Review

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The management of childhood liver diseases in adulthood

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Summary

An increasing number of patients with childhood liver disease survive into adulthood. These young adults are now entering adult services and require ongoing management. Aetiologies can be divided into liver diseases that develop in young adults which present to adult hepatologists i.e., biliary atresia and Alagille syndrome or liver diseases that occur in children/adolescents and adults i.e., autoimmune hepatitis or Wilson's disease. To successfully manage these young adults, a dynamic and responsive transition service is essential. In this review, we aim to describe the successful components of a transition service highlighting the importance of self-management support and a multi-disciplinary approach. We will also review some of the liver specific aetiologies which are unique to young adults, offering an update on pathogenesis, management and outcomes.

Keywords: Adolescence; Transition; Biliary atresia; Cholestatic liver disease; Autoimmune liver disease; Autoimmune sclerosing cholangitis; Self-management.

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Introduction

The number of patients with childhood liver diseases surviving into adulthood has increased over the last 20 years. Diseases once thought to be only in the domain of paediatric hepatologists are increasingly seen in adult clinics. Greater awareness and expertise is therefore required amongst adult hepatologists to manage this unique cohort and their disease spectrum. In addition, one of the key barriers for a successful transition from paediatric to adult care is an inexperience or a lack of knowledge in treating childhood diseases [1,2].

One of the important developments in health care services for young adults is the setup of sensitive and responsive transition services. Transition services across all disciplines in medicine play an important role in ensuring the health of young adults is maintained through a holistic approach and supportive environment. The importance of transition services cannot be understated. Even without ill health, young adults (18–24 years old) are a high-risk cohort with higher mortality rates compared to 12–17 year olds and higher rates of substance misuse and suicide [3]. Add in the presence of a chronic illness that goes hand in hand with the necessity of regular medication intake and the situation becomes even more precarious. Developmentally appropriate care for young adults remains key.

This article will highlight the important components of a successful transition service, the multidisciplinary approach and the successful outcomes that are possible. We will also review the liver aetiologies that develop in young children but will present to adult hepatologists as well as the aetiologies that occur in children/adolescents and adults concentrating on the practical management of these patient cohorts.

Aims of transition care

There is a need to emphasise that the terms 'transition' and 'transfer' are not synonymous. Transfer only refers to the change in location where care will be delivered, change in health care provider or both [4,5]. Therefore, transfer, is but a component of transition. Transition, on the other hand is not a single event but a purposeful, planned process of moving adolescents and young adults with chronic medical and physical conditions from a child centre to an adult-orientated health care system [5,6]. It is an important milestone for patients, families, carers, and paediatric and adult services as well as potentially representing a period of vulnerability for the individual patient.

Key point

The number of patients with childhood liver diseases surviving into adulthood is increasing. Adult hepatologists need to be familiar with the management of these diseases.

Key point

A sensitive and responsive transition service is required to manage young adults with liver disease.

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Timing of transition

During the transition process, the responsibility of health care moves from the parent or carer to the patient ideally at a pace which is suitable for all. The first stage of transition in the shared management model begins approximately at 10 years of age and involves the introduction of the concept of transition [7,8]. Over the following years, a slow process ensues of engaging and preparing these young children in becoming independent young adults [7,9]. The patient essentially swaps roles with the parent or carer and takes on a more active role in self-care activities (Fig. 1) [9], whilst remaining the primary focus of attention. These self-care activities include taking medications, leading a healthy lifestyle and attending clinics on their own. Moreover, the process needs to be individualised according to physical, developmental, educational, emotional and psychosocial needs of the patient. Although most transition services will typically specify an age range, i.e., 14–18 years, in which patients move to an adult clinic, services need a degree of flexibility, and physicians and health care services may need to adapt to the needs of the individual [10]. Older adolescents and young adults for instance demonstrate higher rates of non-adherence compared to younger children [9,11]. Age alone should not be the single factor which determines readiness of transfer to adult services. Transfer of patient care to adult services should only be during a period of clinical stability. Outpatient services are more flexible with regards to age but this is not usually the case for inpatient care. The availability of a young adult ward is therefore an ideal solution.

One should also acknowledge the challenges faced by both the paediatric and adult teams. There can be reluctance by the paediatric team in 'letting the patient go', which can then have a detrimental effect on the patient. On the other hand, busy adult clinics, resulting in less time devoted to the young adult and their families can make the adult team appear uncaring and uninterested. Dedicated transition clinics are therefore vital [12].

Key point

Self-management support is an important strategy which empowers young adults to participate in their care.

Self-management

Patients require more than just information and therefore, the development of self-management skills are integral to the successful transition of patients [13]. Self-management support encourages the individual to actively participate in the care of their everyday symptoms relating to their medical treatments in addition to maintaining their general health and preventing progression of their medical conditions [14,15]. Table 1 lists the most important self-management skills an individual should acquire prior to transitioning to adult services. These self-management skills are developed by encouraging the patient to talk and answer questions. Initially this can be with their parent(s) present and then eventually on an individual basis. Other strategies may involve asking the patient to prepare 2–3 verbal sentences in advance of the clinic covering the topics of diagnosis, relevant past medical history and medication. This strategy encourages the young adult to develop self-advocacy skills and engage directly with the health care team. Another strategy is the creation of a health care passport, made in combination with the young adult, parent(s) and health care team. A health passport lists the individual's medical history, past procedures, medications, allergies and other health related information. It also highlights any disabilities and specific health care difficulties i.e., being examined, having blood tests, tolerating imaging. These health care passports further empower the young adult and is also an important educational opportunity.

Transition of patients with cognitive delay may pose further difficulties. Identifying cognitive delay should not be limited to IQ testing alone and should encompass adaptive behaviour assessment (i.e., communication and social skills) [16]. Assessment of capacity and the ability to decide upon treatment options needs to be made in conjunction with parents, carers and guardians. We recommend early engagement with parents, and community based services and clear communication between adult and paediatric services.

Key point

Transition services need to be holistic and adopt a multi-disciplinary approach. Successful transition services aim to improve adherence and long-term outcomes

Transition team members and key objectives

Three major categories appear to be integral to every transition service: 1) building and supporting self-management; 2) engagement with the receiving team; and 3) guidance of patients and families [17]. Yet, there is no single accepted model for transition or the constituents of a transition team [18]. A nurse coordinator (transplant and non-transplant), dedicated paediatric and adult hepatologists, specialist social workers and a clinical psychologist are all integral members of a transition team. A multidisciplinary approach is imperative. Members of the extended transition team include youth volunteers and patient mentors who are able to provide a unique insight.

