Deirdre Kelly
Khalid Sharif
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Editors

Atlas of Pediatric Hepatology

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ISBN 978-3-319-69528-0 ISBN 978-3-319-69529-7 (eBook)
https://doi.org/10.1007/978-3-319-69529-7

Library of Congress Control Number: 2018935681

Printed on acid-free paper

This Springer imprint is published by the registered company Springer International Publishing AG part of Springer Nature
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To all the children and families from whom we have learnt so much

Preface

Pediatric liver disease is a significant cause of morbidity and mortality worldwide. Recent advances in molecular genetic techniques and research into genomics and proteomics have extended our understanding of pathophysiology and provided opportunities for targeted therapy.

Advances in diagnosis and treatment, particularly the successful development of transplantation, have dramatically improved the outcome of infants and children with liver, bowel and renal disease so that many can now expect to grow into adult life.

Despite these advances, the recognition of the physical signs and symptoms of liver and other diseases remains an essential part of diagnosis, investigation and management.

The purpose of this atlas is to provide a summary of the key clinical signs and symptoms of liver disease and indicate how best to diagnose and treat them.

The book should interest adult gastroenterologists and hepatologists, both specialist and general paediatricians and trainees as well as those providing guidance to nurses and allied health professionals.

Birmingham, UK — Deirdre Kelly

Acknowledgement

The investigation and management of paediatric liver disease require skill, compassion and a dedicated multidisciplinary approach. We are indebted to our colleagues in the Liver Unit, in Birmingham Women's & Children's Hospital and elsewhere in the world for their expert knowledge and help with this book, which we hope will aid the management of children with liver disease everywhere.

We are particularly grateful to Dr. Rachel Brown for contributing all the pathology pictures and text and sharing her unique expertise; to Dr. Mani Thyagarajan who provided all the radiology pictures, text and their interpretation.

Very special thanks also to Dr. David Milford who wrote the chapter on Liver and Renal Disease.

Contents

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The Jaundiced Baby

1

Jane Hartley

Jaundice is common in the neonate and up to 60% of babies are jaundiced. The most common cause is physiological jaundice which resolves by day 14. Continuing jaundice after 14 days (21 days in preterm infant) requires urgent investigation. Those who are found to have unconjugated jaundice (indirect hyperbilirubinemia) should be investigated for hypothyroidism, urinary tract infection and haemolysis.

Those who have conjugated hyperbilirubinaemia (direct hyperbilirubinemia) >20 μmol/l have liver disease and should be discussed with a hepatology centre to guide further management. There is a wide differential diagnosis (Table 1.1) but the optimal management of biliary atresia, the commonest single cause of neonatal liver disease, is time dependent, hence the need for urgent referral.

The main presenting features to consider are conjugated jaundice, pale stools (Fig. 1.1), dark urine, failure to thrive and bruising or bleeding. Pale stools are found in biliary atresia and choledochal cysts, in which there is obstruction to the biliary tree, or in diseases in which biliary excretion is reduced such as in alpha 1 antitrypsin deficiency, Alagille syndrome or progressive familial intrahepatic cholestasis (PFIC).

Table 1.1 Common differential diagnosis of infant conjugated hyperbilrubinemia

Differential diagnosis	Investigation	Specific treatment
Biliary atresia	Ultrasound, intra operative cholangiogram	Kasai portoenterostomy
Choledochal cyst	Ultrasound, MRCP	Hepaticojejunostomy
Alpha-1-antitrypsin deficiency	Level Protein phenotype (PiZZ)	General management of cholestasis (see below)
Hypothyroidism/hypopituitarism	Thyroid function test (TFT), cortisol, glucose	Replace hormone deficiency
Galactosaemia	Urine reducing substances, Gal-1-Put level in serum	Lactose free diet
Tyrosinaemia type 1	Urine succinyl acetone DNA for mutations	Nitisone, low tyrosine diet
Alagille syndrome	Dysmorphism, peripheral pulmonary stenosis on ECHO, butterfly shaped thoracic vertebrae on x-ray, posterior embryotoxon on eye examination, DNA for *JAG1 or NOTCH2*	General management of cholestasis and pruritus
Congenital infection e.g., Toxoplasma Cytomegalovirus Herpes Simplex	Serology urine and blood PCR	Supportive management Ganciclovir may be beneficial for congenital CMV
Progressive familial intrahepatic cholestasis type 1, 2 and 4	Low GGT, specific liver histology, genetics (*ATP8B1*, *ABCB11*, *TJP2*)	General management of cholestasis and pruritus
Progressive familial intrahepatic cholestais type 3	Mutations in ABCB4	General management of cholestasis
Storage disease e.g. Niemann Pick C	Enlarged spleen, storage cells on bone marrow and liver biopsy (can be difficult to see in young children), genetics (*NPC1 & 2*), Filipin staining of fibroblasts	General management of cholestasis
Neonatal hepatitis	Diagnosis of exclusion and hepatitis on liver biopsy	General management of cholestasis
Intestinal failure associated liver disease	History of intestinal failure, specific findings on liver biopsy	Ursodeoxycholic acid, encourage enteral diet, prompt treatment of sepsis

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D. Kelly et al. (eds.), *Atlas of Pediatric Hepatology*, https://doi.org/10.1007/978-3-319-69529-7_1

Fig. 1.1 This pale stool is from a 5 weeks old baby with conjugated jaundice associated with low GGT. With intensive nutritional support his liver biochemistry, stool colour and growth have completely normalised

1.1 Biliary Atresia

This child with biliary atresia was referred at 4 weeks of age with conjugated bilirubin 103 μmol/l (0–18 μmol/l), GGT 560 IU/l (0–12 IU/l) and pale stool. Following a 4 h starve, an ultrasound scan of the abdomen showed an abnormally small gallbladder (Fig. 1.2) which is suggestive of biliary atresia.

Developmental anomalies of polysplenia (Fig. 1.3), absent IVC and preduodenal portal vein, congenital cardiac disease and situs inversus occur in up to 20% of infants with biliary atresia, the biliary atresia splenic malformation syndrome (BASM).

If the stool colour is equivocal a radionucleotide excretion scan (TiBIDA) (Fig. 1.4) (with 3 days of phenobarbitone pre-treatment) may demonstrate the lack of excretion of bile from the liver. The diagnosis is confirmed by demonstrating biliary obstruction with an intraoperative cholangiogram (Fig. 1.5).

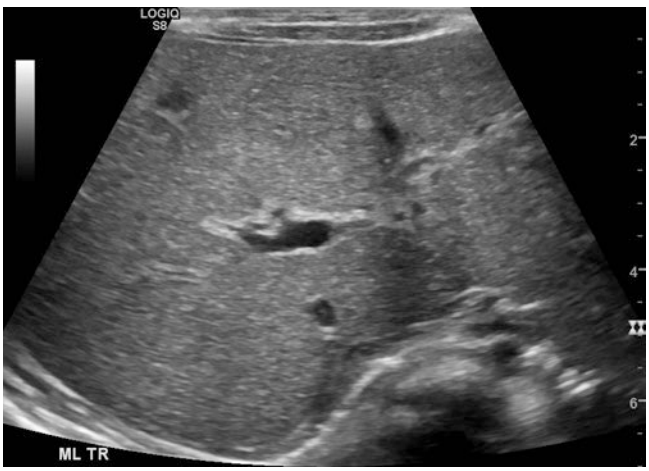

Fig. 1.2 Ultrasound sagittal section of the liver and gall bladder fossa reveals a small abnormally shaped gall bladder (less than 1.9 cm in length)

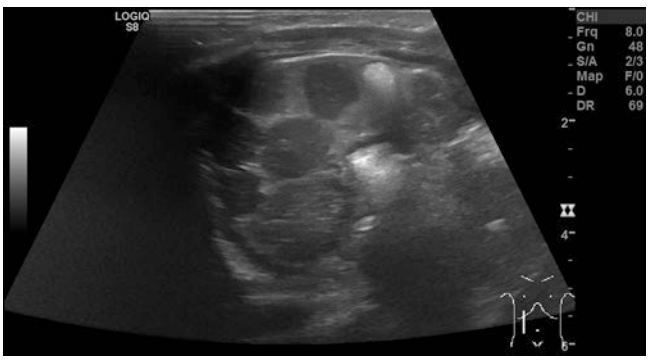

Fig. 1.3 Ultrasound coronal section of the right upper abdomen reveals multiple splenunculi in keeping with polysplenia

Treatment is the Kasai portoenterostomy which is a palliative surgical procedure for biliary atresia which re-establishes bile flow by removing the sclerosed section of the biliary tree (Fig. 1.6), cutting into the liver to find an area with patent bile ducts and suturing a jejunal roux loop to this area of liver (Fig. 1.7).

A liver biopsy at the time of Kasai usually shows the histological changes of cholestasis, abnormal biliary ductules and hepatic fibrosis (Fig. 1.8). Similar features are found in alpha 1 antitrypsin deficiency, severe neonatal hepatitis syndrome and progressive familial intrahepatic cholestasis type 2.

The Kasai procedure will be successful in up to 60% of cases. For those in whom bile flow is not established then liver transplant within infancy will be required. Complications following the Kasai procedure include cholangitis, the development of chronic liver disease and portal hypertension. Despite a successful Kasai porto-enterostomy, most children will require transplantation either in childhood or in adult life.

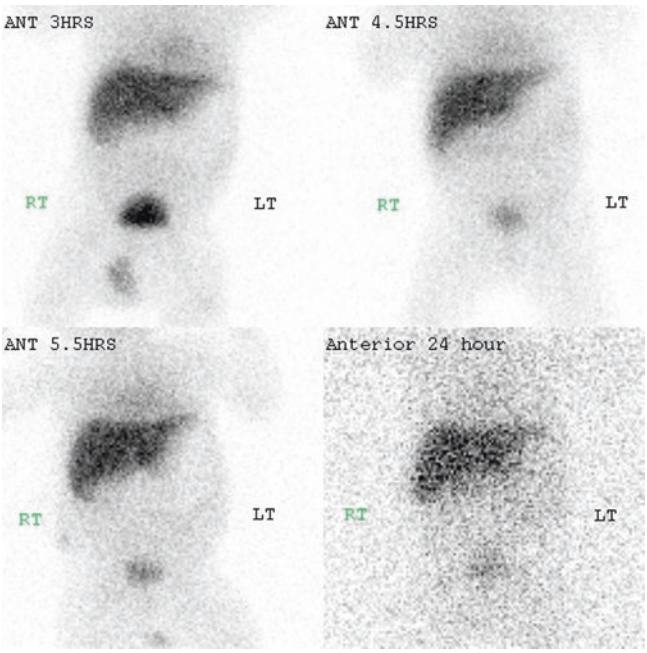

Fig. 1.4 TIBIDA scan reveals lack of delineation of gall bladder and lack of secretion in to the intestines 24 hrs after an intravenous TIBIDA injection in keeping with biliary atresia

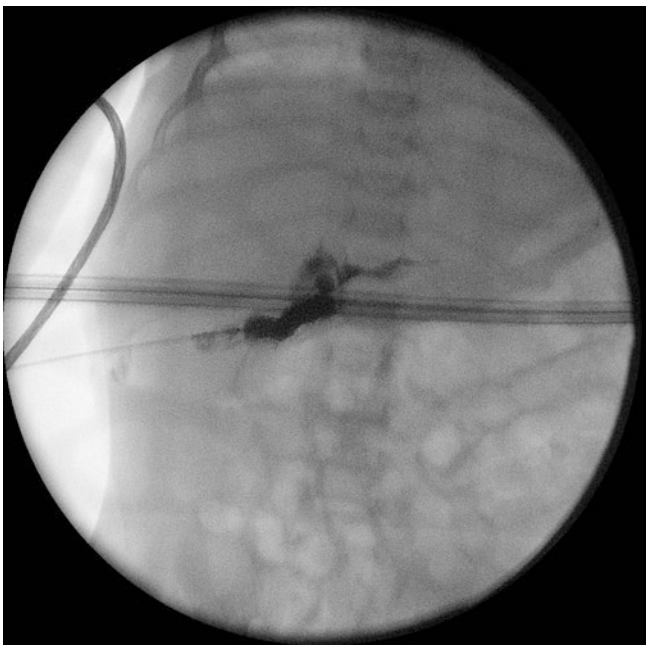

Fig. 1.5 Direct puncture of the gall bladder intraoperatively reveals lack of flow of contrast into the intra or extra hepatic biliary ducts in keeping with biliary atresia

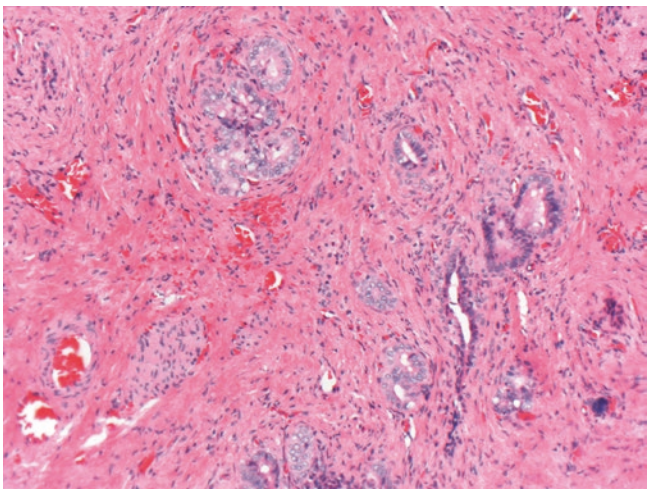

Fig. 1.6 H&E original magnification ×200. Tissue excised from the hilar plate demonstrates fibrosis with variably intense lymphocytic infiltrates, small epithelial lined ductules are seen within this but there is typically no dominant duct identifiable. Sometimes a fibrous nodule denotes a destroyed duct (not demonstrated here)

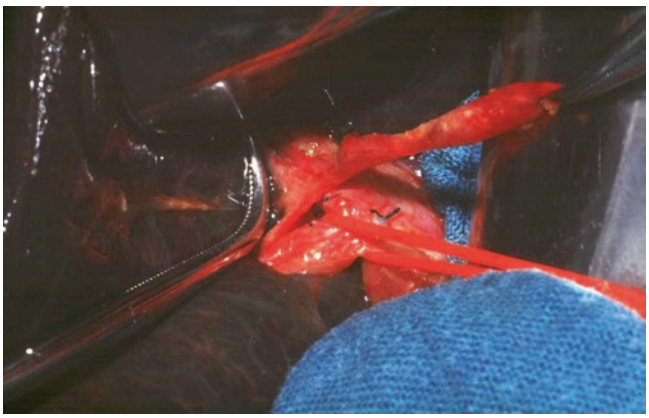

Fig. 1.7 The surgical Kasai procedure

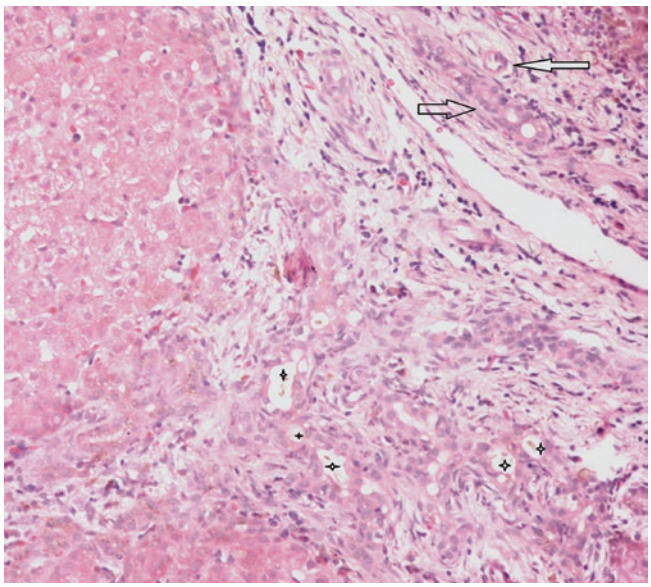

Fig. 1.8 H&E original magnification ×200. Normal portal structures are seen at the top right-hand corner of this image. The white arrow is pointing at the hepatic artery branch, adjacent to this, and of similar size, there is a slightly longitudinally sectioned bile duct (open arrow). At the periphery of the portal tract there are numerous ductules (marked with a star) and many of these contain a plug of bile. This 'biliary' appearance of the portal tract as expected in biliary atresia is a peripheral manifestation of large duct obstruction irrespective of the cause

1.2 Choledochal Cyst

It is important to exclude a choledochal cyst which may have a similar presentation to biliary atresia. Infants may present slightly later than those with biliary atresia and the symptom onset may be sudden. An MRCP (Fig. 1.9) will delineate the biliary anatomy and be diagnostic. Treatment is surgical removal (Fig. 1.10) and a portoenterostomy is formed for bile drainage. It is important to operate before biliary fibrosis develops. There is a risk of cholangiocarcinoma in untreated cysts.

