BRIDGING PAEDIATRIC LIVER DISEASES TO ADULT CARE: WHAT DOES THE GASTROENTEROLOGIST NEED TO KNOW?

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ABSTRACT

Advances in medical and surgical therapy mean that significant numbers of children with previously fatal liver disease are surviving into adult life. In particular, 80% of transplant recipients now survive for over 20 years. Gastroenterologists and hepatologists who treat adult patients need to be aware of the clinical management and complications of diseases originating in infancy, such as biliary atresia, progressive familial intrahepatic cholestasis, Alagille syndrome, and metabolic diseases such as hereditary tyrosinemia type 1. They need to be familiar with the long-term consequences of liver transplantation in childhood, e.g. renal failure, recurrent disease, osteoporosis, and post-transplant malignancies, especially post-transplant lymphoproliferative disease, which differs in presentation and evolution from adult transplant recipients. Survivors of childhood illness require a different approach to that for young adults presenting after 18 years of age. Adult physicians need to consider the emotional, social, and sexual health of these young people, and be aware of the high rate of non-adherence, both for clinic appointments and medication, as well as the implications for graft loss, particularly after transition to adult services. Developing adequate transitional care for these young people is based on effective collaboration at the paediatric–adult interface and is a major challenge for paediatric and adult providers alike in the 21st century.

Keywords: Paediatric liver disease, liver transplantation, adolescent transition.

INTRODUCTION

Over the last 25 years there have been significant advances in medical technology and therapy that have improved the diagnosis and management of paediatric liver disease. Children with previously fatal diseases now survive into adult life in increasing numbers. In particular, the success of liver transplantation means that the survival rate for child and adolescent recipients of liver transplantation is 80% over 20 years, thus most children with liver disease can now expect to become adults.[1,2]

In our programme in Birmingham, we have transferred nearly 800 young people with liver disease or post-transplant to adult services (Table 1 and Table 2). The majority of children with liver disease had viral hepatitis, autoimmune liver disease, or cystic fibrosis (CF), while nearly 200 were post-transplant. The aim of this paper is to familiarise gastroenterologists caring for adults with the specific differences of childhood liver disease and how to manage the long-term complications both of paediatric liver disease and of liver transplantation in adult services. In particular they need to be familiar with rare diseases originating in infancy, such as biliary atresia, progressive familial intrahepatic cholestasis (PFIC),[1-4] Alagille syndrome (AGS), and metabolic diseases such as hereditary tyrosinemia type 1 (HT-1) and CF, as few of these children survived into adulthood prior to recent developments in medical and surgical management. They also need to be aware of the different phenotypes of these diseases and their multi-organ involvement, which may include cardiological, renal, and/or neurological progression, and also the risk of hepatocellular carcinoma (HCC) in all children with prolonged chronic liver disease.

Table 1: Birmingham programme: outcome of transfer to adult care 1989–2014 (n=862).

Patient category	Transferred, n	Current status	Died, n
Transplanted	236	215 alive	19
Chronic liver disease	626	10 transplanted	2
		595 alive, 2 awaiting transplant	31

Table 2: Diagnosis of 519 patients with chronic liver disease transferred to adult care in the Birmingham programme (1989–2012).

Diagnosis	Transferred, n	Alive, n	Died, n	Transplanted, n
Viral hepatitis	147	146	1	0
Cystic fibrosis liver disease	99	85	14	5 (2 died)
Autoimmune liver disease	84	82	2	2 (2 died)
Other	82	80	2	0 (1 on waiting list)
Metabolic syndrome	32	32	0	1 (1 on waiting list)
EHBA	25	25	0	1
Fatty liver disease	23	23	0	0
Alagille syndrome	11	10	1	0
Wilson's disease	9	9	0	0
A1AT deficiency	5	5	0	1
Intestinal failure	2	2	0	0

EHBA: extrahepatic biliary atresia; A1AT: alpha-1 antitrypsin.