The importance of transition services

Much of the literature in this regard is derived from transplantation services. Studies performed in adolescent transplant recipients provide information which is transferable to adolescents with chronic liver disease. Current data suggests that up to one-third of adolescents are non-adherent with medication and their clinic visits, leading to worsening liver

function and possible organ failure [7,9,19,20]. The prevalence of non-adherence in adolescent transplant recipients can be as high as 50% [20]. One must remember, that some degree of non-adherence is part of normal adolescence behaviour [21]. Transition services therefore, have to minimize this risk taking behaviour and its consequences. Barriers to successful transition include inexperience or a lack of knowledge in managing paediatric liver diseases and uncertainty in the management of sexual and substance abuse issues [1].

Non-adherence with medications, especially immunosuppressants, is associated with an increased incidence of graft failure and mortality [22]. In addition, non-adherence to immunosuppression medication appears to be more prevalent during transfer and was identified as a significant cause of graft loss in 16% of paediatric liver transplant recipients and 14% of paediatric renal transplant recipients, respectively [23–27]. In stark contrast, recent data from a single UK centre study demonstrated comparable graft survival following liver transplantation between a transition group and two cohorts of young adults [28]. In the same study, the most common indication for re-transplantation was disease recurrence as opposed to non-adherence, leading to chronic rejection. It is therefore clear that future studies are required to determine the long-term effects of a transition service on patient and graft survival and adherence to medications.

Reasons for non-adherence with medication are multifactorial but can be divided into five broad categories: socioeconomic factors, patient derived factors, disease related factors, treatment related factors and health care system/health care team factors (Table 2) [29]. Key risk factors include lower socioeconomic status, passive parent involvement, side-effects related to medications and poor communication with health care teams [27,30–34].

Table 1. Checklist of self-management skills that should be reviewed by the adult hepatology team during transition.

Health promotion. The individual:
• is able to contact his/her health care team
• knows when and how to access emergency health care services (including mental health services)
• can create and use a portable medical history
• is able to make and attend clinic appointments
• is able to maintain a health care record i.e., copies of clinic letters
• is able to communicate with health care providers independent of parents/carers
Medications. The individual:
• is able to describe his/her medications, indications and prescribed regimens
• is able to request repeat prescriptions

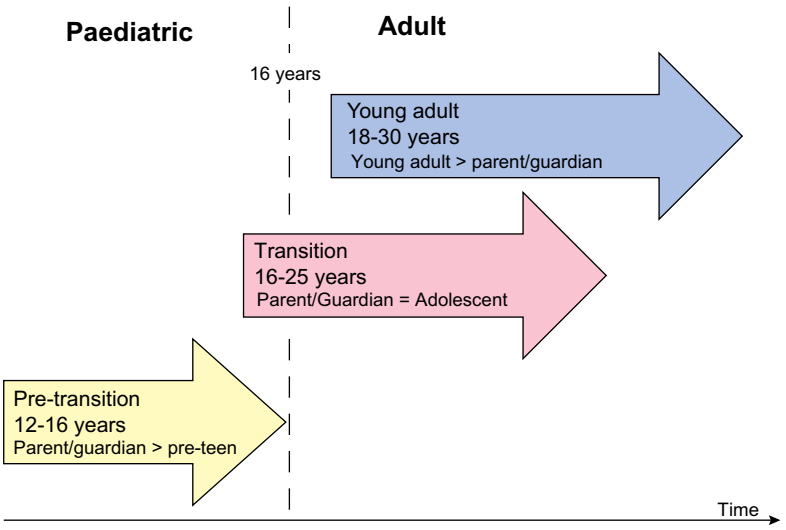

Fig. 1. The transition process.

The majority of studies appear to focus on the paediatric perspective. A recent study attempted to delineate the adult perspective thereby hoping to provide new insights and identifying unidentified barriers to care [2]. Using a web-based survey of USA adult hepatologists, respondents reported less than 50% of transition patients had an adequate knowledge of their condition and parent/guardian present at the time of their first review in the adult service. One-third reported having no transition strategy and only 15% had a formal transition programme. Poor adherence to medications and limited knowledge of their condition coupled with poor self-management of their condition were identified as barriers to successful engagement of transition patients [2]. Success is achievable. An integrated transition clinic with an emphasis on improving young adult's health care experience through a young adult clinic, improved patient adherence to medication and engagement with health care providers resulting in reduced renal transplant failure rates [35].

General advice:

- **Sexually active young adults**. Young adults may be sexually active and therefore appropriate sexual education and contraceptive advice is often required. Immunosuppression i.e., mycophenolate mofetil and sirolimus may therefore need to be changed due to the associated teratogenicity in male and female patients [36]. Single hormone progesterone is recommended which can include a depot shot or daily pills. Intrauterine devices appear to be safe. In the event of a successful pregnancy, a gastroscopy is recommended between the 20–24th week of gestation in patients with cirrhosis or portal hypertension to screen for varices [37].

Table 2. Risk factors for non-adherence and approach. Modified from Dobbels *et al.* [20].

	Risk factor	Approach
Socioeconomic factors	Social isolation Family instability Poor parental support Single parent families Cost of medication or clinic visits	Social worker review Review eligibility for financial support.
Patient derived factors	Poor understanding of condition Mental illness Previous non-adherence Past history of child abuse Low self-esteem Post-traumatic stress disorder	Patient passports Clinical psychology review
Disease related factors	Duration of illness Lack of symptoms Substance misuse	Review of clinical status Peer support groups
Treatment related factors	Side effects Number of medications Cost of medication	Regular review of medications
Health care system/health care team factors	Poor communication between the different health care teams, patient and parents Poor relationship between health care teams, patient and parents Lack of continuity of care Clinic attendance resulting in time off school or work	Weekly multi-disciplinary meetings Identification of key care providers Evening clinics

Non-teratogenic medications i.e., azathioprine and ursodeoxycholic acid (UDCA) can be continued in pregnancy and whilst breast feeding.

- **Risk taking behaviour**. Young adults with chronic liver disease and those who have undergone liver transplantation are just as likely to exhibit similar risk taking behaviours as the general population [38]. Further information and education is therefore required regarding smoking, the use of illicit drugs and alcohol. Binge drinking is a key issue and problematic pattern of alcohol use in young adults [39]. These issues need to be addressed while in paediatric care, early in the process of transition.
- **Bone health**. Some young adults will require long-term corticosteroids. We recommend an assessment of bone densitometry every 3–5 years. Vitamin D levels should also be assessed and treated accordingly.
- **Side effects of medications**. The requirement for long-term immunosuppressive agents can lead to the development of renal impairment, hypertension and diabetes. A yearly review for the development of these complications is recommended. Patients taking long-term azathioprine are recommended to apply sun protection to exposed areas.