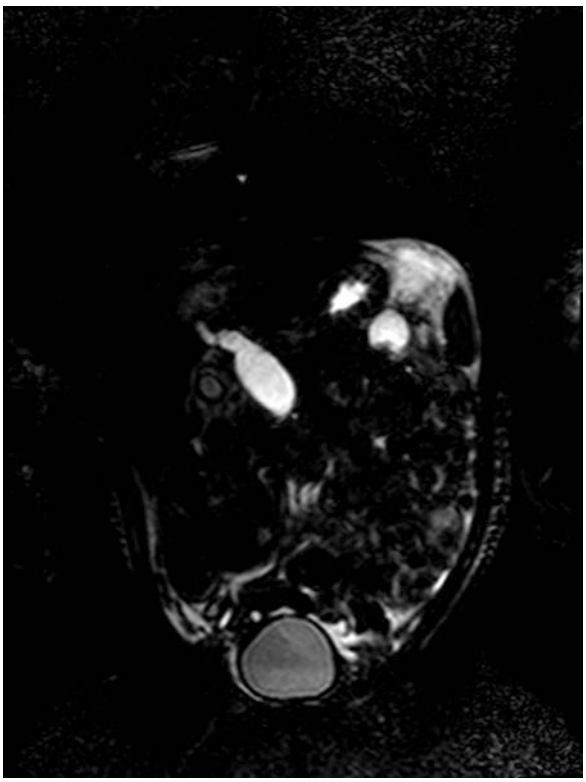

Fig. 1.9 MRCP T2 space sequence of the liver and biliary system reveals fusiform dilatation of the common bile duct in keeping with Choledochal cyst

Fig. 1.10 Macroscopic image of an excised choledochal cyst. A catheter is present in the gallbladder. The cyst has been excised in continuity with extrahepatic bile ducts. Microscopically there are no specific features, the cyst has a simple fibrous wall lined by bland biliary type epithelium which is often denuded

1.3 Alpha-1-Anti Trypsin Deficiency

This autosomal recessive disease is due to abnormalities in the Serpina 1 gene. It may present with similar features to biliary atresia with pale stools, raised conjugated jaundice, GGT and raised transaminases. The gallbladder may be small on ultrasound scan and a radionucleotide excretion scan may not show excretion. The diagnosis is made by identifying a low alpha 1 antitrypsin level and a protein phenotype of PiZZ. A liver biopsy may have a similar appearance to (Fig. 1.11) biliary atresia although DPAS positive globules are usually also seen.

The prognosis is variable as with intensive nutritional support most infants with alpha 1 antitrypsin deficiency will clear their jaundice, however some will require transplantation in infancy or in later childhood. Children require follow up to detect the complications of chronic liver disease such as portal hypertension. In adults with alph-1-antitrypsin deficiency, exposure to cigarette smoke leads to early emphysema. Therefore all families require appropriate counselling. In older patients the typical DPAS globules can be clearly seen on liver biopsy (Fig. 1.12).

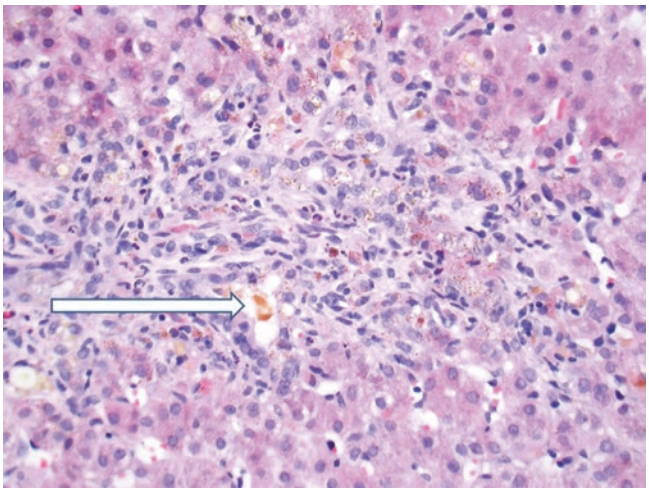

Fig. 1.11 H&E original magnification ×400. In alpha-1 antitrypsin deficiency 'biliary' features can be seen in portal tracts closely mimicking those seen in biliary atresia. The arrow is pointing to a bile plug in a ductule similar to those seen in Fig. 1.8. In the neonate the DPAS positive globules illustrated in Fig. 1.12 are not identifiable and therefore alpha-1 antitrypsin deficiency should always be considered and investigated by other means in the differential diagnosis of biliary histology. The small brown granules in this image are iron, a non-specific finding in the neonate

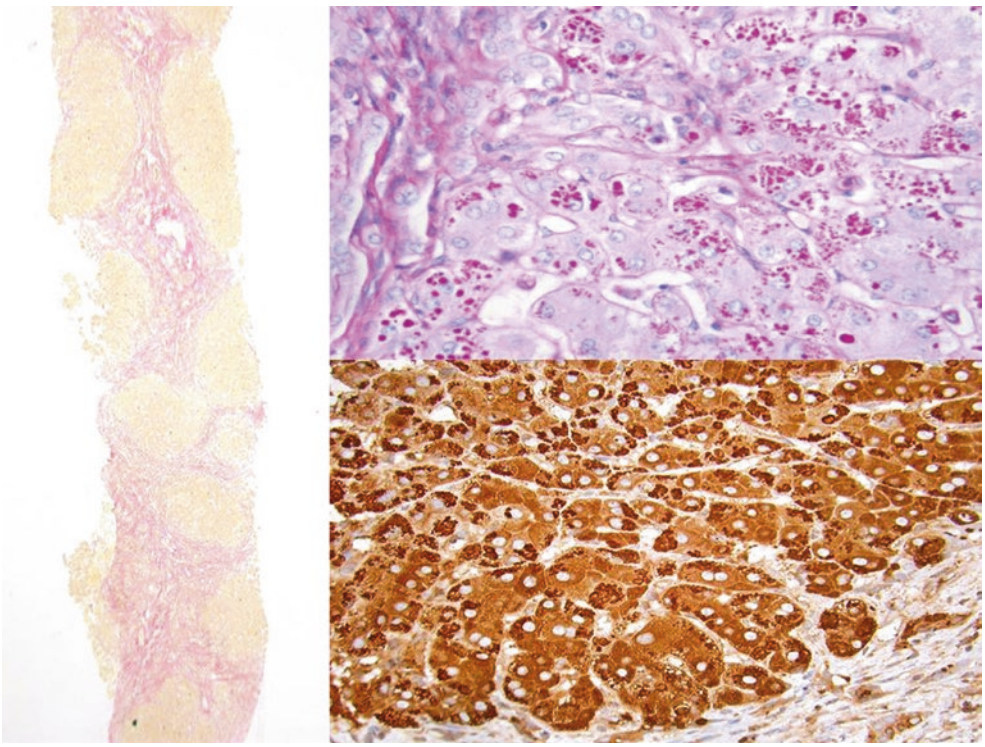

Fig. 1.12 The left hand panel is a core liver biopsy, original magnification ×25 Haematoxylin Van Gieson stain. Nodules are present indicating cirrhosis. In the top right-hand panel the DPAS stain (original magnification ×400) highlights pink/purple hepatocellular globules which are confirmed as alpha-1 antitrypsin by immunohistochemistry in the lower right-hand panel (dark brown granules)

1.4 Alagille Syndrome

Alagille syndrome is an autosomal dominant condition due to mutations in either *JAG1* or *NOTCH2*, may also mimic biliary atresia with raised conjugated hyperbilirubinaemia, high GGT and raised transaminases. The typical facial features (Fig. 1.13) become more prominent with age but can be difficult to identify in neonates. Other clinical features of Alagille syndrome include congenital heart disease with mild peripheral pulmonary stenosis, butterfly shaped vertebrae (Fig. 1.14a, b), and posterior embryotoxon of the eye.

A liver biopsy (Fig. 1.15) typically shows a reduced number of portal tracts with bile ducts. Despite good nutritional support and fat soluble vitamin supplementation, infants continue to be mildly jaundiced and develop intense pruritis and xanthomata (Fig. 1.16). Pruritus is disabling and requires significant medical management. A surgical biliary diversion procedure may improve pruritus or resolution of xanthomata.

Childhood mortality of 20–30% is related to complex congenital cardiac disease. Progression of liver disease is variable.

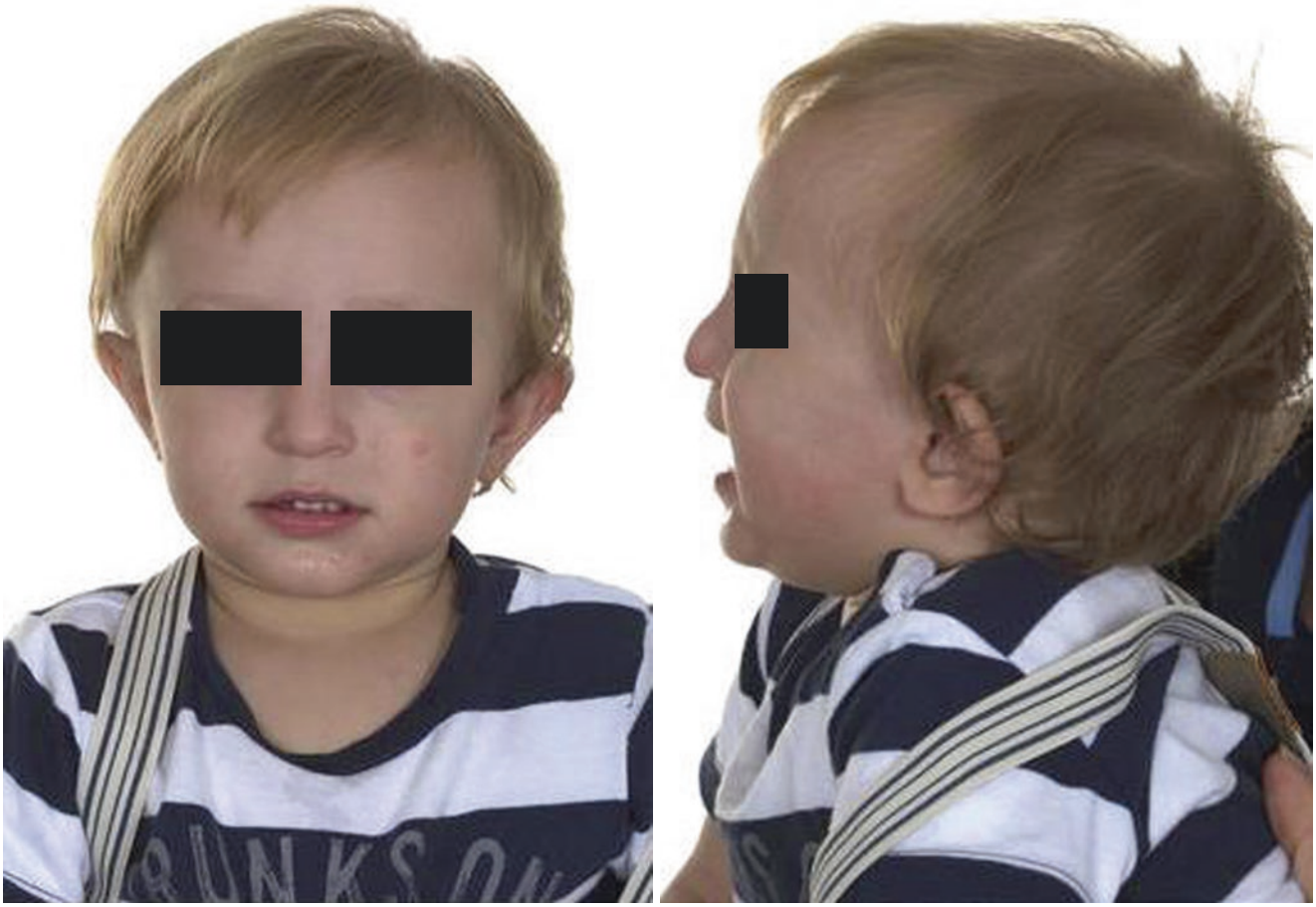

Fig. 1.13 Typical face of a child with Alagille syndrome showing a pointed chin, hypertelorism, thin nose and prominent forehead

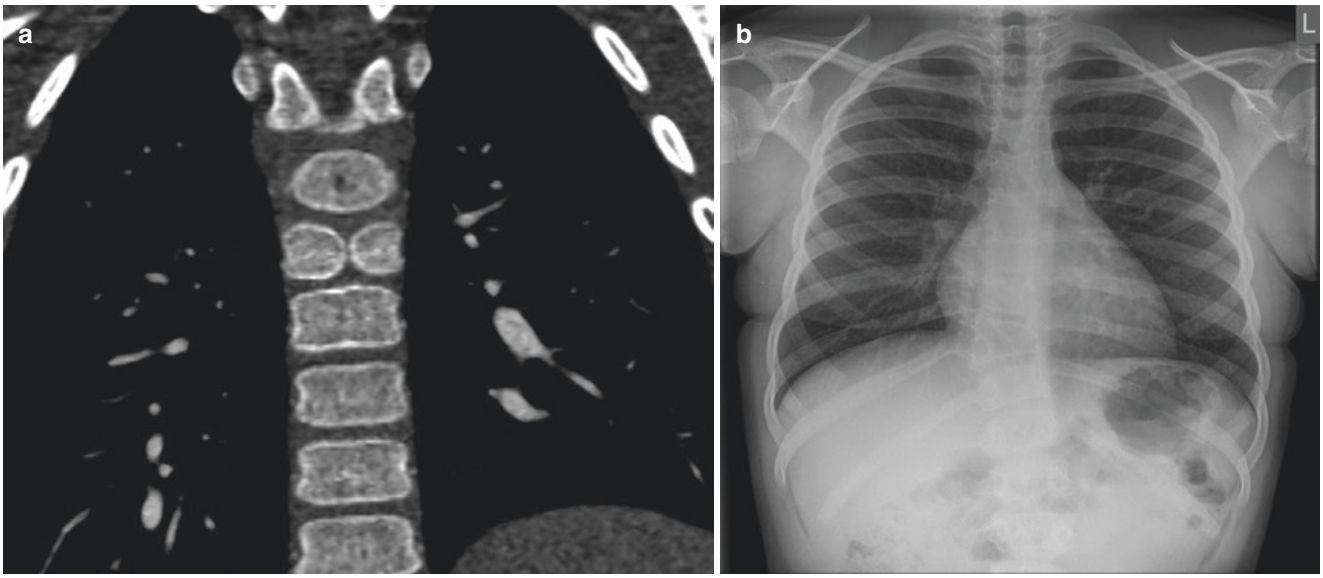

Fig. 1.14 (**a** and **b**) CT Sagittal and coronal reconstruction of thorax reveals butterfly vertebrae of T6, typically seen in Alagille syndrome. These can also be seen on plain spinal xray

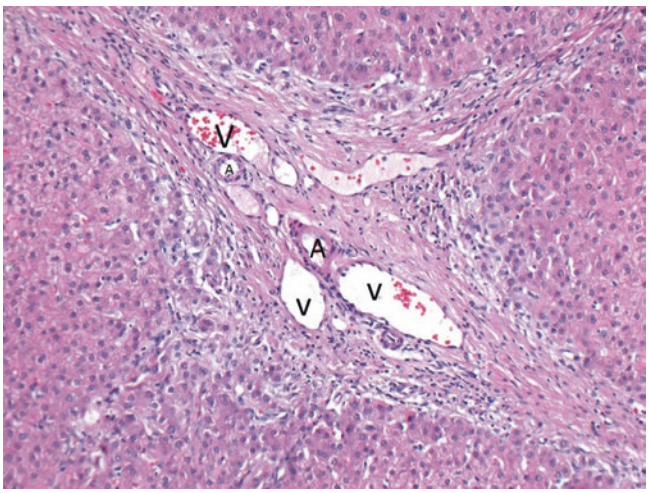

Fig. 1.15 H&E ×200. This mildly expanded portal tract contains portal vein branches 'V' and hepatic arteries 'A'. In normal portal tracts a bile duct should be seen in close proximity to, and a similar size to the hepatic artery branch. The bile duct is missing here denoting bile duct paucity. The histological appearance is identical in syndromic and non-syndromic causes

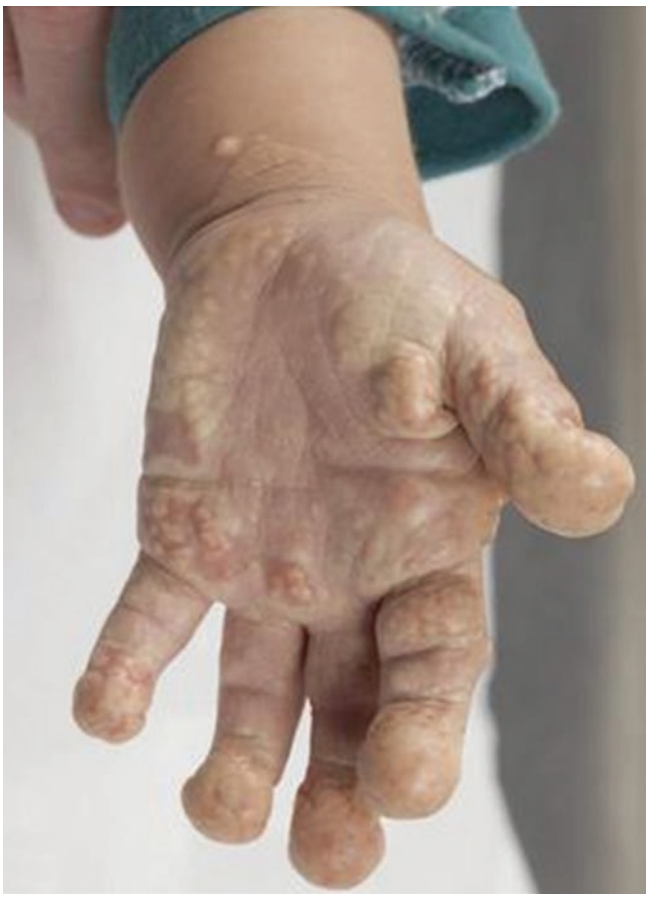

Fig. 1.16 Extensive xanthoma of the hands in an infant with Alagille syndrome

1.5 Progressive Familial Intrahepatic Cholestasis (PFIC)

Conjugated jaundice, severe pruritus, and fat soluble vitamin deficiency are clinical features of progressive familial intrahepatic cholestasis. It is a progressive disease and many will come to transplantation. Type 1, 2 and 4 are all associated with low GGT whilst type 3 has high GGT. All are involved in the transport of bile salts but have differing histological features. Mutation analysis confirms the diagnosis (Table 1.1). PFIC1 (Fig. 1.17a) is a multisystem disease, affecting the gastrointestinal tract, pancreas and hearing. Diarrhoea may be worse following transplant as bile salts now reach the intestine and cannot be reabsorbed from the ileum. PFIC2 is due to a lack of bile salt export pump (BSEP) which is visible on immunohistochemical staining of the liver (Fig. 1.17b, c). BSEP expression is confined to the liver, but the condition is associated with a risk of hepatocellular carcinoma. PFIC 4 is a multisystem disorder which involves the lungs and the neurological system (Fig. 1.17d).

