15.24.7 Liver and biliary diseases in infancy and

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15.24.7 Liver and biliary diseases in infancy and childhood 3191 15.24.7 Liver and biliary diseases in infancy and childhood Richard J. Thompson ESSENTIALS Most liver diseases that occur in adults also occur in children, but some present almost exclusively in early childhood. Neonatal jaun- dice is common and usually short-lived. Onset before 24 h, or con- tinuation beyond 2 weeks, strongly suggests an underlying pathology. Biliary atresia is an important cause, with surgery and liver transplant- ation allowing many patients to survive to adolescence and adult- hood. Some genetic causes of cholestasis (e.g. MDR3 deficiency) can present in adults. A long list of metabolic disorders present with evidence of liver involvement, with later manifesting diseases including those with ac- cumulation of material in the liver. Liver transplantation is an excel- lent treatment for many of these disorders, and a growing number of metabolic disorders that do not cause liver disease per se are now being successfully managed through liver replacement, with patients surviving into adult life. Introduction Nearly every liver disease that occurs in adults also occurs in chil- dren. However, there are important liver diseases that present almost exclusively in early childhood and others where the presentation and treatments are notably different from those seen later in life. The year of life with the highest likelihood of presentation with liver disease is the first. In most cases, the connection to the mother, via the placenta, prevents liver disease causing problems before birth, although antenatal-onset liver failure and even cirrhosis have been documented. The diseases with the greatest differences from those seen in adult life are discussed here. Neonatal cholestasis Neonatal jaundice is common. The overwhelming majority is unconjugated and short-lived. Onset before 24 h, or continuation beyond 2 weeks, strongly suggests an underlying pathology. However, if more than 20% of the bilirubin is conjugated at any stage, underlying liver disease is sufficiently likely to require investigation. Pigment in neonatal stool is derived almost exclusively from bile, and newborn urine is colourless. Pale stools and dark urine are therefore the clinical features most suggestive of neonatal cholestatic liver disease.

Biliary atresia Biliary atresia is the most common diagnosis underlying neonatal cholestasis and it is the exclusion of this diagnosis that drives much of the investigation of these babies. The cause is unknown, but sev- eral different underlying aetiologies may result in a very similar clin- ical phenotype. Several common viruses, including cytomegalovirus, have been implicated, although their exact contribution is still unclear. The car- dinal feature is an inflammatory sclerosis, usually involving the en- tire biliary tree. Complete occlusion is usually limited to the hepatic bile ducts, but this does cause acholic stools. Intraoperative cholangiography comes closest to being a diag- nostic test. A decision in favour of surgery is usually arrived at using a combination of investigations, which do vary depending on local facilities. Ultrasonography, in highly skilled hands, can be strongly suggestive. Although invasive, percutaneous liver biopsy is per- formed in most cases and usually reveals highly suggestive features (Fig. 15.24.7.1). The adoption of the Kasai portoenterostomy dramatically changed the outlook for babies with biliary atresia, and when combined with the availability of liver transplantation has improved 2-year survival from less than 5% to greater than 90%. In addition to surgery, several anti-inflammatory agents have been tested in this condition, though none have yet been shown to improve disease outcome. α1-Antitrypsin deficiency The PiZ allele for the SERPINA1 gene is widely distributed, but the frequency is greatest in northern Europe such that homozy- gotes are as common as 1 in 3000 individuals in several countries. Only approximately 10% of such individuals present with neonatal cholestasis. Within that group, the outcome of the disease is also highly variable, with a quarter progressing rapidly and needing early liver transplantation. It remains quite unclear why there is such variable presentation and outcome among individuals who are all homozygous for the same allele. Truly effective treatment for patients presenting in infancy will require inhibition of the polymerization of the mutant protein and a significant increase in serum levels. While such targeted therapy is awaited, the severe group require liver replacement, with a much larger cohort going on to develop chronic liver disease. At presentation, α1-antitrypsin deficiency can appear very similar to biliary atresia and needs to be excluded before surgery in Fig. 15.24.7.1 Histological appearances of biliary atresia, showing marked portal tract expansion, bile duct proliferation, and bile plugs (haematoxylin and eosin, original magnification ×100). Image courtesy of Dr Maesha Deheragoda.