Liver diseases that develop in young children which will present to adult hepatologists

Biliary atresia

Biliary atresia (BA) is a progressive sclerosing, inflammatory cholangiopathy of unknown aetiology. Affecting between 1/5000–1/19,000 newborns, this rare disease usually presents within the first three months of life with conjugated hyperbilirubinaemia and cholestasis [40]. BA is classified anatomically according to the level of the most proximal biliary obstruction, the most common form being type 3 (>90%) (Fig. 2) [40]. Twenty percent of patients with BA demonstrate anatomical variants including polysplenia and asplenia (also known as biliary atresia splenic malformation syndrome (BASM), gastrointestinal, venous and cardiac malformations [41]. Untreated, it progresses rapidly to biliary cirrhosis and death within two years.

The Kasai procedure (portoenterostomy [KPE]) was first introduced by Morio Kasai in the 1950s and has significantly improved outcomes for BA [42]. Liver transplantation remains the only other primary option for patients with BA and particularly for those who fail a KPE [43]. A KPE does not cure BA. 70% of patients post-Kasai with satisfactory biliary drainage will develop progressive fibrosis/cirrhosis and portal hypertension with recurrent cholangitis appearing to be one of the driving factors and are all indications for transplantation respectively [40]. BA is the most common indication for a liver transplant at a paediatric liver transplant centre and has good outcomes which are comparable to the entire cohort [44–46]. Common histological findings include established cirrhosis with a central hypertrophic area and relative atrophy of the periphery of the liver [47]. In the hypertrophied area of the liver, the liver architecture can be near normal with bile ducts whereas the atrophic area usually shows severe fibrosis and only a few bile ducts remain [48]. Data is now available on long-term follow-up in BA patients post-KPE [49–54] (Table 3) ranging from 23–46% at 20 years [49,50,52]. Individuals surviving into adulthood with their native liver appear to have appropriate cognitive development with one study reporting that 88% were employed or attending higher education [53].

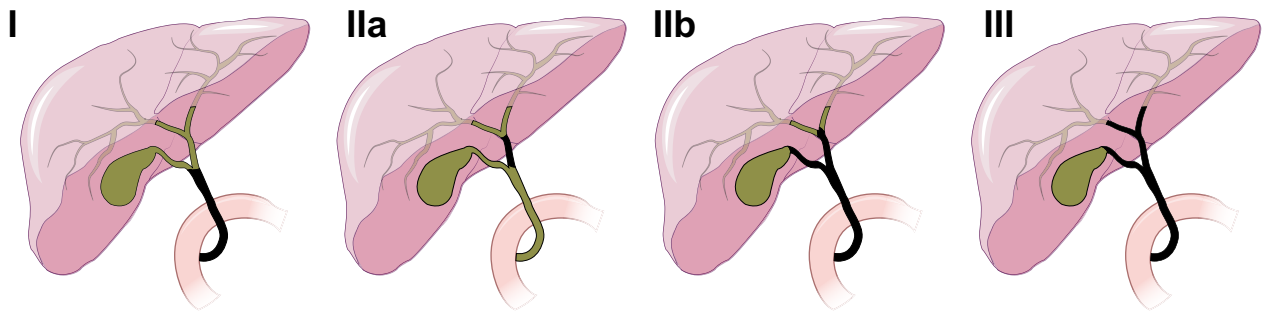

Fig. 2. Classification of biliary atresia. Type I, bile ducts are patent from the porta hepatis to the common bile duct and cystic duct; Type IIa, bile ducts are patent to the common hepatic duct; Type IIb, the cystic, common duct are obliterated; Type III, obstruction from the extrahepatic bile ducts to the porta hepatitis (>90% cases).

Table 3. Long-term outcomes in patients with biliary atresia post-Kasai portoenterostomy.

Author	N	Transplant free survival at 20 years (%)	Study period
Lykavieris *et al.*	271	23	1968–1983
Chardot *et al.*	403	30	1986–2009
Shinkai *et al.*	28	44	1970–1986
De Vries *et al.*	104	43	1977–1988
Nio *et al.*	80	49	1970–1986

Key management issues:

- **Management of portal hypertension**. Clinical, radiological and endoscopic evidence of portal hypertension is evident in over two-thirds of patients with 30% suffering a gastrointestinal bleed [49]. Patients with known oesophageal varices should undergo a yearly gastroscopy. Management of the complications of portal hypertension and its sequelae should therefore follow accepted international guidelines [55].
- **Management of cholangitis**. Cholangitis is commonly seen early after the Kasai surgery. The majority of the patients surviving into adulthood without a transplant do not develop cholangitis and are not on any antibiotic prophylaxis [56]. Cholangitis, if it occurs, should be treated appropriately with intravenous or oral antibiotics depending on the clinical and biochemical severity at presentation. The patency of the Roux loop should be investigated with either cholescintigraphy and hepatobiliary scintigraphy or enteroscopy.
- **Timing of liver transplantation**. Data suggests that up to two-thirds of patients with BA post KPE surviving into adulthood will develop hepatic complications [57]. BA post KPE appears to be the leading indication for liver transplantation for patients in transition services [28]. Timing of liver transplantation and acceptance onto adult waiting lists can be difficult. Due to preserved synthetic liver function, patients with BA may have low MELD scores and therefore may not fulfil minimal listing criteria. We recommend referral to a liver transplant centre following the first episode of hepatic decompensation or increase in the conjugated bilirubin fraction.
- **Hepatocellular carcinoma (HCC) risk**. The development of HCC appears to be rare in children and optimal surveillance strategies in young adults remains undefined [58]. A 6 monthly ultrasound scan is recommended in addition to measurement of serum alpha-fetoprotein levels.

Genetic cholestatic disorders

Progressive familial intrahepatic cholestasis (PFIC) comprises a heterogenous group of autosomal recessive liver disorders presenting in infancy or early childhood [59,60]. However it can also present in adulthood with episodes of cholestasis induced by medications such as the oral contraceptive pill (OCP), antibiotics or pregnancy. PFIC can be divided into types -1,-2 and -3 according to the genetic defects in the canalicular transporters (Fig. 3). Approximately 10–15% of cases of cholestasis in children are due to PFIC [59]. The diagnosis can be made by genetic testing which is readily available.