Similar histological features can also be seen in severe neonatal hepatitis of unknown aetiology (Fig. 1.18) in which there is severe cholestasis which resolves with supportive therapy but with prolonged hepatic transaminitis.

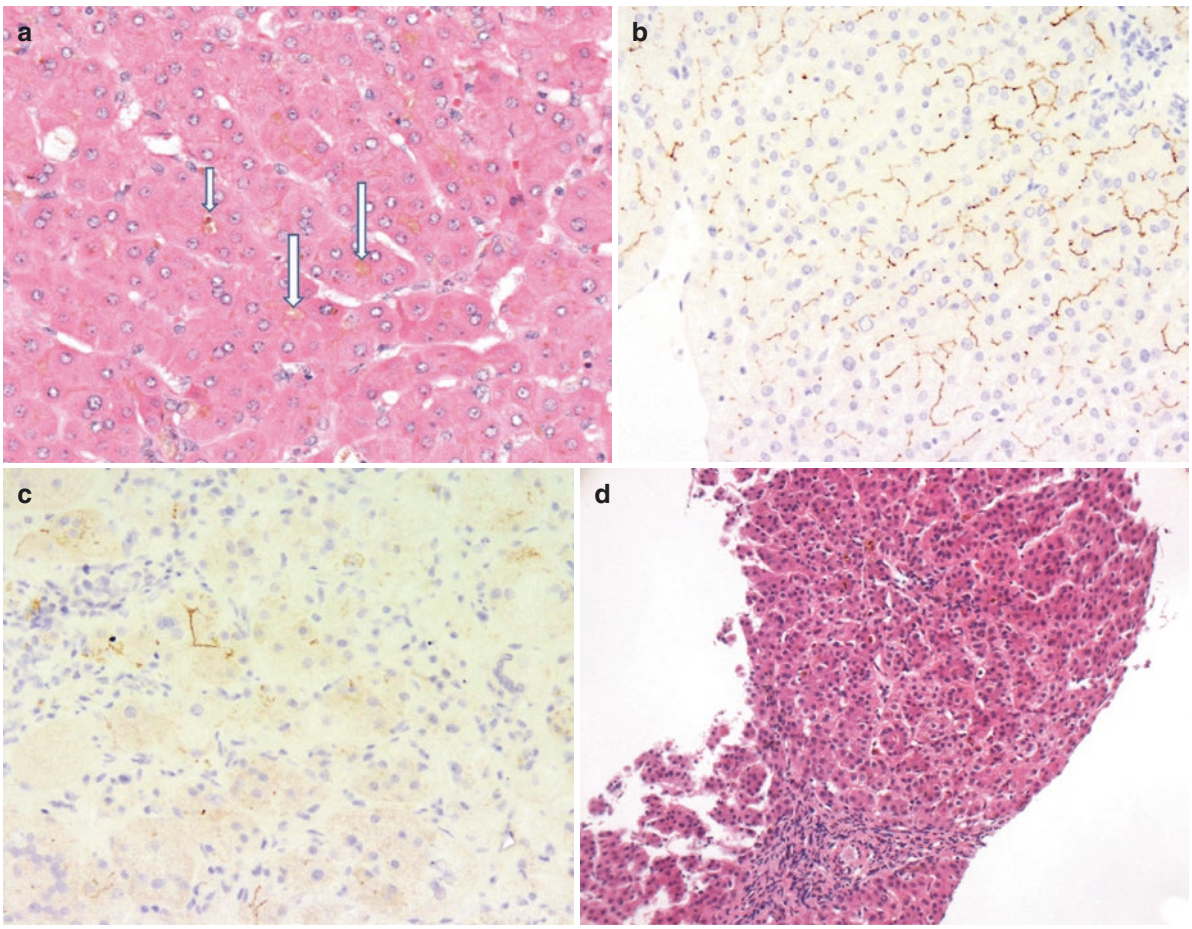

Fig. 1.17 (**a**) H&E ×400. The arrows in this image are pointing at canalicular plugs of bile. Portal tracts are normal in this case. This pattern is referred to as a 'bland cholestasis'. It is a pattern recognised to occur, usually in older individuals, as a drug reaction. In the neonate it can be an indicator of PFIC1. (**b**) Immunohistochemistry for bile salt export pump (BSEP) ×400. Canalicular enzymes can be stained by immunohistochemistry. In this control section of normal liver the delicate 'twig like' pattern of canalicular positivity can be seen. (**c**) Immunohistochemistry for BSEP ×400. In this test section a canalicular pattern of staining is seen only very focally. It should be noted that there is parenchymal disarray here in line with the neonatal hepatitis like pattern present. It is therefore important to include appropriate controls. Absence of BSEP staining is a helpful indicator of disease but there can be abnormally functioning BSEP protein even with a normal staining pattern. The presence of staining therefore does not exclude the disease. (**d**) PFIC4: H&E ×100. In this medium power image there are bile plugs within the canaliculi. There is slight parenchymal disarray. The portal tract towards the bottom of the field is rather crushed but has a slight 'biliary' appearance

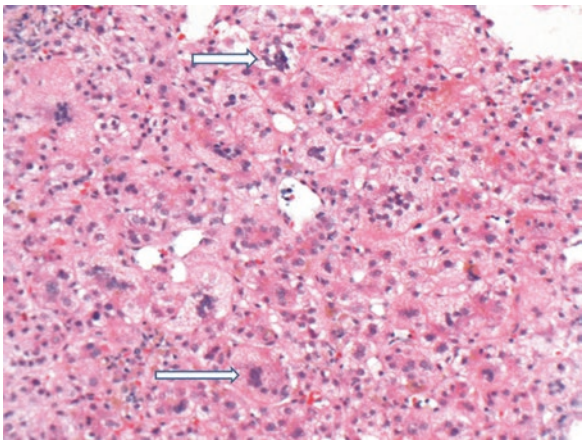

Fig. 1.18 H&E ×200. The arrows in this image are pointing to 'giant cells' which are actually multinucleate hepatocytes. They are typical of a neonatal hepatitis pattern. 'Neonatal hepatitis' is not a diagnosis but rather a description of a histological pattern. The differential diagnosis is wide including infectious and metabolic causes, often the aetiology remains unknown or can be multifactorial

1.6 Rare Causes of Neonatal Liver Disease

Niemann Pick C is an autosomal recessive disorder which causes cholesterol ester storage in the liver, spleen and brain. It may present with fetal ascites, jaundice or acute liver failure in the neonatal period and with hepatosplenomegaly and neurological involvement in older children. Paralysis of upward gaze in older children is pathognomonic. Diagnosis is confirmed by genetic analysis. The liver disease may resolve, but neurological disease progresses. Liver transplantation is contraindicated, but enzyme replacement with Miglustat may prevent progression of disease (Fig. 1.19). A jaundiced neonate in whom the cholestasis resolves but skin pigmentation develops should lead to the consideration of *McCune Albright syndrome*. This can be genetically confirmed by identifying mutations in the *GNAS* gene. A debilitating and painful complication of the condition is bone dysostosis (Fig. 1.20a, b). McCune Albright syndrome is also associated with the development of fibronodular hyperplasia and hepatoblastoma.

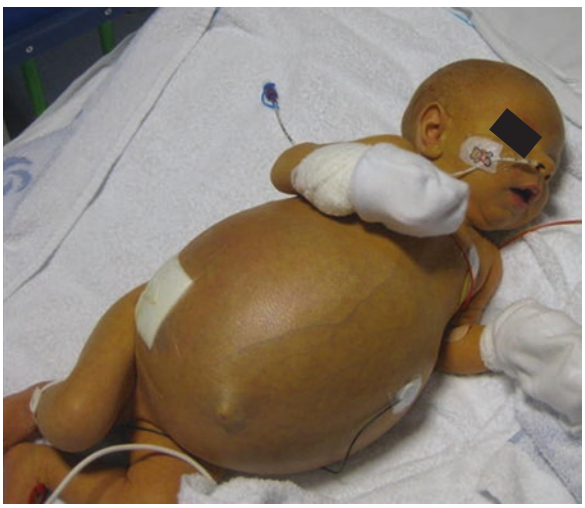

Fig. 1.19 This child initially presented with conjugated jaundice with a low GGT and failure to thrive despite nutritional management. He developed rapidly progressive liver disease and massive ascites

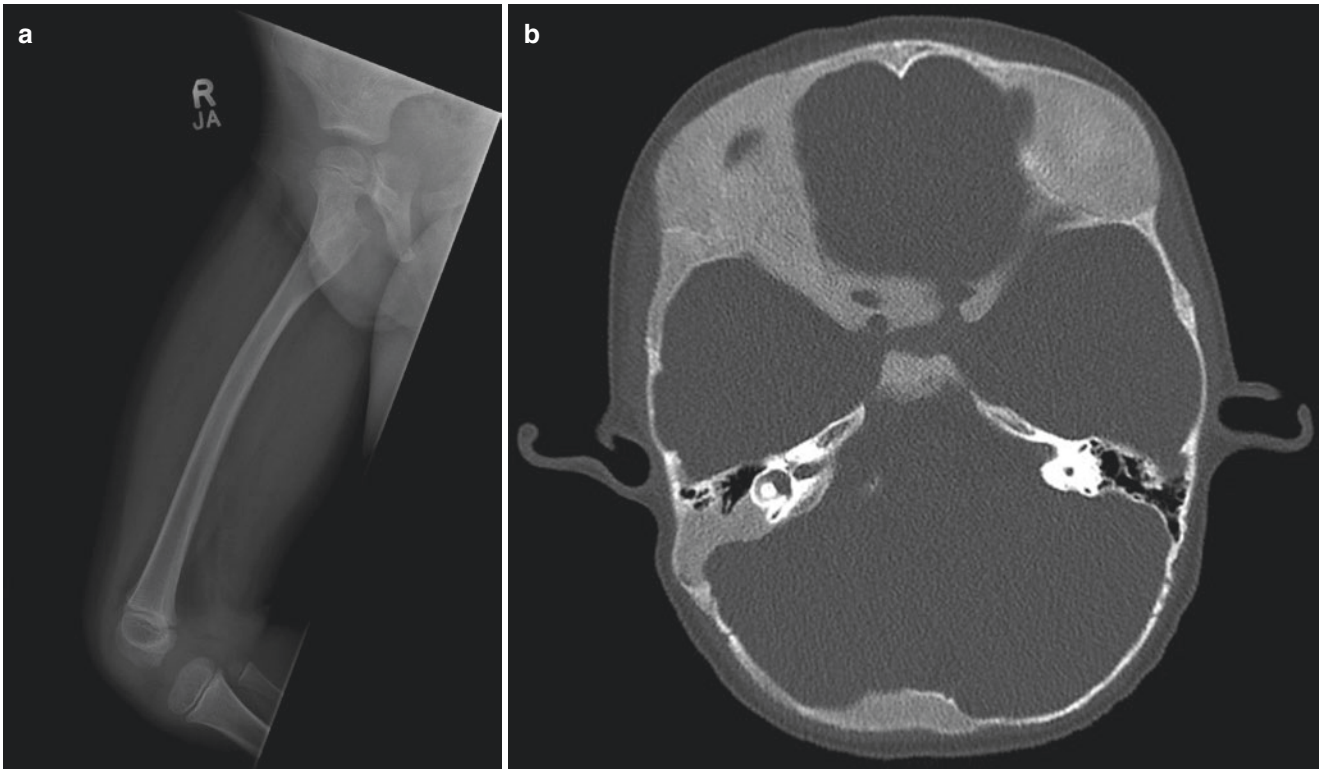

Fig. 1.20 (**a** and **b**) Frontal X-ray of the right femur and axial CT scan of the skull at the level of temporal bones reveal presence of multiple expansile lesions with ground glass matrix in keeping with fibrous dysplasia

1.7 Intestinal Failure Associated Liver Disease (IFALD)

Intestinal failure in infancy occurs due to short bowel (surgical resection such as for necrotising enterocolitis), dysmotility (such as Hirschsprungs disease) or enteropathy (such as microvillous inclusion disease) (Fig. 1.21). Infants require parenteral nutrition to maintain nutrition and hydration. The development of IFALD is associated with immaturity of the liver, recurrent episodes of sepsis and an inability to tolerate any enteral feed. It is less common now due to advances in surgical and nutritional management. Children with irreversible intestinal failure and progressive liver disease, require liver transplantation with or without an intestinal transplant (Figs. 1.22 and 1.23).

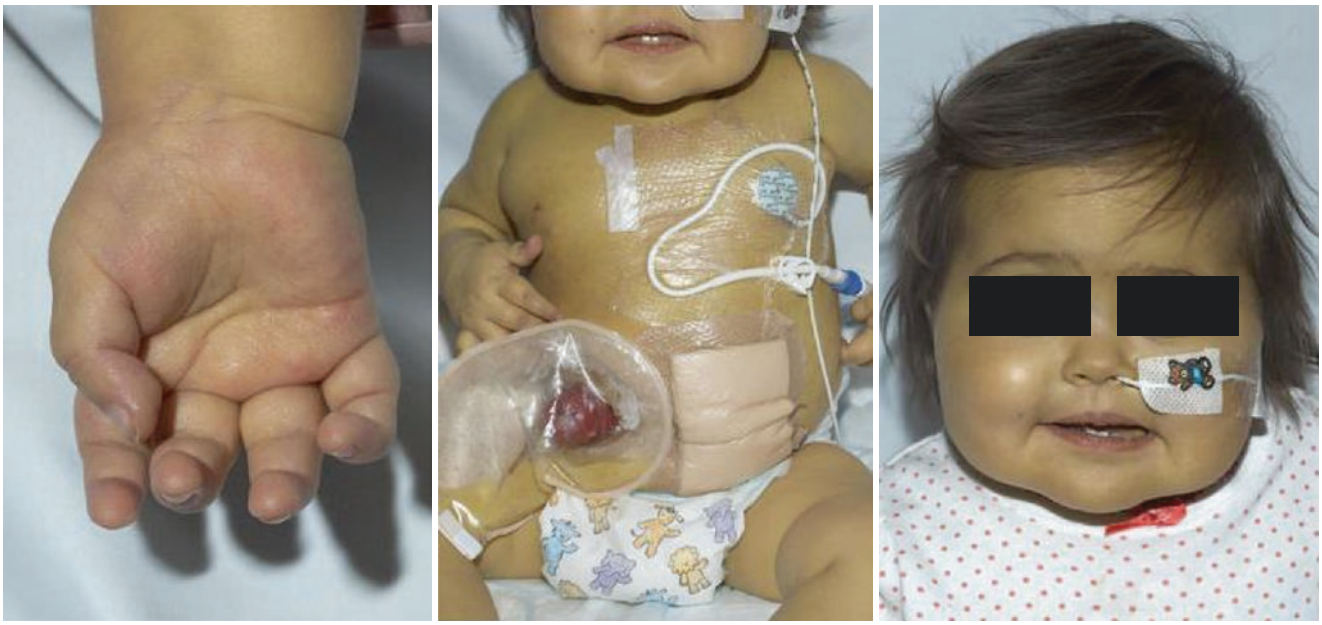

Fig. 1.21 A jaundiced infant with IFALD awaiting liver and small bowel transplant. Note her stoma, mucous fistula, nasogastric feeding tube and central venous catheter

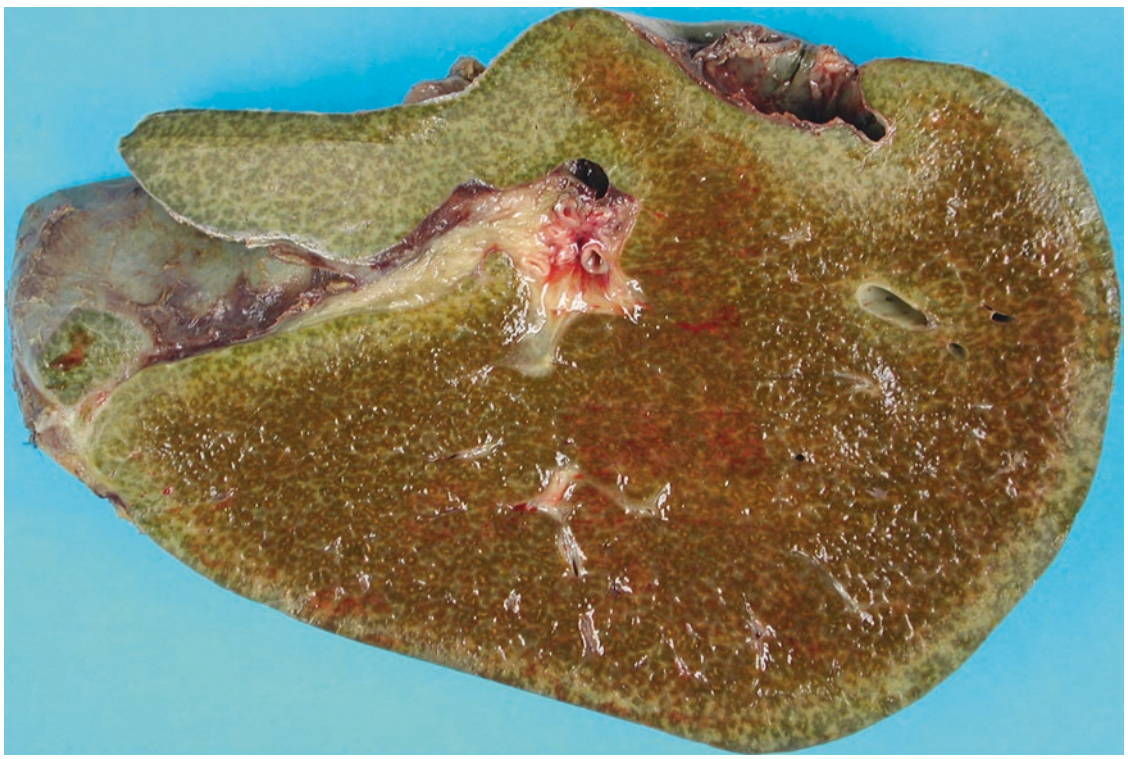

Fig. 1.22 Macroscopic image of a slice through a liver removed at the time of transplantation in intestinal failure associated liver disease. Intense cholestasis gives the green colour, there is a fine reticular pattern of fibrosis