section 15 Gastroenterological disorders 3192 high-prevalence areas. Serum levels of α1-antitrypsin are unreliable in excluding the diagnosis, which should be based on isoelectric fo- cusing or genetic testing. Genetic cholestasis Several multisystem syndromes associated with neonatal-onset cholestatic liver disease have been described. In addition, a rapidly growing number of defective genes have been found to underlie cholestatic disorders with onset in all age groups (Table 15.24.7.1). Syndromic cholestasis Alagille syndrome was defined clinically with a phenotype including intrahepatic cholestasis with a variable spectrum of other features, notably involving the facies, heart, eyes, and bones. The defect lies in the Notch signalling pathway, with most patients having heterozygous mutations in Jagged 1, a Notch ligand. A few patients instead have mu- tations in NOTCH2. The mutations are not fully penetrant, with family members having partial, sometimes trivial, phenotype. Mutations in NOTCH2 are probably less penetrant than those in JAG1. The com- bination of cardiac disease, notably peripheral pulmonary stenosis, with end-stage liver disease can make these patients particularly diffi- cult to manage and may preclude liver transplantation. Nonsyndromic cholestasis Progressive familial intrahepatic cholestasis is a useful clinical de- scription which has been steadily unravelled into distinct pheno- types following the discovery of different genetic defects. However, in each case it has also become clear that there are later-onset vari- ants, and that even presentation in adulthood does not preclude

progression to end-stage liver disease. For most diseases there is a reasonable genotype/phenotype correlation, with severe early-onset disease being associated with severely damaging mutations on both alleles. Milder disease results from more subtle variants, or in some cases mutations only on one allele. The bile salt export pump (BSEP) is the main transporter of bile salts from the hepatocyte into bile. Complete failure of bile acid transport leads to severe, unremitting liver disease, with extreme pruritus. Presentation is in the first few months of life, with giant cell hepatitis (Fig. 15.24.7.2) and normal serum levels of γ glutamyl transferase. Severe BSEP deficiency has a 15% risk of hepatocellular carcinoma formation, most occurring in the first 5 years of life. Individuals with no BSEP protein are at three times greater risk than other BSEP-deficient patients. The same group are also at risk of post-liver transplantation graft dysfunction due to alloantibodies blocking the function of BSEP in the donor organ. Table 15.24.7.1 Major genetic causes of cholestasis Disease Genes Inheritance Protein Characteristic liver features Extrahepatic features Notes Alagille syndrome JAG1 or NOTCH2 AD Jagged 1 or Notch 2 Paucity of bile ducts Cardiac, ophthalmic, renal, intestinal, pancreatic Cardiac diseases may determine prognosis. Subtle immune dysfunction ARC syndrome VPS33B or VIPAS39 AR VPS33B or VIPAR Failure of polarization of hepatocytes Arthrogryposis, renal dysfunction, and ichthyosis NISCH CLDN1 AR Claudin 1 Sclerosing cholangitis Ichthyosis TJP2 deficiency TJP2 AR TJP2 (ZO2) Abnormal tights junctions on TEM Possibly gastrointestinal and neurological Hypercholanaemia through to PFIC Neonatal sclerosing cholangitis DCDC2 AR DCDC2 Hypoplastic sclerotic biliary tree, bile duct proliferation on biopsy Minimal renal involvement BSEP deficiency ABCB11 AR BSEP Giant cell hepatitis None HCC, post-transplant alloantibodies MDR3 deficiency ABCB4 AR or AD MDR3 Small duct cholangiopathy, ICP None Clinical presentation can be late. HCC and cholangiocarcinoma FIC1 deficiency ATP8B1 AR FIC1 Bland cholestasis Gastrointestinal, pancreas, renal Variable phenotype complicates liver transplant AR, autosomal dominant; AD, autosomal recessive; HCC, hepatocellular carcinoma; ICP, intrahepatic cholestasis of pregnancy; PFIC, progressive familial intrahepatic cholestasis; TEM, transmission electron microscopy. Fig. 15.24.7.2 Histological appearances of BSEP deficiency, showing multinucleated giant cell transformation, a nonspecific feature of severe cholestasis is young children (haematoxylin and eosin, original magnification ×200). Image courtesy of Dr Maesha Deheragoda.