PFIC1, also known as Byler's disease is caused by a mutation in the *ATP8B1* gene on chromosome 18 (18q21-22). *ATP8B1* encodes FIC1 (familial intrahepatic cholestasis 1) protein and is located on the canalicular membrane of hepatocytes. It plays an integral role in phospholipid translocation. Proposed mechanisms for cholestasis include reduced bile salt secretion due to farnesoid X receptor (FXR) downregulation and overloading of bile acids in hepatocytes due to bile salt export pump (*BSEP*) downregulation and increased bile acid synthesis within hepatocytes [61,62]. High expression of the *ATP8B1* gene is also noted in the cholangiocytes, small bowel, kidney and pancreas and may account for the symptoms of diarrhoea and pancreatic insufficiency in PFIC1 patients. Other associated clinical features include short stature, severe pruritus and deafness. Laboratory tests classically demonstrate a normal or low gamma-glutamyl transferase (GGT),

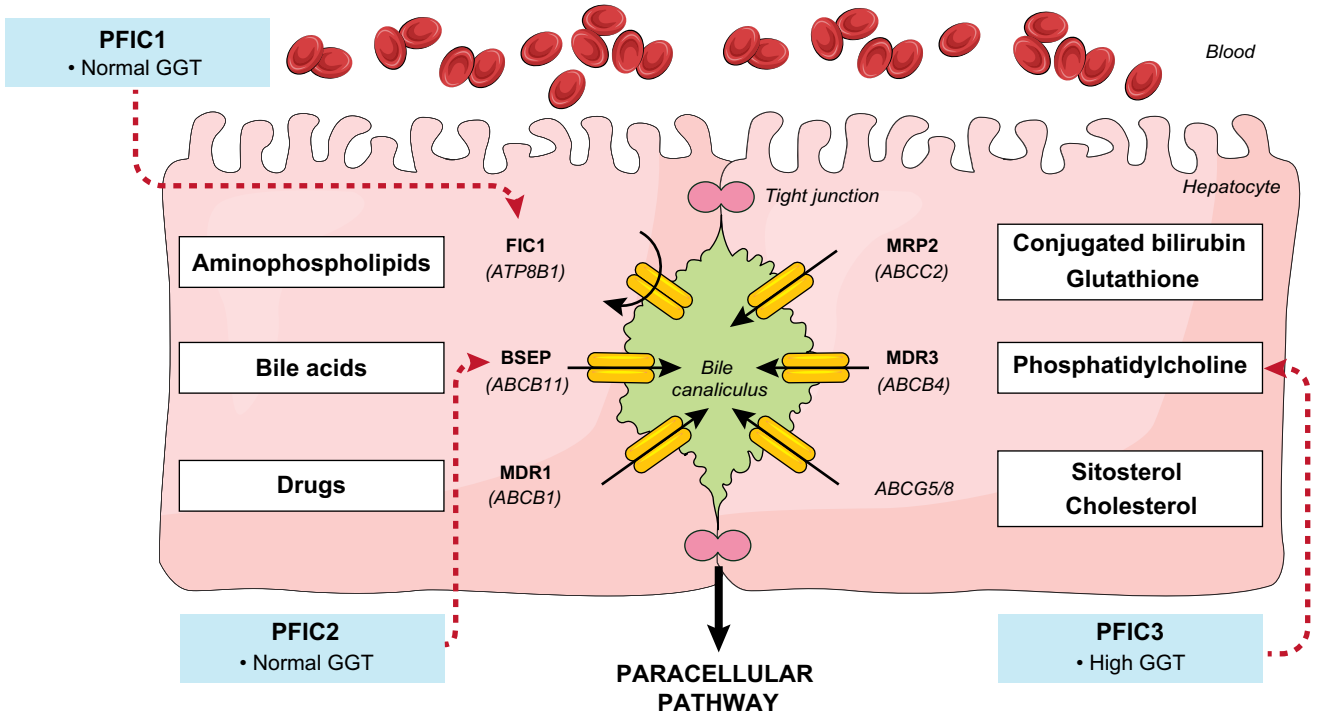

Fig. 3. Hepatobiliary transporters and their role on PFIC. Red dotted arrows demonstrate the phenotype expressed when a mutation occurs in the targeted transporter gene. PFIC1, progressive familial intrahepatic cholestasis type 1; PFIC2, progressive familial intrahepatic cholestasis type 2; PFIC3, progressive familial intrahepatic cholestasis type 3; MDR1/3, multi-drug resistance protein 1/3 (*ABCB1/4* gene); GGT, gamma-glutamyl transferase; FIC1, familial intrahepatic cholestasis 1 (*ATP8B1* gene); BSEP, bile salt export pump (*ABCB11* gene); MRP2, multidrug resistance associated protein 2. Modified from Joshi *et al.* [37].

mild elevation in transaminases and high bile acid levels. Histological features include bland, canalicular cholestasis with absent centrilobular GGT immunostaining, and portal and centrilobular fibrosis (see Fig. 4C).

PFIC2 (also known as BSEP deficiency) is caused by mutations in the *ABCB11* gene which encodes for the ATP-dependent canalicular BSEP located on chromosome 2 (2q24) [63]. Defects result in decreased bile salt excretion and subsequent accumulation within hepatocytes and hepatocellular damage. Patients with PFIC2 commonly present in the neonatal period with severe pruritus, normal or low GGT and grossly elevated raised transaminases and serum bile acids. In both PFIC1 and PFIC2, the normal or low serum GGT is due to failure of bile acid excretion at the canicular level. Extrahepatic symptoms are uncommon. Histological features include canalicular cholestasis, inflammation, portal fibrosis and giant cell transformation. In most cases, absence of canalicular BSEP expression can be demonstrated with immunohistochemistry (see Fig. 4D). Low GGT PFIC can also be associated with tight junction protein 2 (TJP2) deficiency, the defect resulting in disruption of the tight junction [64–66].

PFIC3 is associated with a high GGT and is caused by defects in the adenosine triphosphate-binding cassette subfamily B, member 4 (*ABCB4*) gene which encodes the multidrug resistance class 3 (MDR3) protein. The MDR3 protein is located on chromosome 7 (7q21) and is involved in phospholipid translocation. PFIC3 is one manifestation of MDR3 deficiency. Others manifestations include cholelithiasis, intrahepatic cholestasis of pregnancy, drug-induced cholestasis and a cholangiopathy/biliary cirrhosis in adults. MDR3 deficiency results in biliary epithelial and canalicular damage due to hydrophobic bile salt accumulation. Clinical features of PFIC3 include pruritus and an absence of extrahepatic symptoms. Histological changes include bile duct damage, ductular proliferation and biliary fibrosis (see Fig. 4E).