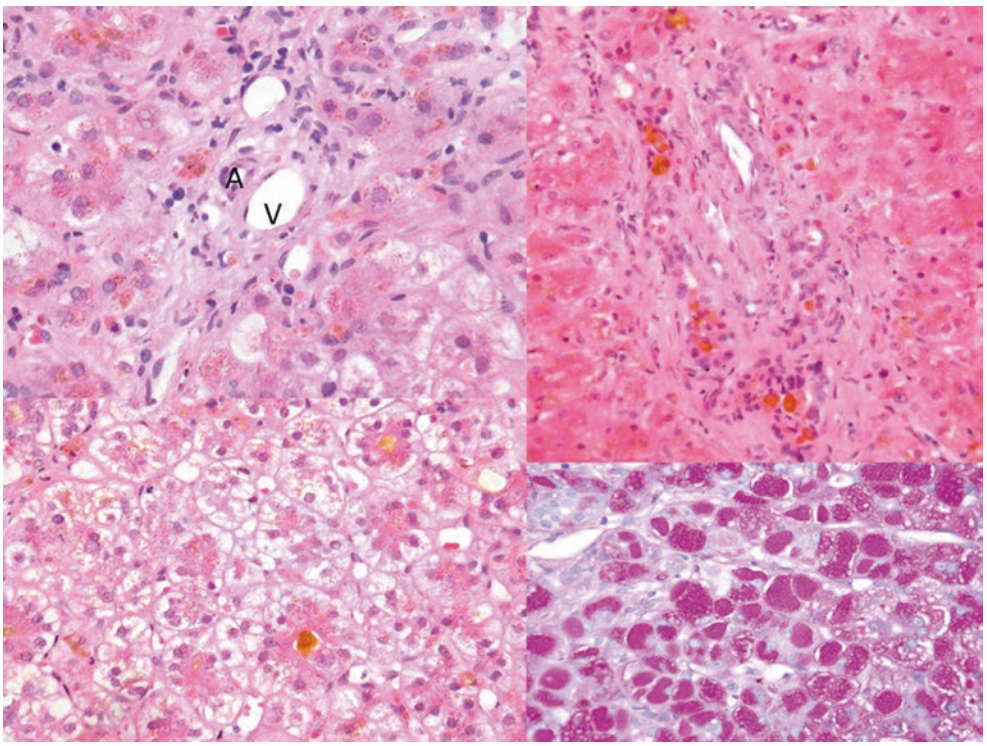

Fig. 1.23 This composite microscopic image shows some of the variable histological features which can be seen in intestinal failure associated liver disease. Infants in particular are vulnerable to losing bile ducts, in the top left hand panel there is an artery 'A' and vein 'V' but no bile duct. In the bottom left hand panel yellow bile is present within canaliculi in the parenchyma, cholestasis and hepatocyte ballooning are a frequent finding. In the top right hand panel this portal tract has a very biliary appearance, the yellow plugs of bile are here present within ductules at the margins of the portal tract mimicking large duct obstruction. In the bottom right hand panel a PAS stain shows inclusion-like cytoplasm in the hepatocytes, these are not always completely digested by diastase, these inclusions represent altered glycogen and can also be seen in the settings of polypharmacy and immunosuppression

1.8 Unconjugated Jaundice

Unconjugated jaundice may be pathological if it is due to Criggler Najjar syndrome (CN) in which mutations in *UGT1A1* leads to an enzyme deficiency in bilirubin conjugation leading to high levels of unconjugated bilirubin which may lead to kernicterus. The babies are usually jaundiced within 24 h of birth (Fig. 1.24). In type 2 CN there is some enzyme function and phenobarbitone therapy upregulates the enzyme and reduces bilirubin levels. In type 1 CN there is no enzyme activity and treatment consists of phototherapy to reduce bilirubin levels to avoid kernicterus and liver transplant (Fig. 1.25) is required.

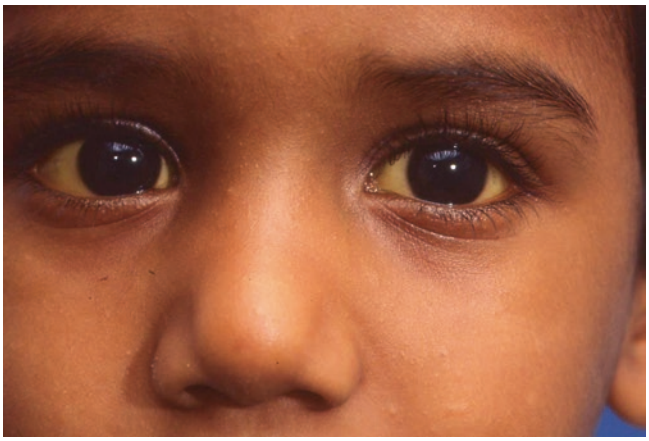

Fig. 1.24 Jaundice in the sclera of a child with Crigler Najjar type 2

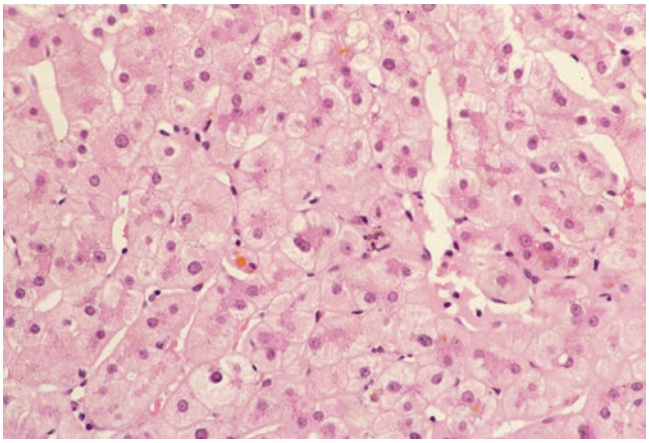

Fig. 1.25 H&E ×400. A couple of bright yellow bile plugs are seen within canaliculi, this is a subtle change, microscopy can be normal

1.9 Management of Jaundice

Nutrition: bile is necessary for the intestinal absorption of long chain triglycerides (the main fat component of breast milk and standard formula milks) and fat soluble vitamins. In a cholestatic infant malabsorption of fats means the infant may appear hungry despite high volumes of feed. Increasing the proportion of medium chain triglycerides (such as infatrini peptisorb), which do not require bile for absorption, improves nutrition and satiety. Liver disease is highly catabolic and hence the infant may also require additional calories, (provided as carbohydrate or fat) enterally by nasogastric tube feeding, if necessary.

Fat soluble vitamins: fat soluble vitamins are absorbed with long chain triglycerides and hence supplementation is required (Table 1.2).

Table 1.2 Initial fat soluble vitamin dose recommendations. Thereafter, levels should be monitored and doses adjusted accordingly

Fat soluble vitamin	Dose
Vitamin A	5000 units once daily
Vitamin D as ergocalciferol	1200 IU per day
Vitamin E	50 mg once daily
Vitamin K	1 mg once daily

1.10 Pruritis

Intense pruritis can severely impair quality of life in children with cholestasis. It is refractory to medical management and surgical intervention with a biliary diversion or liver transplantation, may be required (Fig. 1.26).

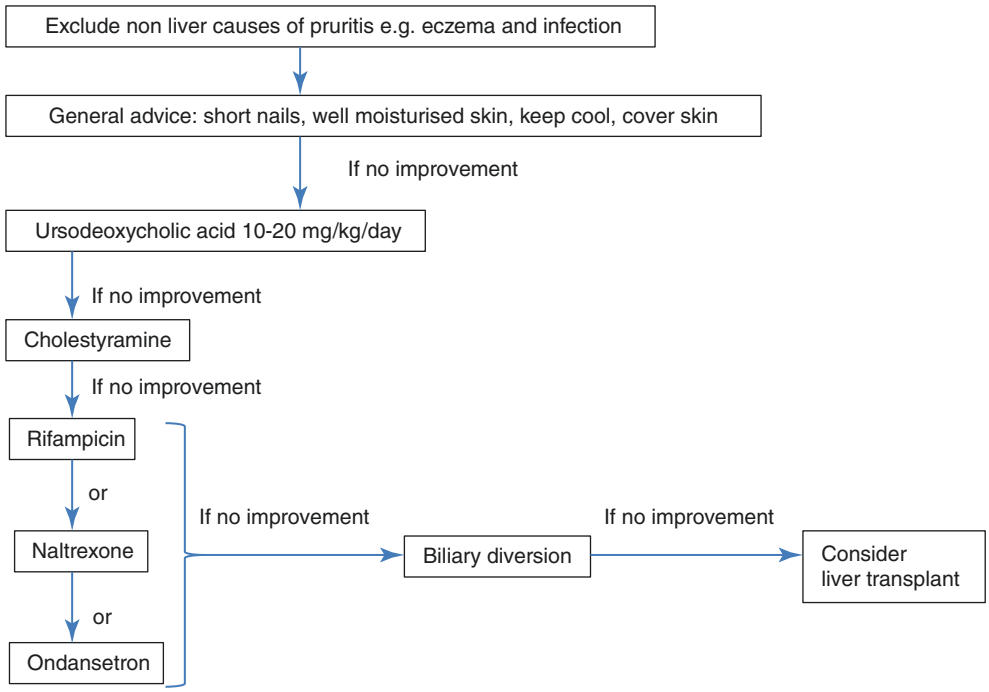

Fig. 1.26 Flow diagram demonstrating the stepwise approach to the management of pruritis. Antihistamines are not included as they do not alter pruritis associated with cholestasis however the sedative effect may be a useful adjunct in some children

Further Reading

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The Acutely Ill Baby

2

Jane Hartley

Acute liver failure is due to necrosis of the liver leading to loss of liver function. The definition includes coagulopathy and encephalopathy. Other organs are often affected and there is a high mortality rate despite intensive care support. The initial clinical features are subtle with poor feeding, difficulty waking and poor temperature control, which can be difficult to detect in young infants. Initial investigations will show prolonged prothrombin time, hypoglycaemia, increased transaminases and bilirubin. A neonate with acute liver failure or liver dysfunction should be referred immediately to a tertiary paediatric liver centre for further advice, investigations and management. Many will require timely transfer for specialised care and consideration for transplantation. The most common causes are infection and metabolic disease (Tables 2.1 and 2.2) whilst liver vascular disease e.g. haemangioendotheliomas also present as an acutely ill baby with hepatomegaly, preserved liver biochemistry, heart failure and consumptive coagulopathy.

2.1 Sepsis

Herpes simplex is one of the more common causes of liver failure in neonates. It is usually due to exposure at the time of birth from genital herpes, although in some cases no cause is identified. The typical vesicular skin manifestations of herpes may not be initially present or may be subtle (Fig. 2.1) hence there needs to be a high index of suspicion. Infection is multisystem and often overwhelming requiring intensive care support. Acyclovir should be commenced as quickly as possible as it is possible to attenuate the disease. However if presentation for treatment is delayed then despite intensive support babies will succumb to the multiorgan failure (Fig. 2.2).

Enteral viruses may cause similar clinic features and clinical course. There may be a history of diarrhoeal illness or pyrexia in the mother prior to birth.

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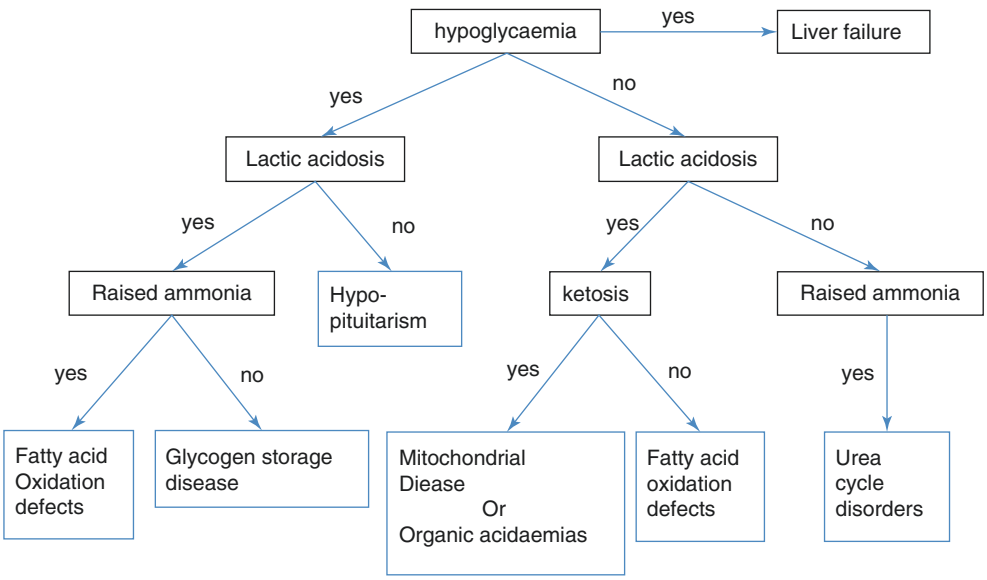
D. Kelly et al. (eds.), *Atlas of Pediatric Hepatology*, https://doi.org/10.1007/978-3-319-69529-7_2

Table 2.1 The differential diagnosis of a young child with liver failure

Differential diagnosis	Investigation	Specific treatment and outcome
Herpes simplex	Immunofluorescence of vesicle swab, blood and urine PCR	Acyclovir Multisystem disease with high mortality
Coxsacchie virus	Stool PCR	Supportive, liver transplant
Neonatal haemochromatosis	Iron storage in salivary gland, MRI	Plasmapheresis and immunoglobulins, liver transplant
Mitochondrial disease	High lactate, mitochondrial DNA from blood, muscle or liver, muscle biopsy shows ragged red fibres, EEG	Life limiting disease
Galactosaemia	Reducing substances in urine, galactose-1-phostphate uridyl transferase deficiency	Lactose free diet but learning difficulties and infertility occur
Tyrosinaemia type 1	Presents later in infancy Urinary succinyl acetone, increase alpha fetoprotein, DNA for mutations	Nitisinone therapy, dietary restriction of protein. Risk of hepatocellular carcinoma
Urea cycle disorders	Raised ammonia, normal lactate and abnormal plasma amino acids	Emergency management of hyperammonaemia, hepatocyte transplant, liver transplant if unstable
Lysosomal storage disorders e.g. Niemann Pick C, Gauchers and Wolman's disease	Storage cells, DNA for mutations	Enzyme replacement therapy, palliative care due to neurological progression
Fatty acid oxidation defects	Lactic acidosis, acyl carnitines, raised ammonia and Creatine Kinase	Avoid fasting using corn starch 60% mortality at first presentation
Familial haemophagocytic lymphohistiocytosis	Raised triglycerides, pyrexia, low platelets, white and red blood cells, low fibrinogen, low albumin, hepatomegaly DNA for mutations and CD50 levels	Chemotherapy (steroids and etoposide) Stem cell transplant Liver transplant is contraindicated as there is multisystem involvement

Table 2.2 A flow diagram to aid diagnosis of metabolic disease in infants with acute liver failure



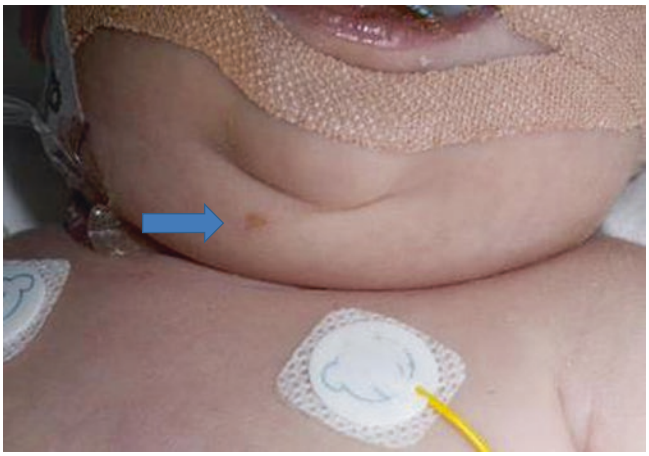


Fig. 2.1 This is a typical skin lesion of Herpes simplex infection in a child who presented at 8 days of age with poor feeding. There were no other lesions apparent. A swab from this lesion identified Herpes simplex type 1 confirmed by a high HSV PCR

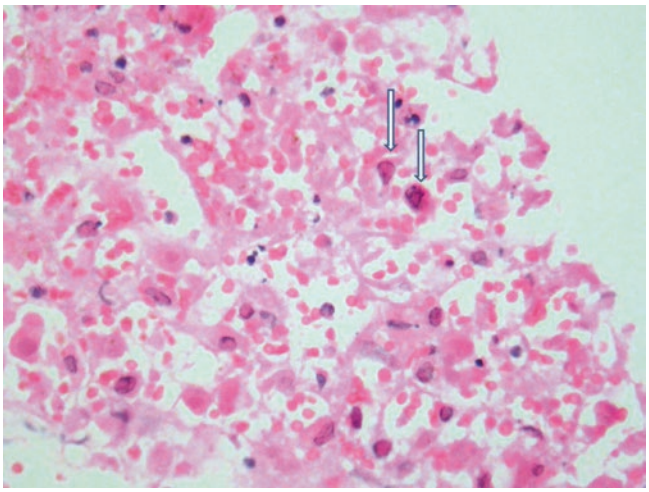


Fig. 2.2 Post mortem liver from the above child who died within a few hours of presentation to medical attention, despite being given aciclovir. H&E × 400. This section is from the edge of a large liver abscess. The arrow is pointing at hepatocytes containing viral inclusions in a case of herpes simplex virus infection. The affected nuclei have a 'groundglass' purple appearance