15.24.7 Liver and biliary diseases in infancy and childhood 3193 Multidrug resistance protein 3 (MDR3) is a transporter, similar to BSEP, but essential for the entry of phospholipids into bile. A re- duction in MDR3 function leads to reduced lipids and increased free bile acid concentrations in bile. This results a cholangiopathy, which may be microscopic and not radiological. Mild cases show signifi- cant improvement with ursodeoxycholic acid. Individuals with biallelic mutations generally present in childhood. Those with re- duced function from both alleles, or even just complete loss of func- tion from one allele, can present with progressive liver disease in adulthood. Both hepatocellular carcinoma and cholangiocarcinoma complicate late disease. Familial intrahepatic cholestasis 1 (FIC1) is a protein that con- tributes to the maintenance of plasma membrane lipid asymmetry. Deficiency of this transporter leads to cholestasis and abnormal- ities in other epithelia, including diarrhoea, pancreatic and renal tubular dysfunction, and deafness; all to a very variable degree. The multisystem nature of the disease means that liver transplantation is much less satisfactory than in the previous two conditions. The liver parenchyma is a polarized epithelium with some of the transport processes described previously contributing to the vectorial transport from blood to bile. The canalicular space is the apical domain of the epithelium. This space is separated from the basolateral space by an array of cell–cell junctional com- plexes. The

most apical component of these structures are the tight junctions, themselves largely composed of claudins. Mutations in claudin 1 result in the syndrome of neonatal ichthyosis and scler- osing cholangitis. Mutations in tight junction protein 2, which is a cytoplasmic component of these structures, underlies a spectrum of diseases spanning isolated hypercholanaemia and severe early-onset liver disease. Numerous defects in cilia formation or function have been shown to underlie a range of diseases usually manifesting as renal and hep- atic phenotypes. Fibrocystic disease of the liver is strongly associ- ated with autosomal recessive polycystic kidney disease. Mutations in DCDC2 have recently been associated with neonatal sclerosing cholangitis, along with minimal renal involvement. Management of cholestasis Much of the management of cholestatic liver disease revolves around minimizing the impact of the disease on the rest of the child. Treatment is therefore centred on vitamin supplementation and nu- trition. Liver transplantation has always been the fallback option, especially in the conditions where the disease is isolated to the liver. Depletion of bile acids has, however, been attempted by various means to alleviate pruritus, but also in the hope of changing the natural history of the disease. The most common option is partial external biliary diversion through creation of a fistula between the anterior abdominal wall and the gall bladder. The proportion of pa- tients in which this works varies between diseases, but might be as high as two-thirds. Pharmacological alternatives to this surgery may become available. Neonatal liver failure Neonatal liver failure is probably significantly underdiagnosed. In very sick newborns with multiorgan failure, it is often unclear where the primary problem lies. Equally, some of the causes of neonatal liver failure are in fact part of a multisystem disease. Many cases still do not have a diagnosis and may well reflect undiagnosed meta- bolic disorders or are the consequence of infection, viral or other- wise. Liver biopsy is rarely a diagnostic option and other modalities are relied upon. Other than support of the multisystem failure, the key questions are whether a diagnosis with a specific treatment can be made, and equally if there is a contraindication to liver transplantation. Gestational alloimmune liver disease This condition was called neonatal haemochromatosis for many years, its diagnostic features being iron deposition in multiple or- gans with severe liver damage of antenatal onset. Although the exact disease mechanisms have not been established, there is good evi- dence that transplacental maternal alloantibodies are implicated. Exogenous immunoglobulin during subsequent pregnancies dra- matically reduces the severity of the disease, which otherwise re- curs in greater than 70% of cases. Iron may be an epiphenomenon. Liver transplantation is an excellent, though extremely challenging, treatment. Haemophagocytic lymphohistiocytosis Isolated bone marrow failure may be the only manifestation of haemophagocytic lymphohistiocytosis, but multisystem disease often presents with liver failure. Haemophagocytosis may be seen in the bone marrow of acutely sick patients of any age. However, in the newborn period this is usually due to a recessive genetic defect. Mutations in the perforin gene (PRF1) are the most common causes and highlight the fact that the underlying defect is in T lymphocytes, although it is macrophages that are seen to be causing the damage. Treatment requires immunosuppression and bone marrow trans- plantation. Liver transplantation is not indicated. In addition to gestational alloimmune liver disease and haemophagocytic lymphohistiocytosis, which are particular to new- born infants, neonatal liver failure can be the result of any number of infectious agents, and several of the metabolic diseases discussed in the following sections. The most noteworthy infectious cause is herpes simplex infection which is very often multisystem in nature and associated with very poor survival. Metabolic liver disease A long list of metabolic disorders present with evidence of liver in- volvement, particularly in the first few months of life. Clinical pres- entation can be through failure of energy supply, hepatocellular synthetic failure, or failure of clearance of toxic metabolites, the most evident being jaundice. Later