Gastroenterologists caring for adults should also be aware of the long-term consequences of liver transplantation in childhood, e.g. renal failure, recurrent disease, osteoporosis, atherosclerosis, and post-transplant malignancies, especially post-transplant lymphoproliferative disease which may present with gastrointestinal (GI) bleeding or anaemia.[1,2] Although adult providers will be expert in managing adult liver disease pre and post-transplantation, managing young adults who have been exposed to long-term immunosuppression poses different challenges. For example, they will need to consider a different approach to young people who have survived childhood illnesses compared with young adults presenting after the age of 18 years, as those surviving childhood illness may require greater psychosocial support. As with all young adults, physicians will need to consider their emotional, social, and sexual health. They should also be particularly aware of the high rate of non-adherence both for clinical appointments and medication, and the implications for graft loss, particularly after transition. The challenge of developing adequate transitional care for these young people is based on effective collaboration at the paediatric–adult interface and is a major challenge for paediatric and adult providers alike in the 21st century.

The support of societies such as the Children's Liver Disease Foundation in the UK (www.childliverdisease.org) or the British Liver Trust (www.britishlivertrust.org.uk) may be beneficial to both patients and providers, both before and after transition.

BILIARY ATRESIA

Extrahepatic biliary atresia is a disease of unknown aetiology with no proven genetic basis. It occurs in approximately 1 in every 15,000 live births.[3] There is a syndromic or embryonic form (biliary atresia splenic malformation syndrome) in 10–20% of cases with other congenital anomalies,

such as polysplenia, situs inversus, cardiac anomalies (e.g. atrial and ventricular septal defects), and absence of the inferior vena cava.[4] The perinatal or acquired form is more common and represents 80–90% of cases. The underlying pathogenesis is unknown, but is likely to be multifactorial based on the interaction of genetic and environmental factors.[4]

Initial management is based on early diagnosis and palliative surgery, Kasai portoenterostomy, in which the biliary tree is excised to expose biliary channels, with a Roux loop being created for drainage. The operation is considered to be successful if there is restoration of biliary flow within 6 months, but is dependent on the patient's age at the time of surgery, the expertise of the surgeon, and the extent of fibrosis at operation.[4] In general, success rates are approximately 60%. Although biliary atresia is the main indication for liver transplantation worldwide and accounts for 76% of children under the age of 2 years, 80% of children who have a successful operation survive 15 years or more without transplantation.[4] There are several studies of long-term outcome following successful Kasai.[5,6] The majority of survivors have cirrhosis and portal hypertension, but have normal fertility, complete primary and secondary education, and are in employment.

Issues for Adult Providers

Adult providers need to be familiar with the aetiology of biliary atresia in which the intrahepatic ducts are malformed and there is a portoenterostomy, which means that interventional radiology, such as a percutaneous transhepatic cholangiogram, is not a feasible investigation for progressive cholestasis. They will be experienced with managing the complications of portal hypertension and biliary cirrhosis, but need to be aware of the potential for cholangitis (requiring therapeutic and prophylactic antibiotics) leading to biliary cirrhosis and the need for transplantation. In young adults with end-stage liver disease, malnutrition, fat-soluble vitamin deficiencies, and metabolic bone disease are frequent issues and should be managed using standard adult guidelines.[4,5]

ALAGILLE SYNDROME

AGS is an autosomal dominant condition with an incidence of 1 in every 100,000 live births.[7] It is a multisystem disorder with cardiac, facial, renal, ocular, and skeletal abnormalities. The condition is caused by mutations in the *JAG1* gene encoding Jagged-1, which is a ligand of Notch-1. There are many different mutations and a high frequency of sporadic cases, while <1% have mutations in the gene encoding Notch-2.[8]