2.2 Gestational Alloimmune Liver Disease (GALD)

The development of maternal alloimmune immunoglobulins directed to the foetal liver antigen causes activation of the terminal complement cascade. This results in toxic iron accumulation in the liver and other extrahepatic sites. Babies are often born preterm, with intrauterine growth restriction, and in some cases with antenatal ascites (Fig. 2.3). The disease starts many weeks before birth and presents within a few days of delivery. Hepatic transaminases may be normal whilst the synthetic function is severely affected causing hypoglycaemia, coagulopathy and jaundice. Diagnosis is based on demonstrating extra-hepatic iron storage, within the salivary glands in a lip biopsy (Fig. 2.4) or in an MRI scan of the abdomen (Fig. 2.5) which shows iron in the pancreas and liver indicative of iron deposition whilst the reticuloendothelial system is spared. Intensive care support is required whilst treatment is instigated. Alloimmune

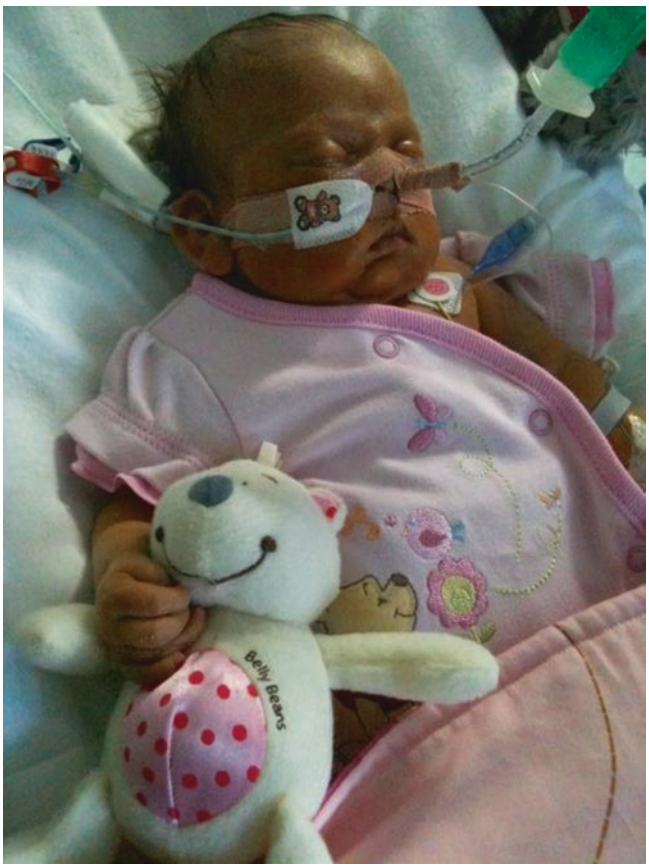


Fig. 2.3 A baby with GALD who was born at 32 weeks gestation and required full intensive care support

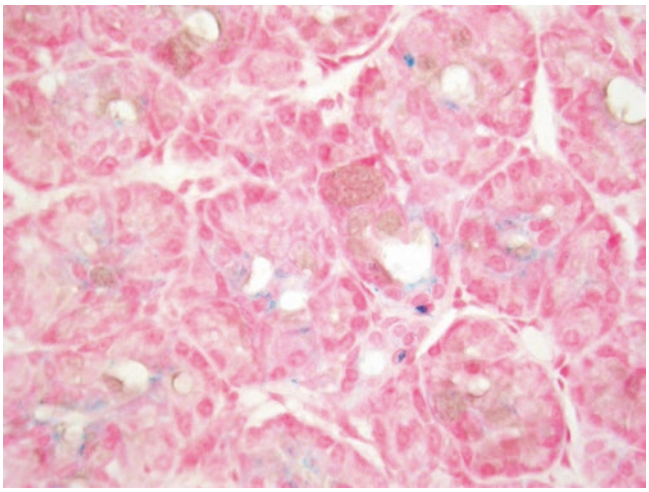


Fig. 2.4 Histology of the lip biopsy in a baby with gestational alloimmune liver disease. Perls stain ×400. The blue granules in this image are iron, they are present in parenchymal cells of a minor salivary gland

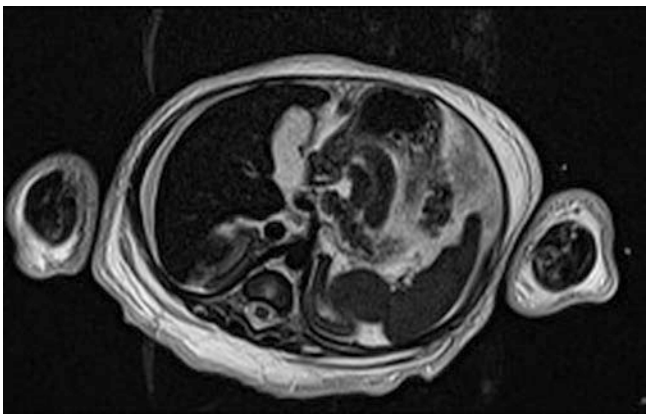


Fig. 2.5 T2 weighted axial sequence of the liver and pancreas reveals hypo intensity relative to the abdominal wall muscles in keeping with iron deposition

antibodies are removed through exchange transfusion and immunoglobulin infusions which may stabilise the condition whilst awaiting liver transplant. There is a high mortality rate due to the overwhelming liver failure and need for multiorgan support. The is a 90% chance of recurrence in subsequent pregnancies, and weekly maternal immunoglobulin infusions from 14 weeks gestation may ameliorate or prevent recurrence.

2.3 Metabolic Disease

2.3.1 Mitochondrial Disease

A persistently high plasma lactate suggests mitochondrial disease. Other indicators include poor muscle tone, raised creatine kinase, cardiomyopathy, seizures, family history and consanguinity. A muscle biopsy (Fig. 2.6) and genetic mutation analysis will provide a diagnosis. This infant presented at 4 weeks with poor feeding. Initial investigations showed a lactate of 9 mmol/l (normal <2.5 mmol/l), prothrombin time 21 s (normal 8–12 s) and raised transaminases. He had severe hypotonia, cardiomyopathy and was the firstborn child to a consanguineous couple. He died aged 8 weeks. DNA mutation testing for mitochondrial disease confirmed homozygous mutations in MPV17. Liver transplant was contraindicated due to the multisystem involvement often leading to death within infancy.

Alpers disease is a mitochondrial disease which can present at any time during childhood due to mutations in *POLG*. It may present with epilepsy and if treated with sodium valproate liver failure develops. This liver biopsy (Fig. 2.7a, b) is from a 3 year old child who developed seizures aged 2 years with developmental regression. The seizure activity deteriorated and he commenced sodium valproate. Liver failure developed within 4 weeks to which he succumbed.

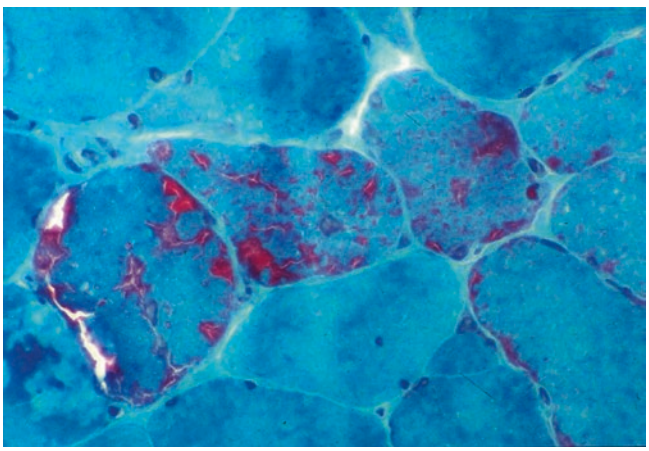


Fig. 2.6 Gomori trichrome stain ×600. Abnormal mitochondria clumped together stain red with this technique, a useful, if relatively rare indicator of mitochondrial disease

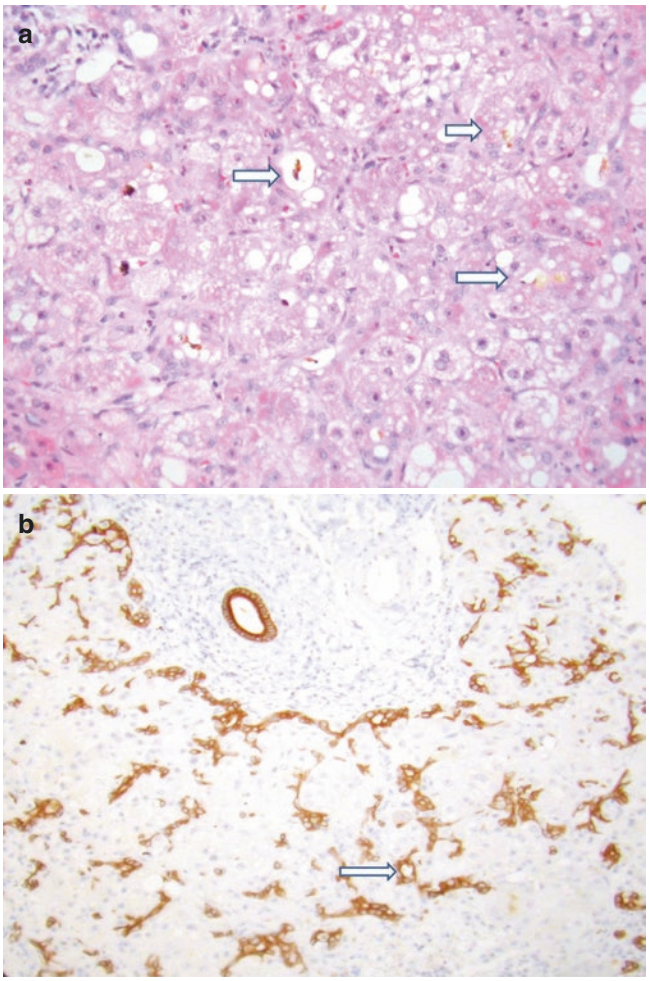


Fig. 2.7 (**a**) H&E ×200. This liver biopsy shows a combination of steatosis and canalicular cholestasis, the arrows are pointing at bile in distended canaliculi giving an almost pseudo glandular appearance. This combination is a good clue to metabolic liver disorders. This is from a case of Alpers syndrome. (**b**) Immunohistochemistry for cytokeratin 7 ×200. The cells surrounding distended canaliculi begin to assume a biliary phenotype highlighted here by immunohistochemistry in this case of Alpers syndrome

2.3.2 Lysosomal Storage Diseases

Niemann Pick C is a lysosomal storage disease that can present at any age due to mutations in *NPC1* or *NPC2*. Infants usually present with liver involvement, while older children and adults, the neurological signs are more prominent. Splenomegaly is always present and distinguishes the disease from other causes of acute liver failure. Making a prompt diagnosis can be challenging due to the difficulty in identifying the storage cells in liver or bone marrow in infancy. Liver transplantation is contraindicated (see also Chapter 1).

The child shown in Fig. 1.19 presented at 6 weeks of age with distended abdomen, poor blood sugar control, raised PT (19 s (normal 9–13 s)), conjugated hyperbilirubinaemia and transaminitis. His spleen was 3 cm below the left costal margin. Despite a high index of suspicion, two liver biopsies and bone marrow aspirate no storage material was initially identified and he underwent a liver transplant (Fig. 2.8). Following a successful transplant the DNA mutation analysis of *NPC1*

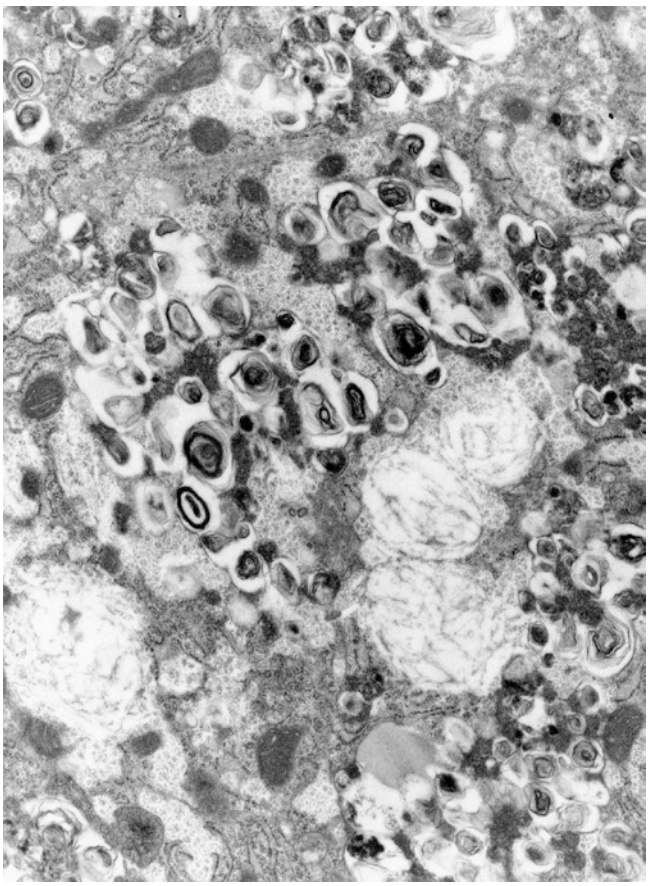


Fig. 2.8 Histology of the explanted liver. The whorled black structures in this image are myelin figures as seen on electron microscopic examination in a case of Niemann-Pick C. Care should be taken to distinguish these from bile which can sometimes assume a fine filamentous structure with a concentric arrangement

showed a compound heterozygous mutations with the pathogenicity of one mutation being unknown. Filipin staining (Fig. 2.9) of cultured fibroblasts showed cholesterol esterification in 50% of cells and hence an equivocal result. He is currently well, aged 7 years with no signs yet of neurological manifestations.

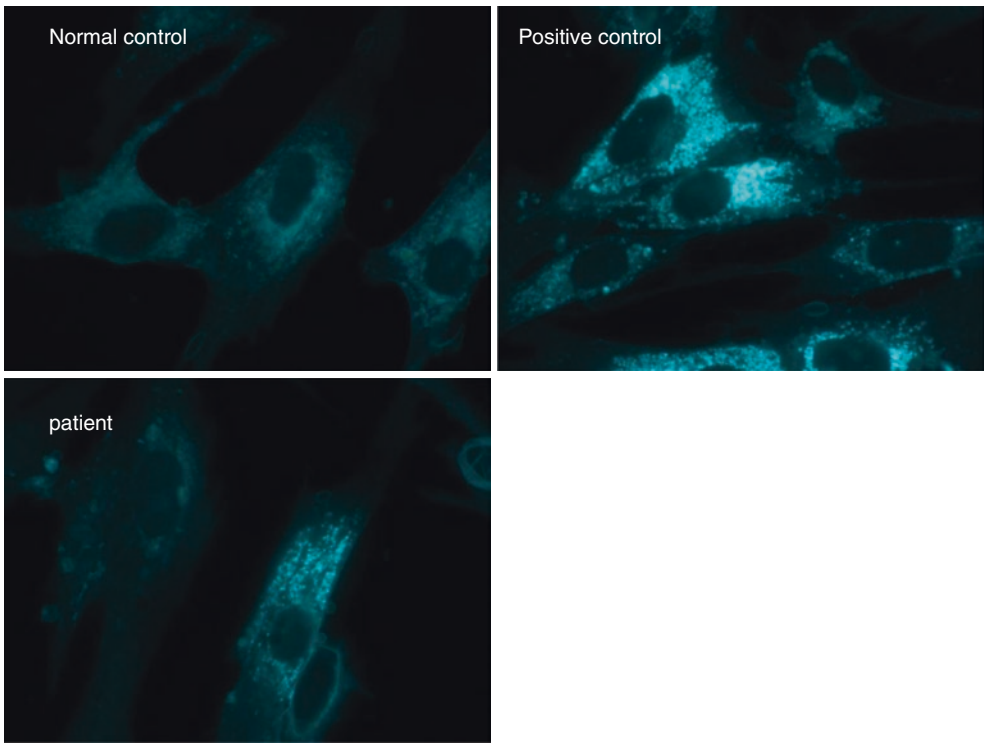


Fig. 2.9 Fifty percent of the filipin stain is positive which is an equivocal result as compared to the positive and negative controls

2.3.3 Galactosaemia

Galactosaemia is an autosomal recessive disorder due to a deficiency of galactose-1-phosphate uridyl transferase. A baby presented at 2 weeks with poor feeding, vomiting and jaundice. On examination he had oil drop cataracts. Initial investigations showed a low blood sugar and prothrombin time 36 s (normal 9–13 s). The transaminases were only moderately raised. Breast feeding was discontinued and he was commenced on soya based milk formula. Within 2 days the PT began to improve and the liver function completely normalised within 14 days. The diagnosis of galactosaemia was made by identifying a deficiency in glucose-1-phosphate uridyl transferase (Gal-1-put) in plasma. It is rare for a child with galactosaemia to require a liver biopsy for diagnosis (Fig. 2.10). A lactose free diet is essential in childhood to avoid liver disease and neurological compromise, however there are likely to be learning difficulties due to the in utero exposure of metabolites and infertility in females.