manifesting diseases include those with accumulation of material in the liver. Liver transplant is an excellent treatment for many of these disorders; indeed, a growing number of metabolic disorders that do not cause liver disease per se are now being successfully managed through liver replacement. Galactosaemia Galactosaemia results from a deficiency of galactose-1-phosphate uridyltransferase. Clinical presentation varies between jaundice or hypoglycaemia, and multiorgan failure. In many countries, the disease is included in neonatal screening programmes, though not

section 15 Gastroenterological disorders 3194 in the United Kingdom. The diagnosis should be made through measurement of galactose-1-phosphate uridyltransferase activity in peripheral red blood cells. Management of the presenting illness should probably be followed by lifelong exclusion of lactose from the diet, though the degree to which this is necessary in adults is not completely clear. Tyrosinaemia type 1 Tyrosinaemia type 1 results from deficiency of fumarylacetoacetate hydrolase, the final step in the tyrosine degradation pathway. Presentation is with a variable degree of liver dysfunction, often with relatively mild jaundice. The disease is caused by toxic intermediate metabolites, notably fumarylacetoacetate and succinylacetone. Detection of the latter in the urine is the most utilized diagnostic test. Untreated, severe liver and renal disease is often complicated by early hepatocellular carcinoma. Treatment has been revolutionized by the introduction of nitisinone, which inhibits 4-hydroxyphenylpyruvate dioxygenase upstream in the metabolic pathway, effectively changing the dis- ease to the much milder tyrosinaemia type 3. Dietary restriction of tyrosine is still required, and hepatocellular carcinoma is not com- pletely prevented, but outcomes have been markedly improved. Early treatment has been shown to be beneficial; hence, a strong case for neonatal screening for this condition has been made. Glycogen storage diseases Glycogen storage diseases are a heterogeneous group of conditions. In the majority of hepatic manifesting forms, the intracellular re- tention of glycogen and the consequent inability to release glycogen during hypoglycaemia are the cardinal features. Types I, III, VI, and IX manifest the classical phenotype, though with different degrees of severity. In most cases, the management focuses on prevention of hypoglycaemia. The avoidance of hepatic adenomas is a major driver to improve control. Of these four types only type III is associ- ated with significant muscle involvement. Glycogen storage disease type IV results from a lack of the glycogen branching enzyme, and results in both cirrhosis and myocardial disease. Mitochondrial disease Although mitochondria contain their own genome, most of the genes required for mitochondrial assembly and function are en- coded by nuclear DNA. Most mitochondrial cytopathies presenting in early life are due to recessive mutations in nuclear genes. Enzymes involved in the respiratory chain are themselves encoded by mul- tiple genes, some nuclear and some mitochondrial. Other defects are in proteins required for mitochondrial DNA replication and result in mitochondrial DNA depletion; these, however, are still usually nuclear. The management of mitochondrial cytopathies is particu- larly difficult because of their multisystem involvement. Liver disease in older children Autoimmune liver disease Autoimmune disease can present at any age but most frequently presents early in the second decade. Subclassification is possible on clinical and serological grounds, and is important in terms of outcome and complications. Autoimmune hepatitis may be diag- nosed in the absence of cholangiopathy and is associated with other autoimmune disorders and inflammatory bowel disease, each in approximately one-fifth of cases. Autoimmune hepatitis type 1 may be diagnosed in the presence of antinuclear and smooth muscle antibodies, but in the absence of liver–kidney microsomal antibodies. Autoimmune hepatitis type 2 more frequently presents with acute liver failure and is diagnosed by the presence of liver–kidney microsomal antibodies. Autoimmune sclerosing

