha-1 antitrypsin deficiency

Alpha-1 antitrypsin (AAT) deficiency is a common inherited genetic disorder, occurring due to a mutant Z allele [18]. With manifestations ranging from liver enzyme elevation to PHT and CLD, AAT deficiency is the most common metabolic disease resulting in LT in the paediatric population with no lung involvement [18]. Often, respiratory involvement manifests during adulthood in the form of COPD [18]. LT has been shown to have positive outcomes for patients with AAT deficiency, with the United Network for Organ Sharing reporting high 5-year survival rates post-LT in children compared with adult LT patients with AAT deficiency [19]. In addition, AAT levels are known to normalise after LT. LT is associated with good outcomes for patients and is considered a suitable treatment option for those with severe liver disease secondary to AAT deficiency.

Niemann–Pick disease type B

Lysosomal disorders, such as Niemann–Pick disease type B, can present with restrictive respiratory features [17]. Niemann–Pick disease results in deficient activity of sphingomyelinase and accumulation of sphingomyelin occurs [17]. With type A typically resulting in neurodegenerative symptoms, Niemann–Pick type B often results in patients experiencing pulmonary manifestations. Although some may be asymptomatic, patients can progress to experience fatal respiratory disease [17]. Pulmonary imaging in these patients has shown diffuse interstitial and nodular infiltrates, which may occur in the absence of symptoms [17]. Patients with Niemann–Pick disease and respiratory manifestations should be considered for early referral to appropriate respiratory clinicians for appropriate management and care.

Lysinuric protein intolerance

Lysinuric protein intolerance is a disorder of amino acid transport and metabolism, that occurs due to an autosomal recessive defect of the cationic amino acids [17]. Common clinical features of this condition in children include failure to thrive and bone marrow abnormalities [17]. Despite respiratory manifestations

being uncommon, they can be fatal and require prompt recognition. Pulmonary alveolar proteinosis (PAP) is a severe consequence of lysinuric protein intolerance and is defined as accumulation of surfactant within the alveolar spaces. PAP more commonly occurs in adults than children, but occurrence in children can be more severe [17]. PAP represents a rare but potentially fatal complication of lysinuric protein intolerance, highlighting the need for appropriate care in these patients.

Post-transplant respiratory complications

LT is at the centre of treatment for children with liver disease. Post-operative pulmonary complications are common, ranging from pleural effusion to pulmonary oedema and infection (table 1). It is known that these complications have further implications, such as a longer stay in hospital and a reduced short-term survival [20]. Additionally, a higher incidence of ventilatory requirements both pre- and post-LT have been established in children with acute-on-chronic liver failure [21].

A single-centre retrospective study aimed to explore pulmonary complications post-LT in children, with the view of identifying modifiable risk factors [22]. A high prevalence of pulmonary complications was reported, with 86% of patients having post-operative pulmonary complications. Pulmonary oedema was the most common early pulmonary complication reported. Several factors were associated with the occurrence of pulmonary complications, including high Paediatric End-Stage Liver Disease (PELD)/Model for End-Stage Liver Disease (MELD) scores and a low serum albumin concentration. Importantly, high PELD/MELD scores were also associated with longer duration of ventilation and a longer stay in intensive care. Hypoxaemia was also reported as a predictor of pulmonary complications. While some of these factors, such as PELD/MELD score are difficulty to modify, it highlights the requirement for a thorough assessment pre-transplant. Identifying the risk factors that predict these adverse outcomes may allow clinicians to identify patients who require early transplantation and escalation of care.

Early post-transplant general respiratory complications

Pleural effusion

Pleural effusion can occur in children post-LT and is typically described as a self-limiting condition [20]. However, large volume pleural effusions can reduce respiratory function, especially in younger children [20]. The majority of pleural effusions occurring in children following LT are small, transient and likely reactive in nature. If there is doubt regarding the nature of an effusion due to its volume, chronicity or the clinical state of the patient then obtaining a sample of the fluid for analysis is indicated. Furthermore, in pleural effusions persisting for more than 1 month, it would be advisable to determine the type of pleural effusion [23]. Fluid culture, cytology and triglyceride level can be used to help define the type of pleural effusion and institute appropriate management. A retrospective study reported that over half of patients had a pleural effusion post-LT and those who required therapeutic interventions required longer admissions to intensive care as well as having greater oxygen dependency [20]. The only reported predictor of these complications was a PELD/MELD score of $\geqslant$18. Despite the inevitable role of other factors in outcomes such as length of intensive care unit stay, this study highlights the importance of severity of liver disease pre-LT. Perhaps a risk stratification tool pre-LT could be established to highlight and predict the risk of pulmonary complications post-operatively in these patients. Undoubtedly there are unmodifiable factors at play, but ensuring timely referral for transplant and recognising unwell patients are important in reducing pulmonary complications and length of hospital stay.