Key management issues:

- The OCP is contraindicated in patients with PFIC [39]. Female patients should be counselled regarding the development of cholestasis during pregnancy.
- **Genetic cholestasis testing**. Phenotypes that should be tested by next generation sequencing include: BSEP deficiency, FIC1 deficiency, TJP2 deficiency, MDR3 deficiency, FXR deficiency, citrin deficiency, transaldolase deficiency, Alagille syndrome.
- **Ursodeoxycholic acid**. Treatment for all forms of PFIC involves the use of UDCA which can lead to an improvement in liver function and in the minority of cases resolution of pruritus [67,68].
- **Pruritus**. Medical management is first line i.e., UDCA, rifampicin, ondansetron [69]. Patients may also benefit from nasobiliary drainage or

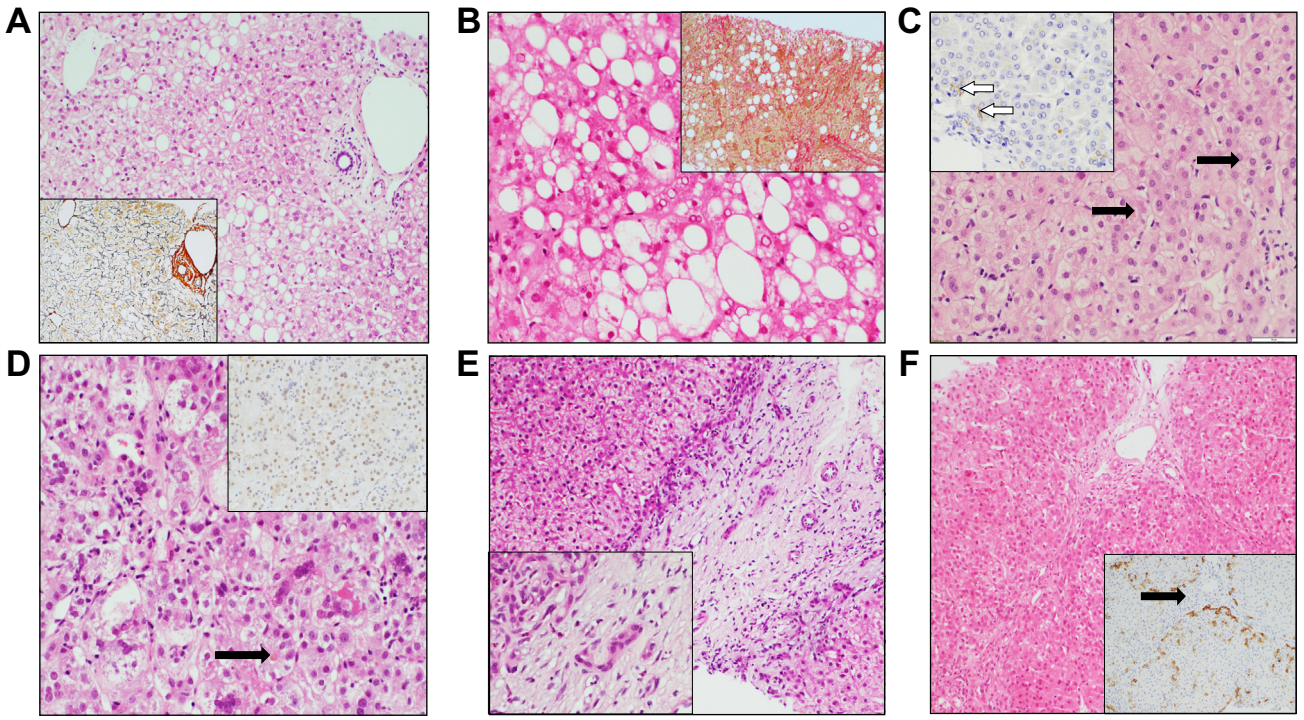

Fig. 4. Histological features from liver biopsies of various liver diseases. (A) A liver biopsy with severe steatosis from a 13 year old girl with non-alcoholic fatty liver disease (NAFLD; H&E 100× magnification). There is mild portal fibrosis (see inset image of reticulin staining, 100× magnification), steatosis and minimal portal inflammation. Portal based fibrosis and inflammation are more frequently seen in paediatric NAFLD than in adult NAFLD. Nuclear glycogenation of periportal hepatocytes is a normal finding in paediatric liver biopsies. Peri-venular and peri-sinusoidal fibrosis (top left main image and reticulin stained inset) are less frequently seen in paediatric NAFLD compared with NAFLD in adult patients. (B) A liver biopsy from a 55 year old man with NAFLD (H&E 200× magnification). There is severe steatosis with ballooning of hepatocytes and nuclear glycogenation. The inset image shows peri-sinusoidal fibrosis (Picro Sirius Red staining, 200× magnification). (C) A liver biopsy from a 6 month old child with ATP8B1 disease/PFIC1 (H&E 200× magnification). The hepatocytes are small and compact with minimal anisocytosis and minimal lobular activity. The black arrows point to pale bile (''Byler bile'') seen within dilated canaliculi. The inset image shows gamma glutamyl transpeptidase immunostaining (200× magnification), which marks canaliculi in periportal regions (white arrows) but is absent in centrilobular regions (inset image). (D) A liver biopsy from a ten week old baby with BSEP deficiency/ABCB11 disease (H&E 200× magnification). There is giant cell hepatitis with canalicular cholestasis (black arrow) and moderate lobular activity. The inset image shows absence of canalicular BSEP expression (bile salt export pump immunostaining, 200× magnification). (E) A 5 year old child with ABCB4 disease/MDR3 deficiency (H&E 100× magnification). There is portal fibrosis with cholangiopathic features in the form of bile duct disarray and a ductular reaction (inset image, H&E 200× magnification). Canalicular MDR3 immunostaining may be absent in a proportion of these patients. (F) A liver biopsy from a 6 month old infant with Alagille syndrome (H&E 100× magnification). There is portal fibrosis with fine fibrous septae radiating away from portal areas. Bile ducts are absent and there is no ductular reaction. The inset image shows CK7 immunostaining (cytokeratin 7, 100× magnification). The arrow points to the portal tract seen in the main image, in which bile ducts are not identified. There is aberrant expression of CK7 in hepatocytes, compatible with chronic cholestasis.

surgical biliary diversion although limited efficacy is reported in patients with established chronic liver disease [70,71]. Bile salt sequestrants can be used in patients with diarrhoea. The role of FXR agonists remains undefined at present. Liver transplantation remains an option in patients with progressive liver disease but recurrence post-transplantation is possible especially in patients with PFIC3 and BSEP deficiency.