Infants present with persistent cholestasis, severe pruritus, hepatomegaly, and failure to thrive that is complicated by GI reflux and severe steatorrhoea secondary to fat malabsorption or pancreatic insufficiency.[9] The characteristic facial features are difficult to identify in infancy, but are obvious in adult life. They include a triangular face with a high forehead and frontal bossing; deep, widely spaced eyes; a saddle-shaped nasal bridge; and a pointed chin. Cardiac abnormalities include peripheral pulmonary stenosis, pulmonary and aortic valve stenosis, and the tetralogy of Fallot. Skeletal abnormalities include abnormal thoracic vertebrae, 'butterfly' vertebrae, and curving of the proximal digits of the third and fourth finger. Ocular abnormalities include optic disease, papilloedema secondary to intracranial hypertension, and posterior embryotoxon. Renal disease varies from mild renal tubular acidosis to severe glomerular nephritis. Hepatosplenomegaly is unusual unless there is progressive fibrosis, which is rare. Management in childhood depends on the severity of associated extrahepatic disease and cholestasis. Intensive nutritional support with fat-soluble vitamins, especially vitamin E, is essential, and pancreatic supplements may be required. Cardiac anomalies require corrective surgery, with balloon dilatation or surgical correction of pulmonary valve or pulmonary artery stenosis.[10]

With adequate support, about 50% of children regain normal liver function without significant cholestasis by adolescence while others require liver transplantation in childhood. Overall mortality is 20–30%, due to cardiac disease or progressive liver disease.[10,11] In a study of 163 children with AGS and liver involvement, 44 (33%) required liver transplantation;[11] overall survival rates were 68% and 62% at 10 and 20 years, respectively. Catch-up growth after transplantation may occur.

Issues for Adult Providers

Issues for adult providers include management of cholestasis, pruritus, and hypercholesterolaemia with extensive xanthoma, but liver failure is rare in adult life. Young adults with significant cardiac disease may develop pulmonary hypertension or

require further surgery. Renal disease requires specific management or renal transplantation as required. Patients have a 50% chance of having an affected child and appropriate counselling is required. Although prenatal diagnosis is now possible, termination is not common because of the varied phenotype.[8]

PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS

PFIC encompasses a group of inherited cholestatic diseases caused by mutations in genes encoding the components of the hepatocellular transport system involved in bile synthesis. They are autosomal recessively inherited, and interaction with modifier genes plays a role in the severity of the clinical phenotype. Modifier genes include the apical sodium-dependent bile acid transporter and the farsenoid X receptor, a bile acid-activated transcription factor which mediates transcriptional repression of genes important in bile acid and cholesterol homeostasis. They are rare, with an incidence of 1/50,000–1/100,000, but show worldwide occurrence and equal sex distribution.

PFIC1 is caused by mutations in *ATP8B1*.[12] Benign recurrent intrahepatic cholestasis type 1 (BRIC1) is also caused by mutations in *ATP8B1* and is an allelic condition to PFIC1. It presents in the first months of life with episodes of jaundice and severe pruritus with very high serum bile-acid levels. Due to the extrahepatic expression of the *ATP8B1* gene, other clinical features include pancreatitis, diarrhoea (loss of the ileal transporter), sensorineural deafness, and short stature.

PFIC2, also known as bile salt export pump (BSEP) deficiency, is caused by mutations in *ABCB11*.[13] BRIC type 2 is also caused by mutations in *ABCB11* and is an allelic condition to PFIC2. BSEP is the major canalicular BSEP in man and extracts bile salts from hepatocytes into canaliculi. Its deficiency presents with persistent cholestasis from birth, coagulopathy secondary to fat-soluble vitamin K deficiency, and pruritus; there are no extrahepatic manifestations.[14] HCC has been reported in infancy and should be monitored with alpha-fetoprotein levels and ultrasound scans.