Pulmonary oedema

Pulmonary oedema has frequently been reported as a complication post-LT in both paediatric and adult populations, reportedly occurring in 14–47% of LT recipients [22, 24]. Adult studies have highlighted pulmonary oedema as a frequent immediate complication post-LT. However, only those with persistent and late pulmonary oedema were associated with adverse clinical outcomes [24]. Adverse clinical outcomes

TABLE 1 Early and late respiratory complications post-liver transplant

Early complications	Late complications
Pulmonary oedema	Pulmonary infection
Pleural effusion	Post-transplant lymphoproliferative disease
Acute respiratory distress syndrome	Immunosuppression-induced interstitial lung disease
Pulmonary infection	
Pneumothorax	
Pulmonary haemorrhage	
Chylothorax	

include prolonged mechanical ventilation and intensive care requirements as well as a prolonged hospital stay [24]. Since pulmonary oedema may result in adverse outcomes post-transplant, it could be useful to identify predictive factors to recognise those at higher risk of pulmonary oedema and its consequences. Several factors that contribute to the development of pulmonary oedema have been identified in adult populations. These include hypoalbuminaemia and intravenous fluid infusion in the perioperative period, as well as severe liver dysfunction pre-operatively [24]. Identifying these risk factors in the perioperative period could help identify children at risk of pulmonary oedema post-LT and aid management to reduce the chance of further complications. It is important to mention, however, that these factors have been identified in adult populations and therefore may not translate to paediatric patients. Therefore, identifying predictive risk factors in paediatric populations would aid clinicians in recognising those at risk of pulmonary oedema post-LT.

Later post-transplant general respiratory complications

Post-transplant lymphoproliferative disease (lung involvement)

Post-transplant lymphoproliferative disease (PTLD), while rare, is known to be one of the most common malignancies after solid organ transplantation [25]. In some cases, it can be associated with Epstein–Barr viraemia [26]. Despite incidence being low, it has been suggested that PTLD is more common after solid organ transplantation among paediatric patients as opposed to adults [25, 26]. Furthermore, the presentation of PTLD is diverse and it may only present with nonspecific symptoms making it challenging to recognise [26]. While the gastrointestinal tract is the most common extranodal site of PTLD, PTLD can also involve the lung in rare scenarios [26]. Despite the potential for radiological changes on chest radiography or computed tomography, pleural involvement in PTLD may be challenging to identify. This is due to similarities with more common post-transplant complications, including pulmonary oedema and infection [26]. Importantly, due to the low incidence of pleural PTLD, clinicians may not feel comfortable in identifying PTLD *via* imaging alone and therefore fail to recognise this complication in paediatric patients [27]. Consequently, it may be important for review by a more experienced respiratory clinician in patients presenting with features of PTLD.

Immunosuppression-induced interstitial lung disease

Both tacrolimus and sirolimus are commonly used immunosuppressive agents in children post-LT and require specific tailoring to the paediatric population when compared with adults [28]. With prolonged exposure to immunosuppressive agents, compared with adults, children have a greater chance of experiencing adverse outcomes secondary to immunosuppression. In an attempt to combat this, dosing is weight-based to reduce the chance of over- and under-immunosuppression [28]. However, immunosuppression in children remains complex and still has its challenges. Despite more common adverse outcomes including medication side-effects and rejection, rare cases of tacrolimus- and sirolimus-induced interstitial lung disease have been reported [28]. This complication occurs more commonly in the autoimmune disorder subgroup (*e.g.* rheumatoid arthritis and systemic lupus erythematosus). Although it is a rare complication, it is vital to recognise and an important complication to consider when using immunosuppressive agents in the paediatric population.

Conclusions

Current understanding of respiratory involvement in liver disease includes, but is not limited to, the risk of HPS, PoPH and pulmonary complications after LT. It is important that clinicians are able to recognise these complications in patients and escalate care when required. The development of pulmonary complications is not always overt; however, it can change the disease trajectory for paediatric patients. Formation of protocols for the care of these patients may be beneficial, outlining when escalation or referral to respiratory specialists is required. This may improve the clinical outcomes for those who experience such pulmonary complications.

Key points

- HPS and PoPH are severe complications of CLD and can result in adverse outcomes in paediatric patients.
- Certain diseases, such as AAT deficiency and other metabolic diseases, not only have liver manifestations but also have associated respiratory pathology.
- Early and late respiratory complications post-LT include pleural effusion, pulmonary oedema, infection and PTLD.

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