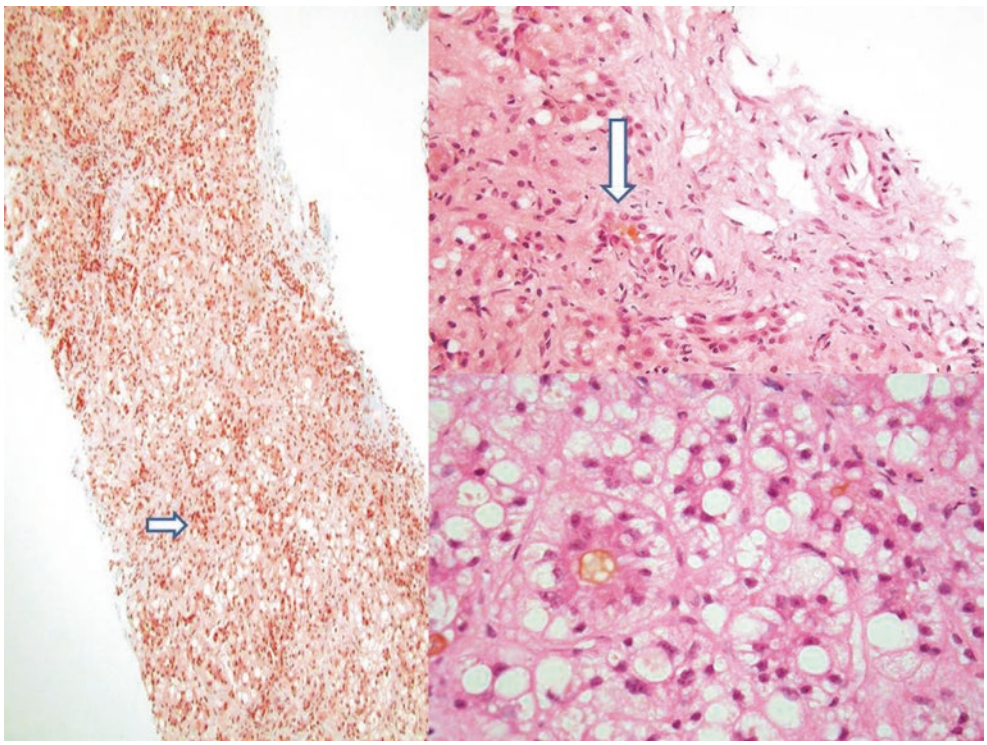


Fig. 2.10 In this case of galactosaemia the left-hand panel (Masson trichrome stain ×100) shows an excess of duct-like structures, one is marked with an arrow. At the top right some orange coloured bile is seen in a ductule giving a slightly 'biliary' appearance. At the bottom right there is a combination of canalicular cholestasis and steatosis, again a good indicator of metabolic liver disease. Note it is quite similar to that seen in Alpers syndrome (Fig. 2.7a, b). It is rarely possible to arrive at a precise metabolic diagnosis from histological findings alone

2.3.4 Tyrosinaemia

A defect in fumaryl acetoacetase leads to the accumulation of toxic metabolites. It presents in variable ways with the most common being acute liver failure in the first 1–6 months of life. In older children failure to thrive, hepatosplenomegaly and rickets are common (Fig. 2.11). There is a high risk of hepatocellular carcinoma (HCC). Nitisinone prevents the formation of toxic metabolites and with a low tyrosine and phenylalanine diet leads to resolution of liver failure in most infants. The risk of HCC is greatly reduced. However if there is poor response to treatment or HCC is detected then liver transplantation is indicated (Fig. 2.12).

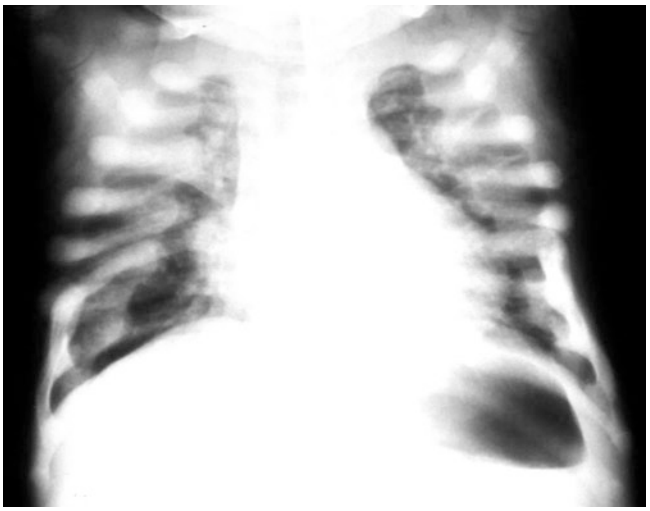


Fig. 2.11 Severe rickets in a child with tyrosinemia

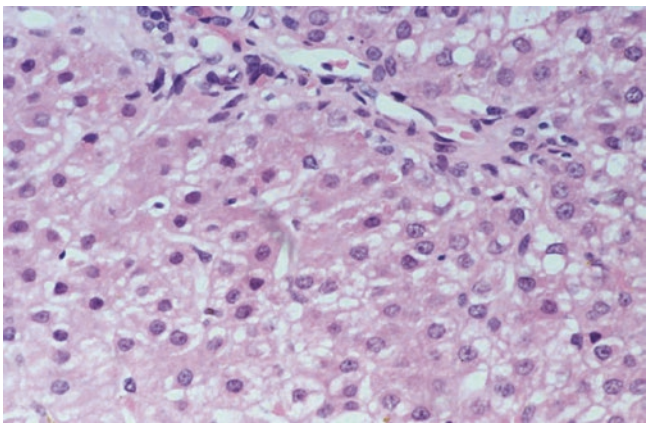


Fig. 2.12 Histology of a liver from a child transplanted for tyrosinemia showing a mixed steatosis and dysplasia of hepatic cells

2.4 Vascular Malformations

This 1 week old baby (Fig. 2.13) presented with increased work of breathing and jaundice. He had multiple cutaneous haemangioimas. He had a large murmur which was loudest over the liver. The liver was enlarged and palpable 3 cm below the costal margin. He underwent an ultrasound (Fig. 2.14) and subsequently a CT scan which confirmed intrahepatic haemangiomas (Fig. 2.15). He developed sequestration of platelets indicative of Kasabach Merrit syndrome. The high output cardiac failure progressed leading to the need for intensive care. Steroids or interferon may be therapeutic in smaller haemangiomas, particularly in those who are positive for immunostaining for GLUT 1.

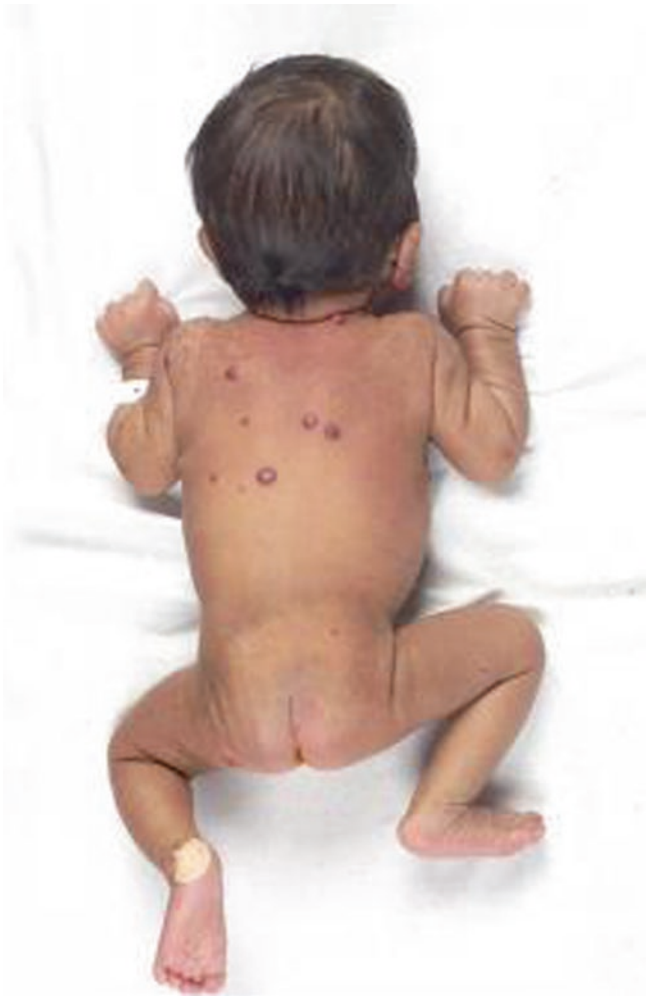


Fig. 2.13 Cutaneous Haemangioendothelioma

In this case there was no clinical response to steroid and the baby underwent angiography (Fig. 2.16) and embolization of the feeding vessel (Fig. 2.17). There was initial stability in the baby's condition following the embolization however further vascular channels developed and he died of heart failure.

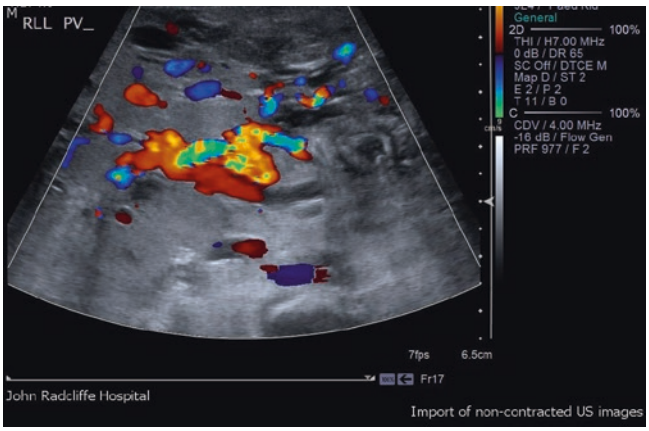


Fig. 2.14 Ultrasound with Doppler of the liver reveals multiple hypo echoic lesions in both lobes of the liver with generalized hypertrophy of hepatic vasculature

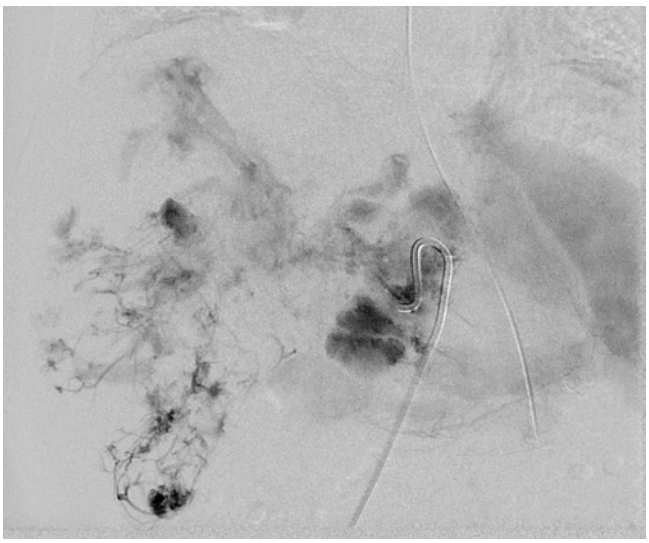


Fig. 2.16 Contrast injection of the hepatic artery reveals abnormal vascular blush of the Haemangioendothelioma within the liver

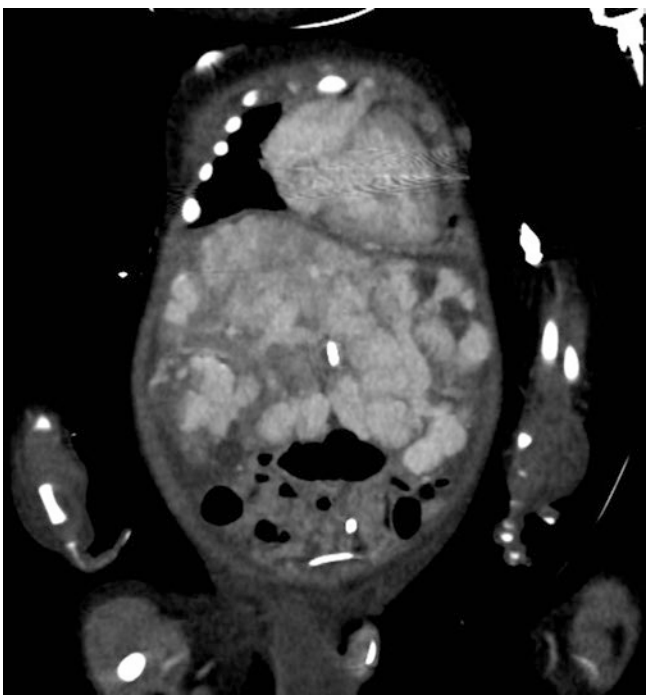


Fig. 2.15 Contrast enhanced CT scan coronal section of the abdomen reveals multiple enhancing lesions of both lobes of liver

Fig. 2.17 Contrast injection of the hepatic artery reveals embolization of the entire hepatic artery with complete lack of enhancement of the previously noted Haemangioendothelioma

Further Reading

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The Child with Splenomegaly

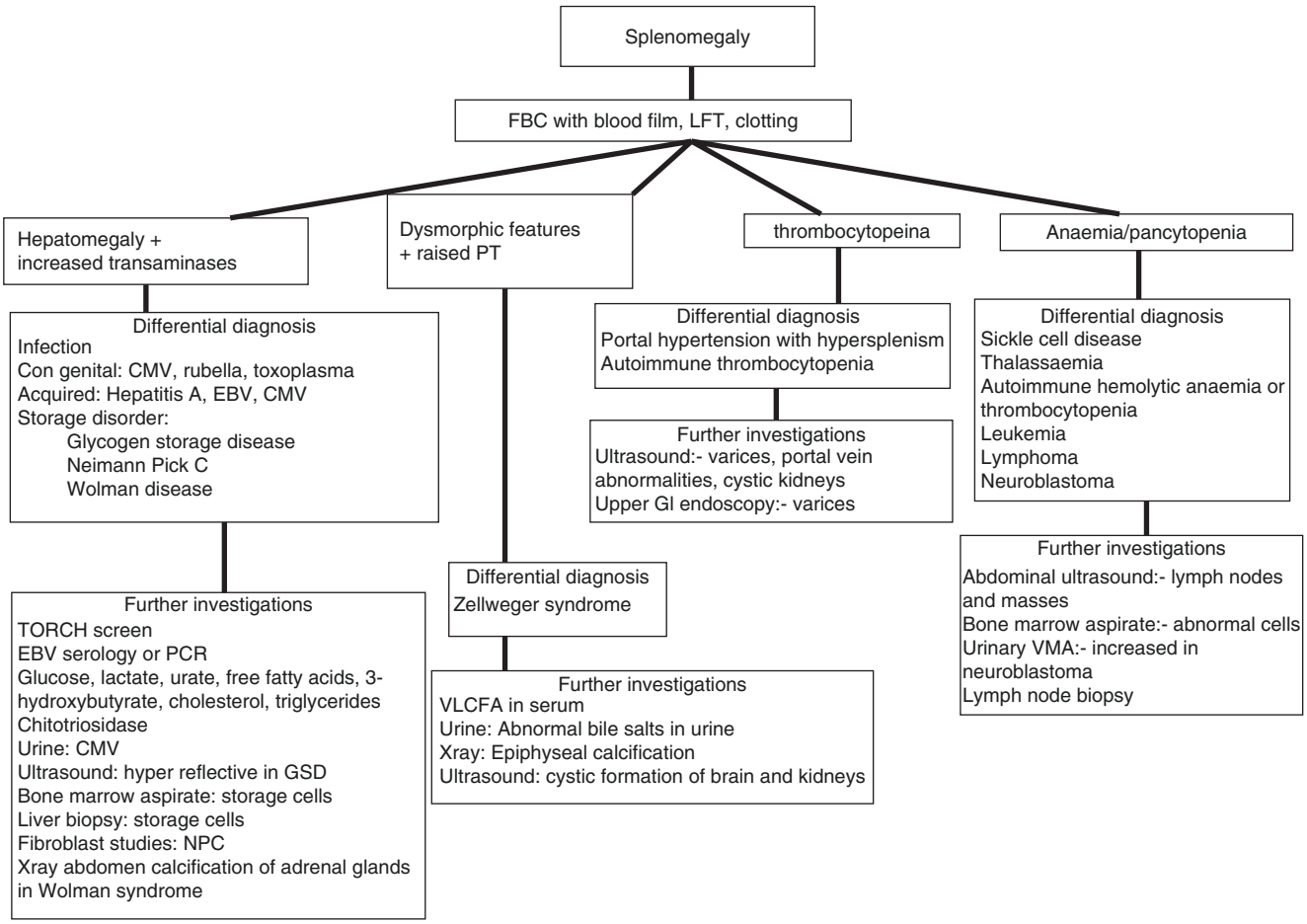
3

Jane Hartley

The spleen should not be palpable under normal circumstances and therefore splenomegaly is an important clinical sign requiring further investigation.

Splenomegaly in a neonate helps guide investigations and management as it usually indicates that the infant has either a congenital infection or storage disease (Table 3.1).

Table 3.1 Differential diagnosis of a young child with splenomegaly



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D. Kelly et al. (eds.), *Atlas of Pediatric Hepatology*, https://doi.org/10.1007/978-3-319-69529-7_3

In older children with chronic liver disease splenomegaly may indicate progressive disease with the development of portal hypertension. In non-cirrhotic portal hypertension or portal vein obstruction, splenomegaly may be the only clinical finding (Table 3.2).

This boy, born at 34 weeks gestation, had a mixed conjugated and unconjugated jaundice within 24 h of birth. He also had petechia and hepatosplenomegaly despite normal antenatal scans. Cytomegalovirus (CMV) infection was identified by blood PCR. An abdominal ultrasound scan showed flecks of calcification throughout the liver (Fig. 3.1). Calcification was also seen on a head CT scan, suggestive of an intra-uterine infection. A liver biopsy showed CMV inclusions (Fig. 3.2). The liver disease induced by CMV usually resolves but treatment with ganciclovir may reduce developmental issues such as impaired vision and hearing. Other congenital infections such as toxoplasmosis (Fig. 3.3) present with similar clinical features. Therapy with spiramycin prevents the progression of neurological and liver disease in toxoplasmosis.