- **Liver transplantation**. Indicated in patients with end-stage liver disease and intractable pruritus and is regarded as curative in PFIC2. The multi-system involvement however persists post-liver transplantation in PFIC1. Specifically, recurrence of steatosis and diarrhoea is seen post liver transplantation and management can be quite challenging [72] Hepatocyte therapy, gene and chaperone therapy, potentiators or specific targeted pharmacotherapy for pruritus and the gene defect are likely to become available in the future [73].
- **HCC risk**. A significantly increased risk of HCC is evident in PFIC2 [74]. Standard HCC surveillance is therefore recommended.

Alagille syndrome

Alagille syndrome is an autosomal dominant disorder which occurs secondary to mutations in the *JAG1* gene in the majority of cases (>95%), although expression is variable [75,76]. The remaining cases are associated with mutations in the *NOTCH2* gene [75]. Presentation is usually at birth or within early life with cholestasis, 'butterfly' vertebral arch defect, typical facial features comprising of deep and low set eyes, and 'triangular facies', and is often

associated with peripheral pulmonary artery hypoplasia or stenosis. Pruritus can be severe. Intrahepatic bile duct paucity is seen on histology though early on, it may be masqueraded by evidence of bile duct proliferation. Bile duct obliteration is progressive resulting in variable fibrosis (see Fig. 4F). End-stage liver disease occurs in approximately 20–30% of cases [77,78]. Renal abnormalities (renal tubular acidosis) can also occur.

Key management issues:

- **Ursodeoxycholic acid**. May help with symptoms and biochemical improvement.
- **Liver transplantation**. Data published suggest a good clinical outcome following liver transplantation but is dependent upon concurrent renal, cardiac and respiratory dysfunction [71,79].

Alpha-1 antitrypsin deficiency

Alpha-1 antitrypsin (A1AT) is a serum glycoprotein synthesized in the liver and in alveolar macrophages. Its primary function is as a neutrophil protease inhibitor. A1AT deficiency remains the most common inherited (autosomal dominant) cause of infantile liver disease [80].

More than 100 variant alleles of A1AT gene (*SERPINA1*) have been identified but the majority of patients with liver disease are homozygous for the Z mutant allele referred to as ZZ or Pi*ZZ [81]. Reduced levels of A1AT are also associated with the PiZNul and PiNulNul variants [82]. Normal levels of A1AT are seen in individuals who carry the most common allele (M). Hepatic injury is caused by the polymerisation and accumulation of the protein product of the Z gene in the endoplasmic reticulum of hepatocytes. Pi*ZZ homozygous individuals are also at risk of developing pulmonary emphysema which occurs due to insufficient availability of A1AT in the pulmonary system to inhibit connective tissue breakdown.

Clinical presentation is variable ranging from abnormal liver function tests to cirrhosis and HCC [81,83]. The clinical penetrance is variable with only 20% of patients with A1AT deficiency developing clinically significant liver disease. Presentation can therefore be in young adults commonly with abnormal liver function tests. The clinical presentation can be very similar to BA and therefore the phenotype should be determined in all suspected cases of BA. A1AT within hepatocytes stains positively with periodic acid-Schiff reagent but are only detectable after 12 weeks of life.

Key management issues:

- Treatment for those presenting with cholestasis is supportive with replacement of fat and water-soluble vitamins. Asymptomatic patients should be reviewed on a 6–12 monthly basis. Alcohol consumption should be minimized as well as smoking and exposure to passive smoking. Baseline lung function should be performed.
- **Liver transplantation**. Liver transplantation is the only therapeutic option in patients with hepatic decompensation often characterised by synthetic failure. Following liver transplantation, A1AT levels should normalise assuming the donor is Pi*MM and pulmonary disease should not progress any further.

Other metabolic disorders

Other metabolic disorders include glycogen storage diseases, lysosomal storage disorders and urea cycle disorders. Table 4 summarises the clinical features and available treatment options. Additionally, patients who were transplanted for cryptogenic cirrhosis may warrant additional testing such as Next Gen sequencing, exome sequencing based on clinical symptoms which may not have been available at the time of transplant.

Diseases that occur in children/adolescents and adults

Autoimmune hepatitis and autoimmune sclerosing cholangitis

Autoimmune hepatitis (AIH) is a chronic, immune-mediated liver disease characterised by high serum transaminases, high immunoglobulin G (IgG) levels, detectable autoantibodies and histologically by the presence of interface hepatitis [84]. AIH is a rare condition both in adults and children, with a reported incidence of 0.4 and 3.0/100,000 children [85,86].

Children vs. adults

Subtle differences are observed in paediatric patients presenting with AIH. Nearly two-thirds of patients in childhood have type 1 AIH (positive anti-nuclear antibody [ANA] and/or anti-smooth muscle antibody [SMA]) and tend to present at the time of puberty often with features of cirrhosis on biopsy [87]. Type 2 AIH (positive anti-liver kidney microsomal type 1 antibody [LKM1] and/or anti-liver cytosol type 1 antibody [anti-LC1]) affects younger patients (median age 7 years). Higher serum bilirubin levels and transaminases at presentation are noted and patients have a higher propensity to present with fulminant hepatic failure [87,88]. Approximately 50% of children will be cirrhotic at presentation [87,89–91]. Type 1 AIH (ANA/ASMA+) is the most common form in adults and tends to present between the ages of 40–50 years, although, it may present at any age level

Table 4. Metabolic disorders in young adults.