cholangitis has an antibody profile similar to autoimmune hepatitis type 1, but includes a cholangiopathy. The typical histology is shown in Fig. 15.24.7.3. The latter disease is associated with other autoimmune disorders and inflammatory bowel disease in approxi- mately half of cases. That the three conditions are distinct entities is reinforced by different HLA associations. Autoimmune liver disease in children is treated with immunosup- pression, usually consisting of oral prednisone, though the addition of steroid-sparing agents such as azathioprine or mycophenolate mofetil is common. Ursodeoxycholic acid is added in the case of autoimmune sclerosing cholangitis. Biochemical and serological remission can be achieved in most cases of autoimmune hepatitis. Immunosuppression can be withdrawn in a substantial minority of type 1 individuals, but rarely in type 2. In autoimmune sclerosing cholangitis, the inflammatory component may be brought under control but ultimately liver transplantation is still required if the underlying damage is severe. Cystic fibrosis Cystic fibrosis is a multisystem disorder characterized by abnor- malities of anion distribution at multiple epithelia. Presentation in infancy is usually with gastrointestinal or respiratory symptoms, though very small numbers present with neonatal jaundice. Patients with hepatic involvement more frequently present later in the first decade with signs of chronic liver disease, notably with portal hypertension and splenomegaly. In most cases, endoscopic manage- ment of portal hypertension is the mainstay of treatment. Splenic
Fig. 15.24.7.3 Histological appearances of autoimmune hepatitis, showing interface hepatitis with lymphoplasmacytic infiltration (haematoxylin and eosin, original magnification ×100). Image courtesy of Dr Maesha Deheragoda.

 embolization has been advocated but is not widely employed. A few patients with cystic fibrosis have now been successfully treated using multiorgan transplantation. For most, their liver disease along with pancreatic insufficiency is largely managed through nutritional supplementation. Wilson disease Wilson disease results from the accumulation of copper in the liver and other organs, notably the central nervous system, as a conse- quence of a functional lack of the Wilson disease protein encoded by ATP7B. Most paediatric patients with Wilson disease present with liver disease, half with chronic liver disease and half with acute liver failure (although the latter is acute on chronic). Numerous diagnostic strategies have been used, reflecting the fact that none are perfect. Caeruloplasmin levels are typically low, but are normal in 20% of cases. Urinary copper excretion, before and after exposure to penicillamine, has been widely used, but is relatively compli- cated and not completely specific. Similarly, liver copper content measurement can be extremely useful, but patients with chronic cholangiopathy can be indistinguishable by this method. Genetic testing is now widely used, and is highly sensitive and specific. The cost and time taken for testing have both fallen significantly. Medical treatment for Wilson disease is very effective, using penicillamine or trientine. Zinc has been used in combination with chelators, separating the oral dosing, but its use as monotherapy is controversial. In the context of acute liver failure, medical therapy may be insufficient to reverse the damage and liver transplantation is required. A scoring system has been widely used to predict the need for transplantation in this context. Transition to adulthood Adolescence is a difficult enough period without the addition of chronic disease. Diseases which require daily medication for main- tenance relapse significantly more often in adolescents. Those with autoimmune disease and transplant recipients cause the greatest concern, but for all patients a planned approach, not only to see them through this period but also to prepare them for adult life, has been shown to make a difference. Transition is not a point in time but rather a period of life through which some can pass much more quickly than others. FURTHER READING Liberal R, et al. (2016). Cutting edge issues in autoimmune hepatitis. J Autoimmun, 75, 6–19. Taylor SA, Whitington PF (2016). Neonatal acute liver failure.

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