PFIC3, also known as multidrug resistance protein 3 (MDR3) deficiency, is caused by mutations in the *ABCB4* gene.[15] *ABCB4* encodes MDR3 that translocates phosphatidylcholine and other membrane phospholipids from the inner to the outer canalicular membrane leaflet, so that phospholipids are available for extraction by bile salts. There is variable cholestasis in this condition and it may present at any time during childhood or adult life with complications of chronic liver disease, such as portal hypertension and liver failure; pruritus is often mild.

PFIC4 has been recently described and is due to truncating mutations of the gene encoding tight junction protein 2 on chromosome 9q21.11. Truncation of the protein causes disruption of the integrity of the cholangiocyte membrane; it is probably localised only to the liver in humans. PFIC1, PFIC2, and PFIC4 have low-normal gamma-glutamyl transpeptidase (GGT) despite marked cholestasis, which is in contrast to the elevated GGT observed in PFIC3. Cholesterol tends to be low. Synthetic function is maintained until liver failure develops.

Issues for Adult Providers

Most patients require liver transplant in childhood and so, with the exception of BRIC and PFIC3, adult providers will only care for those who have survived transplantation. In young people transplanted for PFIC1, management focusses on the extrahepatic manifestations, especially diarrhoea, which is worse after transplantation and requires bile salt resins for control. Graft steatosis leading to cirrhosis and the need for re-transplant may occur.[16] Children transplanted for PFIC2 may develop recurrence due to the development of anti-BSEP antibodies and may need re-transplantation.[17] There is a theoretical possibility that female carriers of PFIC and those with milder phenotypes may become cholestatic in pregnancy.

TYROSINEMIA TYPE 1

HT-1 is an autosomal recessive disorder caused by a defect of fumarylacetoacetase. More than 40 mutations have been described,[18] and there is a high lifetime risk of developing HCC.[19]

Clinical features are heterogeneous, even within the same family. Acute liver failure is a common presentation in infants, while older children present with chronic liver disease, rickets, a hypertrophic cardiomyopathy, renal failure, or a porphyria-like syndrome with self-mutilation. Renal tubular dysfunction and hypophosphataemic rickets may occur at any age.

Table 3: Aims of transition.

1.	To provide high-quality, coordinated, uninterrupted healthcare that is patient-centred, age and developmentally appropriate, future-focussed, culturally competent, flexible, responsive, and comprehensive
2.	To promote skills in communication, decision-making, assertiveness, self-care, self-determination, and self-advocacy
3.	To enhance sense of control and interdependence in healthcare
4.	To maximise lifelong functioning and potential
5.	To support the parent(s)/guardian(s) of the young person during transition and in particular to enhance their advocacy skills

Management should be conducted with a phenylalanine and tyrosine-restricted diet and nitisinone, 2(2-nitro-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC), which prevents the formation of toxic metabolites and allows normal growth and development.[20,21] The long-term outcome of children and young adults who have HT-1 and are treated with nitisinone is unknown, but there are emerging concerns about neurocognitive function.[21]

Issues for Adult Providers

Young adults with HT-1 require long-term monitoring and follow-up with 6-monthly abdominal ultrasound and CT scans, or MRI and alpha-fetoprotein estimation, for early detection of HCC. As the metabolites are also produced by the kidney, monitoring of renal function is essential, especially in those who have been transplanted. Liver transplantation is now only indicated for the development of acute or chronic liver failure unresponsive to NTBC, or suspicion of HCC.[21]

CYSTIC FIBROSIS

CF has an incidence of 1 in every 3,000 live births worldwide.[22] The gene defect is an abnormality in the CF transmembrane conductance regulator located on chromosome 7q31. It is a multi-organ disease mainly affecting the lungs and pancreas. CF-associated liver disease occurs in 27–35% of patients and usually presents before the age of 18 years.[23] Approximately 5–10% of all CF patients will develop cirrhosis and portal hypertension during the first decade of life and present with complications in adolescence or early adult life.[24] Liver failure is a late event accounting for 2.5% of overall CF mortality.[25]

Use of ursodeoxycholic acid (20 mg/kg) may stabilise progression of disease, but there are no large randomised controlled trials. Currently, large numbers of young people have transferred to adult care (Table 2).