Table 3.2 Differential diagnosis of an older child with splenomegaly

Infection	CMV (congenital or acquired) Rubella (congenital) Toxoplasma (congenital) EBV
Portal hypertension	Chronic liver disease Portal cavernoma
Haematological/ malignancy	Leukaemia Lymphoma Sickle cells disease Thalassaemia Autoimmune haemolytic anaemia or thrombocytopenia
Storage disorder	Niemann Pick A,B or C Lysosomal acid lipase deficiency Gaucher disease
Peroxisomal biogenesis disorders	Zellwegers syndrome

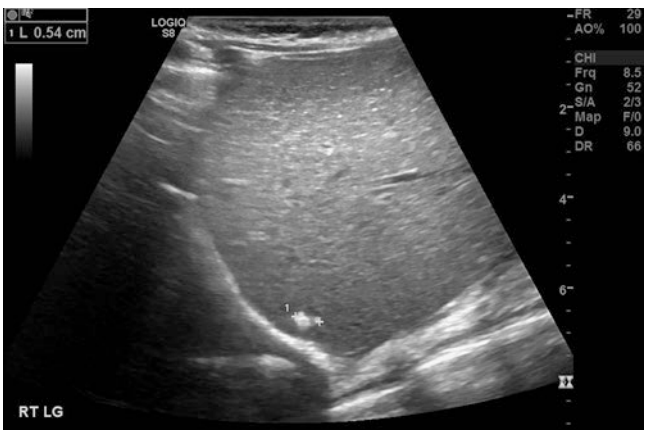

Fig. 3.1 Ultrasound coronal section of the liver reveals calcification in segment 7 of the right lobe of liver in a child with known CMV

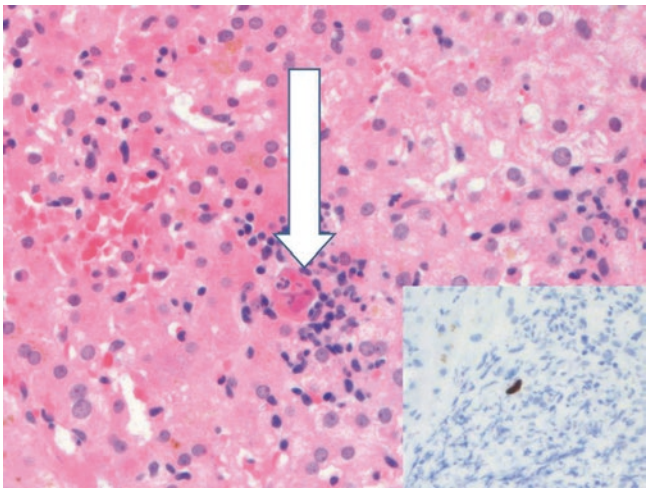

Fig. 3.2 H&E original magnification ×400. The arrow is pointing to a hepatocyte, there is a neutrophil polymorph in the cytoplasm, sometimes a small cluster of these cells is the only clue to CMV infection. The nucleus of the cell has a groundglass appearance. Immunohistochemistry confirms a CMV inclusion in the inset bottom right

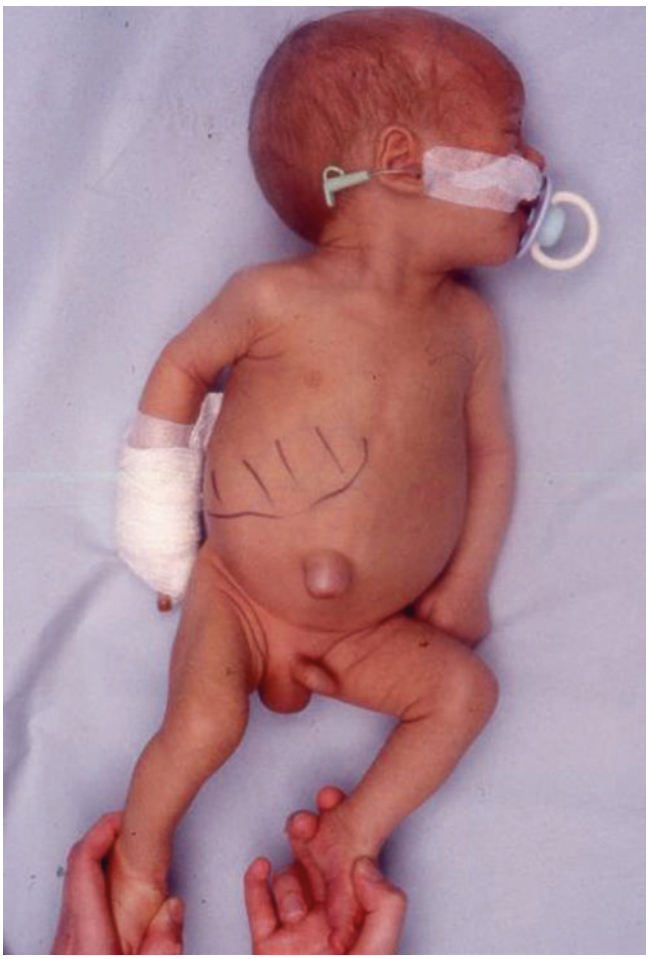

Fig. 3.3 Child with congenital toxoplasmosis. There was a maternal history of pyrexia at 35 weeks gestation. The baby has jaundice and marked hepatomegaly with the spleen tip palpable

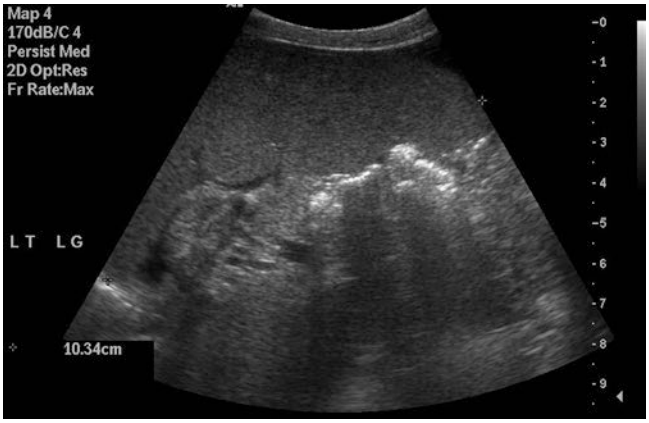

Fig. 3.4 Ultrasound coronal section of the left side of the abdomen reveals splenomegaly

In older children with pyrexia, lymphadenopathy and pharyngitis, an enlarged spleen (Fig. 3.4) may be a sign of acute Epstein Barr virus infection (EBV). Monospot, serology and PCR will be positive for EBV infection. Acute Epstein Barr virus (EBV or infectious mononucleosis or glandular fever) may cause acute hepatitis, jaundice and splenomegaly. Treatment is supportive and there is usually complete resolution of hepatic disease, although fulminant hepatitis is a rare complication.

A portal cavernoma develops when there is thrombosis of the portal vein. The thrombosis may develop due to a procoagulant condition or trauma to the portal vein, such as umbilical catheter insertion in the neonatal period. It may take a number of years for the development of portal hypertension and children may present with splenomegaly or acute haematemesis at any age. On ultrasound the liver parenchyma is usually normal but the portal vein will not be visualised whilst a knot of small blood vessels (cavernoma) replaces the vein (Fig. 3.5). Acute haematemesis requires fluid resuscitation, the commencement of intravenous octreotide, antibiotics and proton pump inhibitors (see Chapter 7, Table 7.3). When haemodynamically stable, an endoscopy with banding or sclerotherapy of varices should be undertaken. If the varices are not controlled through a banding programme then vascular shunt surgery should be considered (see Chapter 7, Table 7.3). A CT scan and portal venography (Fig. 3.6) confirms the vascular anatomy and helps plan the surgery.

Hepatosplenomegaly may develop in any chronic liver disease if there is progression of intrahepatic fibrosis resulting in an increase in the portal venous pressure or if the portal vein is compromised (such as in biliary atresia where the portal vein is often hypoplastic). This CT angiogram (Fig. 3.7) shows hepatosplenomegaly with varices around the splenic hilum and around the stomach wall. If liver synthetic function is good then varices are managed in most

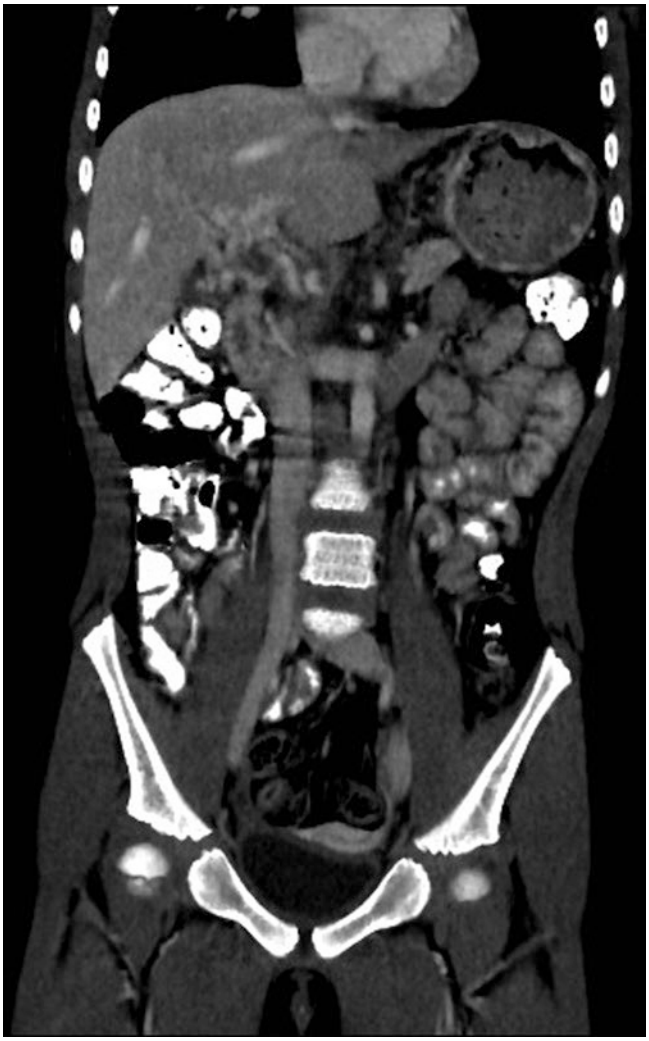

Fig. 3.5 Intravenous contrast enhanced CT scan of the abdomen reveals complete replacement of the portal vein at the porta by collaterals in keeping with portal cavernoma

cases by endoscopic band ligation (Chapter 7; Table 7.3). However liver decompensation may occur following a variceal bleed and liver transplantation should be considered.

Gauchers disease is the most commonly occurring lysosomal storage disorder. It may present at any age including the newborn period. An enzyme defect prevents glucocerebrosidase from breaking down with accumulation in liver and spleen leading to hepatosplenomegaly and bone marrow involvement. Diagnosis is based on genetic analysis. Liver histology may demonstrate Gauchers cells (Fig. 3.8). Enzyme replacement therapy with imiglucerase is now available and successfully treats the condition.

Wolmann's disease (Lysosomal acid Lipase deficiency, LALD) is another lysosomal storage disorder which may present with acute or chronic liver disease and adrenal calcification, visible on abdominal ultrasound (Fig. 3.9) (see also Chapter 5).

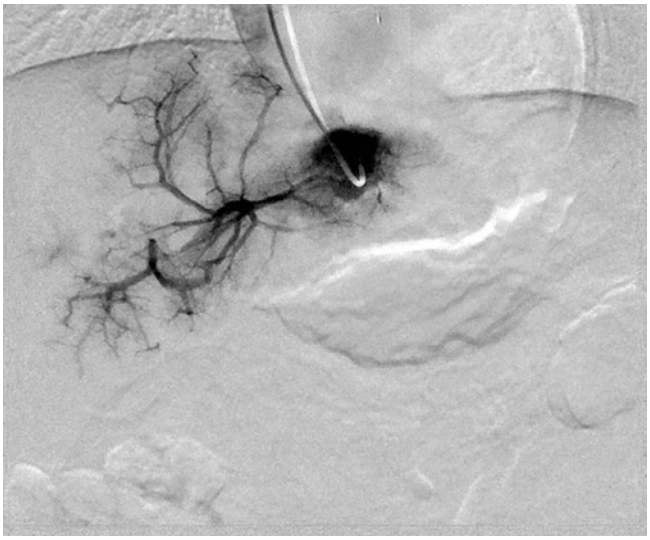

Fig. 3.6 Portal venous phase of hepatic artery angiogram confirms cavernous transformation of portal vein at porta with patent splenic vein and superior mesenteric vein

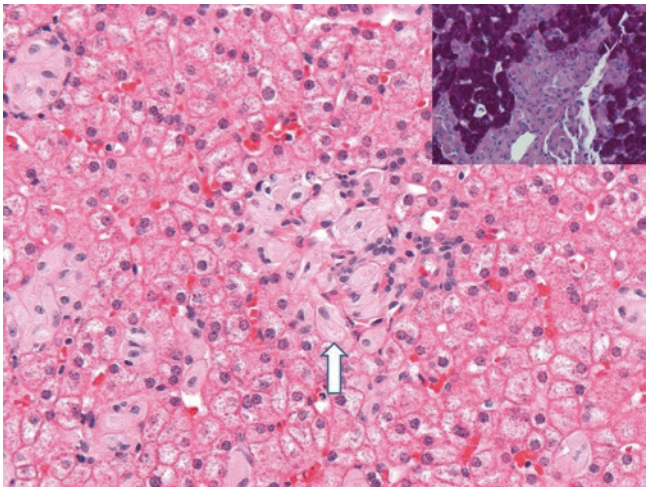

Fig. 3.8 H&E original magnification ×400. The arrow is pointing to a cluster of cells, paler than nearby hepatocytes, with striation of the cytoplasm. These are Gaucher cells. In a PAS stain, top right, the storage cells are only faintly staining in contrast to the strongly positive purple hepatocytes in the background (glycogen positive)

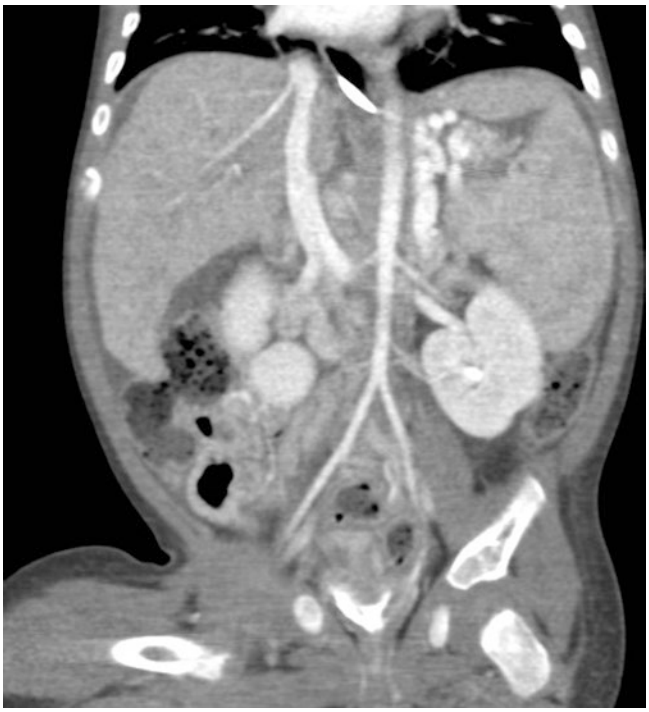

Fig. 3.7 Portal venous phase of intravenous contrast enhanced CT scan of abdomen reveals heptosplenomegaly with varices at splenic hilum and gastric wall secondary to chronic liver disease

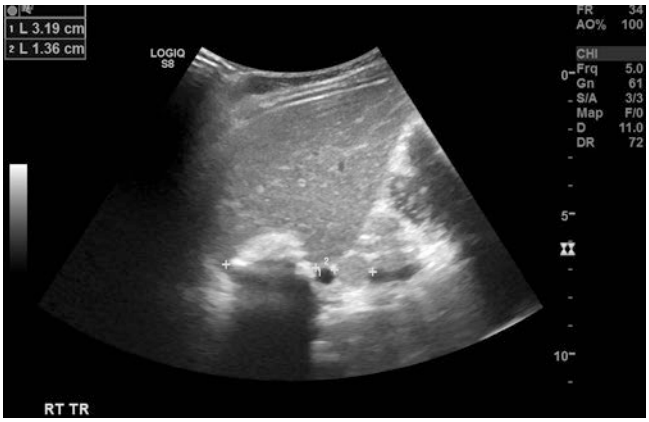

Fig. 3.9 Ultrasound coronal sections of right and left adrenal glands reveal dense adrenal calcification with shadowing

Zellwegers is a peroxisomal biogenesis disorder which presents in infancy. The facial features (Fig. 3.10) are coarse as shown in this picture. There is a prominent forehead, hypotonia, developmental delay, seizures, bone abnormalities with epiphyseal stipling. The diagnosis is usually made by demonstrating abnormal plasma very long chain fatty acids. A liver biopsy in Zellwegers may be non-specific, but

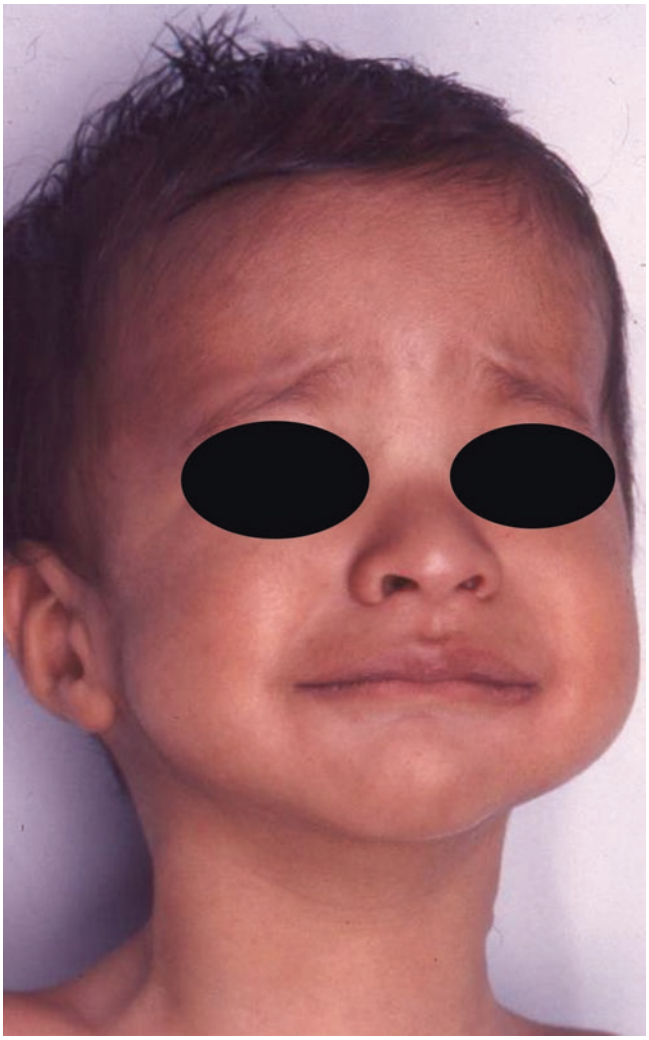

Fig. 3.10 The clinical features of a child with Zellweger syndrome

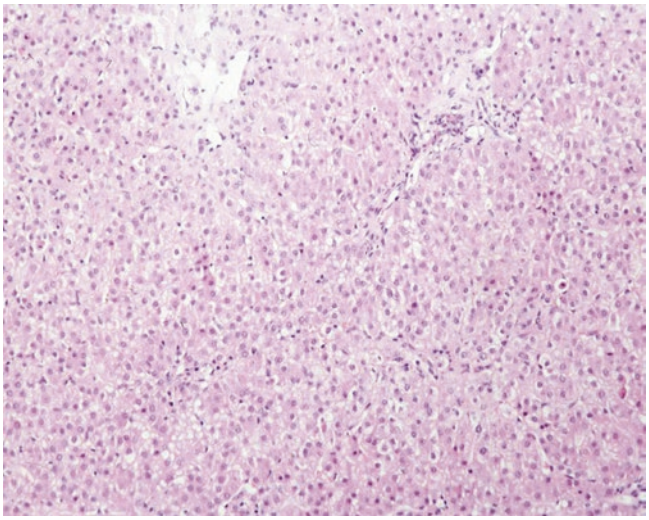

Fig. 3.11 H&E ×200. There is some mild small droplet steatosis towards the bottom left hand corner of the image. H&E appearances are not diagnostic, an absence of peroxisomes can be established by electron microscopy in experienced hands

there may be excess iron, paucity of small bile ducts and abnormal mitochondria on EM (Fig. 3.11). Infants are usually jaundiced and there is rapid progression of liver disease to cirrhosis within a few months with death within the first year secondary to neurological involvement.