Disorder	Defect	Clinical features
Glycogen storage diseases	Type I – Glucose-6-phosphatase	Hepatomegaly, lactic acidosis, ketotic hypoglycaemia, hyperlipidaemia, hypertriglyceridaemia, neutropenia. *Treatment*: uncooked cornstarch, allopurinol, GCSF. Monitoring: Risk of development of hepatic adenoma. Monitoring with USS and AFP is recommended.
	Type III – Glycogen debrancher	Ketosis, hypoglycaemia, hepatomegaly. *Treatment*: uncooked starch. Monitoring: Risk of development of hepatic adenoma. Monitoring with USS and AFP is recommended.
	Type IV – Glycogen branching	Hepatomegaly. *Treatment*: liver transplantation
Lysosomal storage diseases	Fabry's disease – X linked, deficiency or defect in lysosomal hydrolase alpha-galactosidase	Accumulation of globotriasylceramide within lysosomes in renal tubules, interstitial cells, cardiac muscle cells and vascular smooth muscle cells.
	Gaucher's disease – autosomal recessive, mutation in glucocerebrosidase gene (chromosome 1q21). Most common lysosomal storage disease	Deficiency in glucoysl-ceramide-B-glucosidase in leucocytes, hepatocytes and aminocytes. Three subtypes (Type I, II, III). Type I does not have CNS involvement. *Treatment*: replace deficient enzyme.
Urea cycle disorders	N-acetyl glutamate synthetase deficiency	Hyperammonaemia, autosomal recessive, seizures
	Carbamyl phosphate synthetase I deficiency	Hyperammonaemia, autosomal recessive, seizures
	Ornithine transcarbamylase deficiency	Hyperammonaemia, X linked inheritance, seizures
	Argininosuccinate synthetase deficiency (Citrullinemia)	Hyperammonaemia, autosomal recessive, seizures
	Argininosuccinate lyase deficiency	Hyperammonaemia, autosomal recessive, seizures
	Arginase deficiency	Autosomal recessive, seizures
Mitochondrial disorders	Numerous clinical syndromes including: Leber hereditary optic neuropathy, maternally inherited deafness and diabetes, mitochondrial encephalomyopathy with lactic acidosis and stroke like episodes (MELAS)	Isolated myopathy Encephalomyopathy in infancy and childhood External ophthalmoplegia Multisystemic disease with myopathy
Lysosomal acid lipase (LAL) deficiency	Autosomal recessive. Also known as cholesteryl ester storage disease (CESD)	Liver fibrosis and cirrhosis. Increased risk of strokes. High cholesterol and triglycerides (high LDL and low HDL), hepatomegaly *Treatment*: none at present

USS, ultra sound scan; GCSF, granulocyte colony-stimulating factor; AFP, alpha-fetoprotein; CNS, central nervous system; LDL, low density lipoprotein; HDL, high density lipoprotein.

[92]. A female preponderance is observed in both children and adults.

The most common presentation of AIH in childhood (approximately 40%) is usually non-specific and may be similar in phenotype to an acute viral hepatitis i.e., malaise, nausea, vomiting, anorexia, abdominal pain followed by jaundice, dark urine and pale stools [87]. An uncommon presentation in less than 10% of patients is signs and symptoms of portal hypertension. The remaining patients often present insidiously, with more subtle symptoms of weight loss, anorexia, malaise occurring over many years. The presentation in adults is similar and varies from mild biochemical abnormalities to sub-acute liver failure [93]. Differences in autoimmune liver disease between children and adults is summarised in Table 5. Patients diagnosed with AIH under the age of 18 years have an increased risk for disease relapse, are more likely to need liver transplantation and have a reduced life expectancy compared to adults [94,95].

Autoimmune sclerosing cholangitis (ASC) is a unique form of sclerosing cholangitis with gross autoimmune features (positive ANA and/or SMA antibodies, high titres of IgG and interface hepatitis) and a cholangiopathy on imaging, which has been described in children [89]. Liver biochemistry may not be indicative of cholestasis. The seminal publication on ASC highlighted a similar prevalence as type 1 AIH with both sexes being affected equally [89]. Associated autoimmune diseases, in particular, inflammatory bowel disease (IBD) is common in patients with ASC [87,89]. A strong association with HLADRB1*1301 is described in patients with ASC [96].

The International Autoimmune Hepatitis Group (IAIHG) have developed diagnostic criteria for AIH in adults which has been widely used in children [97,98]. Recently, EASL Clinical Practice Guidelines recommend the use of the simplified IAIHG criteria to aid diagnosis, whilst reserving the modified criteria for difficult to diagnose cases [96].

Key management issues:

The treatment goals are to normalise serum transaminases, IgG levels and achieve negative or low titres of autoantibodies ($\leqslant$1:20 ANA or SMA or $\leqslant$1:10 anti-LKM-1) resulting in an improvement in histological inflammation. Equally, additional goals should be to maintain remission and prevent the progression of the disease to cirrhosis.

Table 5. Autoimmune liver disease – children and adults.

	Children	Adults
Sub-type	Type 1–66%	Type 1 >Type 2
Sex	Female >male (3:1) (1:1 – ASC)	Female >male (3:1)
Age of onset*	Type 1–11 years Type 2–7 years ASC – 12 years	40–50 years
Clinical presentation	Acute hepatitis >insidious >acute liver failure	Acute hepatitis >insidious >chronic liver disease >acute liver failure
Concurrent autoimmune disease	Approximately 20% More common in ASC	Common
Cirrhosis at presentation (%)	50	33
Relapse rate (%)	44	40
Liver transplantation rate (%)	10 25 in ASC	10
Recurrence post-liver transplantation (%)	0 in Type 1 and Type 2 66 in ASC	12–42

* Median age. ASC, autoimmune sclerosing cholangitis.

- **Treatment**. The mainstay of treatment in both adults and children is the use of prednisolone. In children 2 mg/kg/day (maximum 60 mg/day) is started and then tapered over a period of 6–8 weeks to a maintenance dose of between 2.5–5 mg/day, whereas, proportionally lower doses (0.5–1.0 mg/kg/day) are used in adults [96]. We recommend azathioprine as a steroid sparing agent (starting dose 0.5 kg/day) in individuals whose transaminases stop decreasing on prednisolone therapy. 6-mercaptopurine (1.5 mg/kg/day) can also be used. Thiopurine methyltransferase (TPMT) activity measurement is recommended prior to initiation of azathioprine. The introduction of azathioprine should be delayed in cases with elevated bilirubin >100 μmol/L. Thioguanine metabolites can be measured to ensure individuals are on appropriate therapeutic doses, adherent and not developing hepatotoxicity [99]. Budesonide (9 mg daily) may be an alternative in patients who are unable to tolerate prednisolone but has limited efficacy in individuals with cirrhosis [100].
- Treatment regimens for ASC are similar to AIH but the addition of UDCA (15–20 mg/kg/day) is also recommended.
- **Refractory disease**. Patients who fail azathioprine therapy or with refractory relapsing disease should be considered for treatment with mycophenolate mofetil, which can lead to remission in approximately 10% of children [101]. Calcineurin inhibitors (cyclosporine and tacrolimus) have also been used with good efficacy, but the data is limited to small numbers and limited long-term follow-up [102–105].
- **Disease relapse**. Relapse is common, affecting approximately 40% of children and 50% of adults and is frequently associated with non-adherence [95,106]. Relapse in disease is confirmed by an increase in autoantibody titres, rise in globulin fraction, serum transaminases and exclusion of non-adherence. Relapse is typically treated with the reintroduction of prednisolone or increase in dose and consideration of alternative therapies [107].
- **Treatment duration**. The optimal duration of therapy remains unknown, although for many children and adolescents, lifelong therapy is needed. Patients often require repeat liver biopsies to determine ongoing evidence of inflammation and fibrosis progression. We recommend treatment withdrawal only after 3 years with the provision of no active inflammation or cirrhosis on liver biopsy, normal liver biochemistry and negative autoantibodies in the preceding 2 years. Studies in both children and adults have reported sustained immunosuppression free rates of up to 40% at 5 years [108,109], although data in adult patients from Europe suggests lower rates of sustained remission [110]. Withdrawal of treatment is not recommended during puberty, pregnancy, concurrent IBD or during the transition period. Patients should be counselled to explain that relapse is common after withdrawal of treatment affecting approximately 70% of patients [109,111,112].
- **Long-term management and liver transplantation**. Adult and children with AIH should have bone density assessment performed every 3–5 years [96]. In addition, patients should also be screened and vaccinated against hepatitis A and hepatitis B viruses. Patients receiving azathioprine or 6-mercaptopurine should be educated on the dangers of excessive sun exposure. Overall the prognosis of AIH in children who respond to treatment is good. However, approximately 10% of patients with AIH and 20% of patients with ASC will require liver transplantation [87,113].