Issues for Adult Providers

Holistic management of CF in young adults includes:

- Standard management of pancreatic deficiency and diabetes if present
- Counselling about adolescent issues, fertility, and lifestyle. Most women are fertile, but menarche and conception may be delayed due to malnutrition and ongoing chronic disease. About 98% of males are infertile due to failure of the vas deferens and should be appropriately counselled
- Managing the combination of CF liver and lung disease, portal hypertension, and hypersplenism. This requires a multidisciplinary approach from both respiratory and hepatology teams for optimum care based on standard adult management
- Making a decision about timing for liver transplantation

The indications for liver transplantation include malnutrition unresponsive to nutritional support, intractable portal hypertension, and hepatic dysfunction. It is essential that transplantation is carried out before pulmonary disease becomes irreversible.[25] The outcome following liver transplantation is good. A number of studies have indicated good if not better initial survival, an absence of significant pulmonary complications, and stabilisation of pulmonary function and nutritional parameters, but deaths from respiratory failure in early adult life should be anticipated.[26]

POST-TRANSPLANT MANAGEMENT

The long-term survival and quality of life post-transplant are influenced by: late technical complications such as hepatic arterial or portal vein thrombosis, biliary strictures, the development

of graft hepatitis or fibrosis, recurrent disease, the side effects of immunosuppression, and adherence, especially after transition to adult care.[27]

Issues for Adult Providers

Patients require:

- Annual monitoring of graft function with regular biochemical liver function tests and abdominal ultrasound
- Screening for renal dysfunction using an estimated chromium ethylenediaminetetraacetic acid glomerular filtration rate
- Measurement of lipids, blood pressure, and glucose or HbA1c for diabetes mellitus and/or metabolic syndrome
- Weight loss or anaemia should prompt evaluation of post-transplant lymphoproliferative disorder by Epstein–Barr virus polymerase chain reaction, endoscopy, and/or abdominal CT scan[27]
- Serial protocol biopsies may indicate the presence of graft hepatitis or fibrosis, which may be a form of rejection and require an increase in immunosuppression[28]

Approximately 10% of young adults require re-transplantation for chronic rejection, mostly related to non-adherence.[28]

TRANSITION TO ADULT CARE

Transition is defined as 'a multi-faceted, active process focussed on the medical, psychosocial, and educational/vocational needs of adolescents as they move from child to adult-centred care'.[29] The aims of transition are listed in Table 3. It requires a multidisciplinary approach, good communication, support, and education for both parents and young people in order to ensure that the young person is equipped to take responsibility for their own care.

The key to successful transition is good preparation, encouraging self-management skills in the young person, and establishing joint clinics between adult and paediatric providers to provide seamless care. It is important that the young person is in good health and emotionally mature enough to move to adult services, which is usually at approximately 18 years of age, but may be later in those with learning difficulties.[29]

Non-Compliance with Therapy

Several studies have identified an increase in non-adherence to medication and hospital visits following transfer to adult clinics, leading to graft loss and the need for re-transplantation in transplant survivors.[29,30] The causes are complex and include the difficulties that young people experience in the psychosocial journey from childhood to adulthood, their need to become self-reliant, and the different approach between adult and paediatric care.[30,31]

The management of non-adherence is difficult and relies on a non-judgemental approach with efforts to improve education, social functioning, and behavioural strategies to encourage self-motivation. In order to ensure a successful transfer to adult care, it is essential to establish a transition team with key workers and trained personnel to manage the process. Support of the adolescent patient is crucial and requires a multidisciplinary approach, including a supportive adult provider.[32]

CONCLUSION

Advances in medical and surgical management have transformed outcomes for children with liver disease, meaning most survive into adult life. Adult providers should be aware of the relevant issues and understand the basis of paediatric liver disease in order to provide optimum care.

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