Non-alcohol related fatty liver disease

Data from the UK and the USA estimates the prevalence rate of obesity to be 9–17% in children and

young adults [114,115]. In parallel to this rising epidemic of obesity, non-alcoholic fatty liver disease (NAFLD) is now the most common cause of chronic liver disease in both children and adults. Male children appear to be more affected than their female counterparts [115,116]. The histological findings in children and adults are different and are summarised in Fig. 4A and B. The long-term prognosis of paediatric NAFLD is unclear, but progression to severe liver disease does occur. Important differential diagnoses include Wilson's disease, urea cycle defects, fatty acid oxidation defects, lysosomal acid lipase deficiency and mitochondrial cytopathies.

Insulin resistance appears to be the final common pathway of a number of different mechanisms including increased pro-inflammatory cytokine production and reduced adiponectin [117,118]. Leptin resistance leads to free fatty acid accumulation in vacuoles which results in hepatocyte injury through oxidative stress, endoplasmic stress and mitochondrial dysfunction [119,120]. Hepatocyte death subsequently results in fibrogenesis through hepatic stellate cell activation [121]. Other pathophysiological mechanisms implicated include single nucleotide polymorphisms in patatin-like phospholipase domain-containing protein (PNPLA3), increased consumption of trans fats and fructose, intestinal dysbiosis and bacterial translocation, and an increase in male sex hormones [122–127].

Key management issues:

- **Treatment**. There are limited treatment options for the treatment of NAFLD in children and young adults. Management strategies should target any modifiable risk factors for the metabolic syndrome. Dietary modifications including improving the quality of school dinners and increased exercise are critical interventions in reducing patient body weight. A study that used an improvement in liver histology as its primary endpoint demonstrated that two years of increased physical activity and lifestyle intervention with an individual calorie diet resulted in a significant improvement in the severity of steatosis, inflammation and hepatocyte ballooning and the NAFLD activity score [128]. The study also reported an improvement in liver enzymes, insulin resistance and serum lipid levels [128]. The TONIC study, a double-blind placebo controlled trial compared vitamin E or metformin for 96 weeks [129]. The primary outcomes was a sustained reduction in alanine transferase whilst secondary outcomes were improvement in histological features and resolution of non-alcoholic steatohepatitis (NASH). Although the primary outcome was not achieved, vitamin E was associated with resolution of NASH and an improvement in hepatocyte ballooning suggesting the need for future studies [129].
- **Newer therapies**. Although not used specifically in children or young adults, the FLINT study assessed the efficacy of obeticholic acid (FXR agonist) in adults with NASH for 72 weeks [130]. Obeticholic acid resulted in an improvement in histology compared to placebo (45% *vs*. 21%, $p = 0.0002$) but nearly one-third of patients developed pruritus and increased serum low-density lipoprotein levels. More data is therefore required on the use of obeticholic acid in patients with NAFLD.
- **Bariatric surgery**. ESPGHAN (European society for paediatric gastroenterology, hepatology and nutrition) have recently published a position statement on the role of bariatric surgery in young adults [131]. The benefits of bariatric surgery are plentiful and include the obvious; reduction in weight and BMI, to the more subtle improvement in systemic inflammation, glucose tolerance and dyslipidaemia. ESPGHAN conclude that bariatric surgery should be considered in patients without cirrhosis and with the support of a specialized multi-disciplinary team [131].

Wilson's disease

Wilson's disease is an autosomal recessive disorder which causes impaired cellular transport of copper resulting in accumulation in the liver, brain and cornea. The genetic mutation is in the *ATP7B* gene located on chromosome 13 [132]. More than 500 different mutations have been described in the Wilson gene but the clinical significance of every mutation remains unclear.

Key management issues:

- A comprehensive history should also include review of neurocognitive development and schooling/academic performance and progress.
- EASL guidelines published in 2012 provide further details on diagnosis and the interpretation of the different investigations [133]. Screening of family members and offspring is recommended.
- Untreated, Wilson's disease is fatal usually from liver disease. Treatment is therefore lifelong. D-penicillamine (750–1500 mg/day BD or TDS) promotes the urinary excretion of copper but also induces metallothioneins, which are endogenous chelators of metals. It should be taken 1–2 h before meals to inhibit the dietary absorption of copper. Pyridoxine supplements are required. D-penicillamine is poorly tolerated in almost one-third of patients and may worsen neurological symptoms. Alternatives include trientine (copper chelator and promoter of urinary copper excretion) which is usually better tolerated than D-penicillamine and zinc (reduces uptake of copper

from the gastrointestinal tract, induces metallothioneins in enterocytes before the bound copper is faecally excreted).
- Liver transplantation should be considered for patients with acute liver failure and those with decompensated liver disease.

Conclusion

Liver diseases once thought to be unique to paediatric hepatologists are now presenting to adult hepatologists. Subtleties and awareness in the management of specific diseases are therefore required. Adult hepatology training curriculums need to incorporate and stress a greater emphasis on young adults with liver disease. The management of young adults with childhood liver diseases requires a multi-disciplinary approach. Engagement of young adults and promotion of self-management are key components adult hepatologists and adult services need to adopt in order to deliver a safe and effective liver transition programme.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Authors' contributions

DJ and MH wrote and edited the article. NG, MS, MD and FD edited and provided expert opinion.

Supplementary data

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