The Child with Abdominal Distention

4

Khalid Sharif

Abdominal distention in children has a wide differential diagnosis, but may be grouped into Ascites, Neoplasm and Organomegaly. This chapter will mainly focus on of hepatobiliary neoplasms.

Neoplasms of the liver are divided into benign and malignant tumours. Benign tumours include Mesenchymal Hamartoma, Focal nodular hyperplasia, and large Hemangiomas, all of which can present with abdominal distention.

4.1 Mesenchymal Hamartoma

Mesenchymal hamartoma is a tumor of infancy, typically seen in children less than 2 years of age. The majority of children present with abdominal distension, and physical examination reveals a large, smooth, non-tender mass. Diagnosis is based on the radiological features (Fig. 4.1a–f). Tumours are usually well demarcated, and histology shows a disorganized appearance of hepatocytes and ductules (Fig. 4.2). Management includes complete resection (if possible), in some cases de-roofing/partial excision is required to relive abdominal distention (Fig. 4.3).

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D. Kelly et al. (eds.), *Atlas of Pediatric Hepatology*, https://doi.org/10.1007/978-3-319-69529-7_4

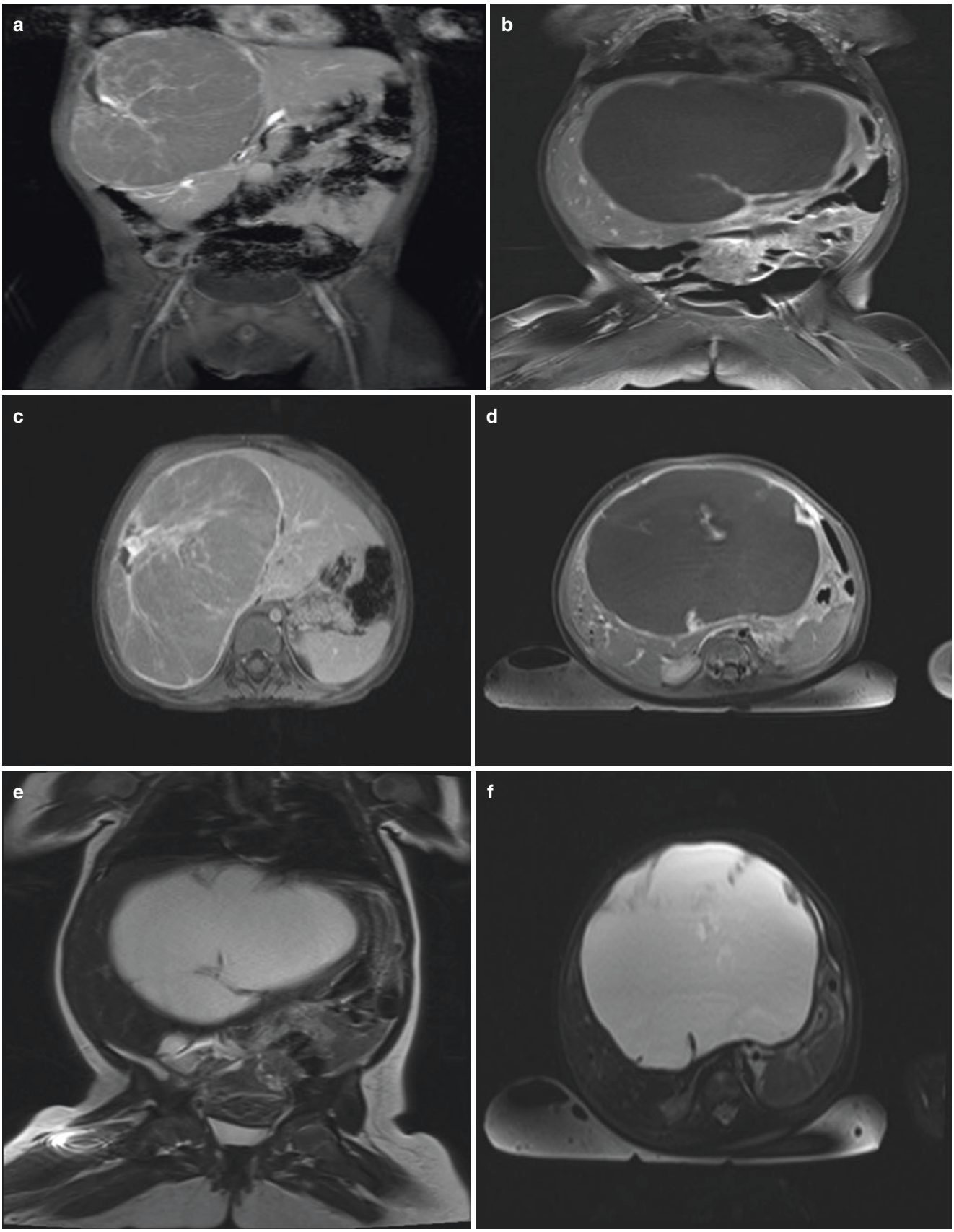

Fig. 4.1 (**a**–**f**) Mesenchymal Hamartoma MRI scan-T1 post gadolinium enhanced fat-sat coronal and axial images reveal large cystic lesion with thin enhancing septae and involving the entire right lobe of liver

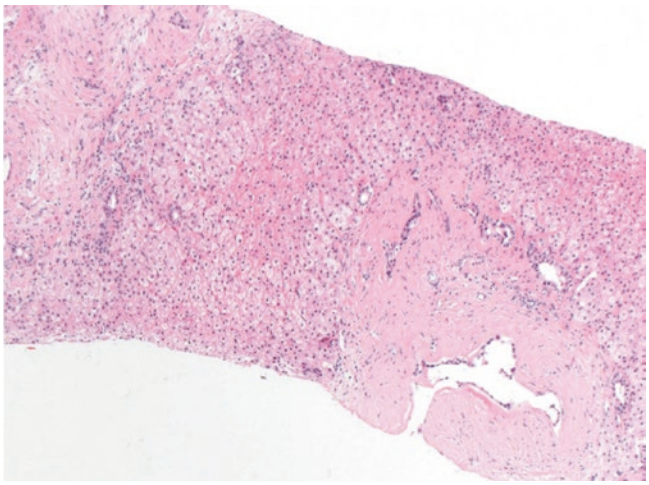

Fig. 4.2 (H&E original magnification ×100). In mesenchymal hamartomas, the structures normally expected in the liver; hepatocytes, bile ducts and connective tissue are seen with a random organisation. Sometimes there can be a cystic component

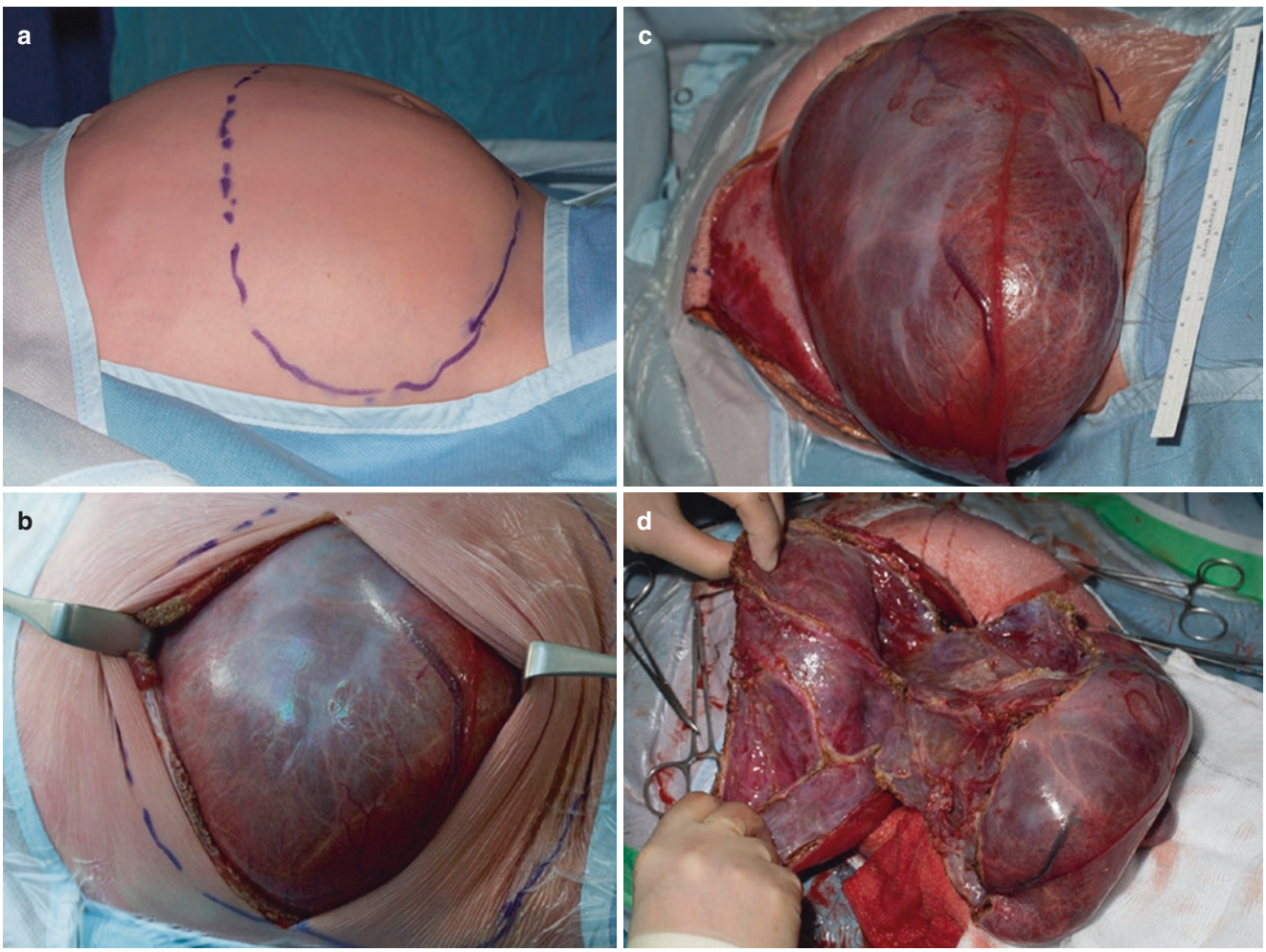

Fig. 4.3 Note the cyst marked on the abdominal wall (**a**), the large mass of the tumour on opening the abdomen (**b** and **c**) which was almost completely excised (**d**)

4.2 Focal Nodular Hyperplasia

Focal nodular hyperplasia (FNH) is rare in the paediatric age group and occurs more commonly in girls than boys. The vast majority of cases are asymptomatic, although some patients present with an abdominal mass or pain. It may occur in normal livers and also in chronic liver disease such as Alagille syndrome (see also Chapter 1). There are characteristic radiological features (Fig. 4.4a–f).

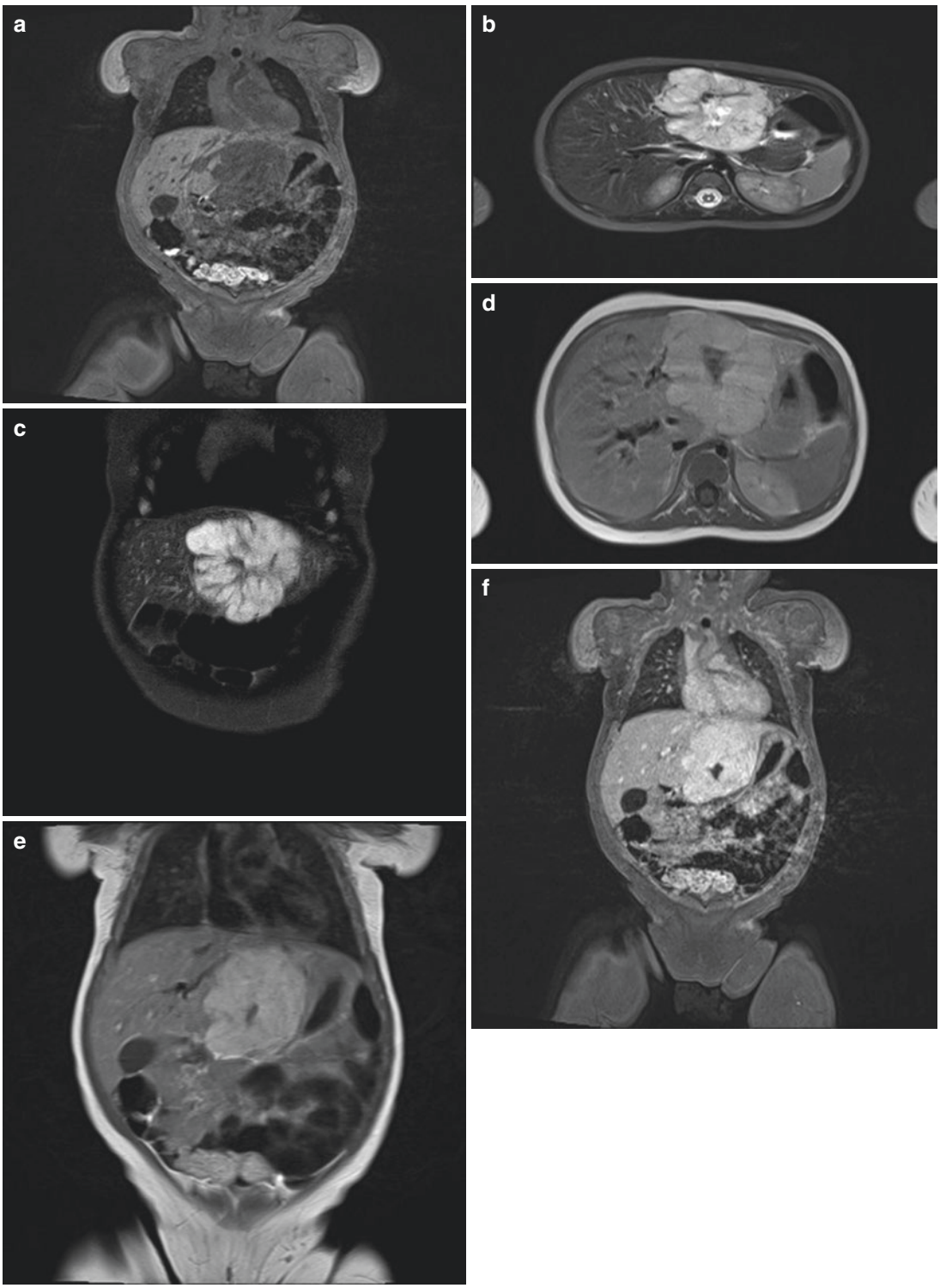

Fig. 4.4 (**a**–**f**) MRI of FNH—There is a large lobulated lesion in the left lobe of liver which is iso to hypo intense to liver on T1WI (**a**), predominantly hyper intense periphery with hypo intense central scar on STIR sequences (**b**, **c**). Following intravenous gadolinium injection there is progressive enhancement of the lesion from periphery to the centre with lack of enhancement of the central scar on delayed images (**d**–**f**)

Histologically, the lesions have features of a well-localized area of liver cell hyperplasia around a fibrous central scar (Fig. 4.5). This central scar shows up clearly on CT or MRI scans. Colloid scans are usually positive, as there are sufficient reticulo-endothelial cells within the mass to take up the isotope. Patients may have single or multiple nodules (Fig. 4.6a–c).

Management is conservative approach unless associated with abdominal pain. Girls requiring oral contraceptives are recommended to use progestogen only preparations. Surgical resection is only required for symptomatic patients, as there is no risk of malignancy. There is risk of recurrence.

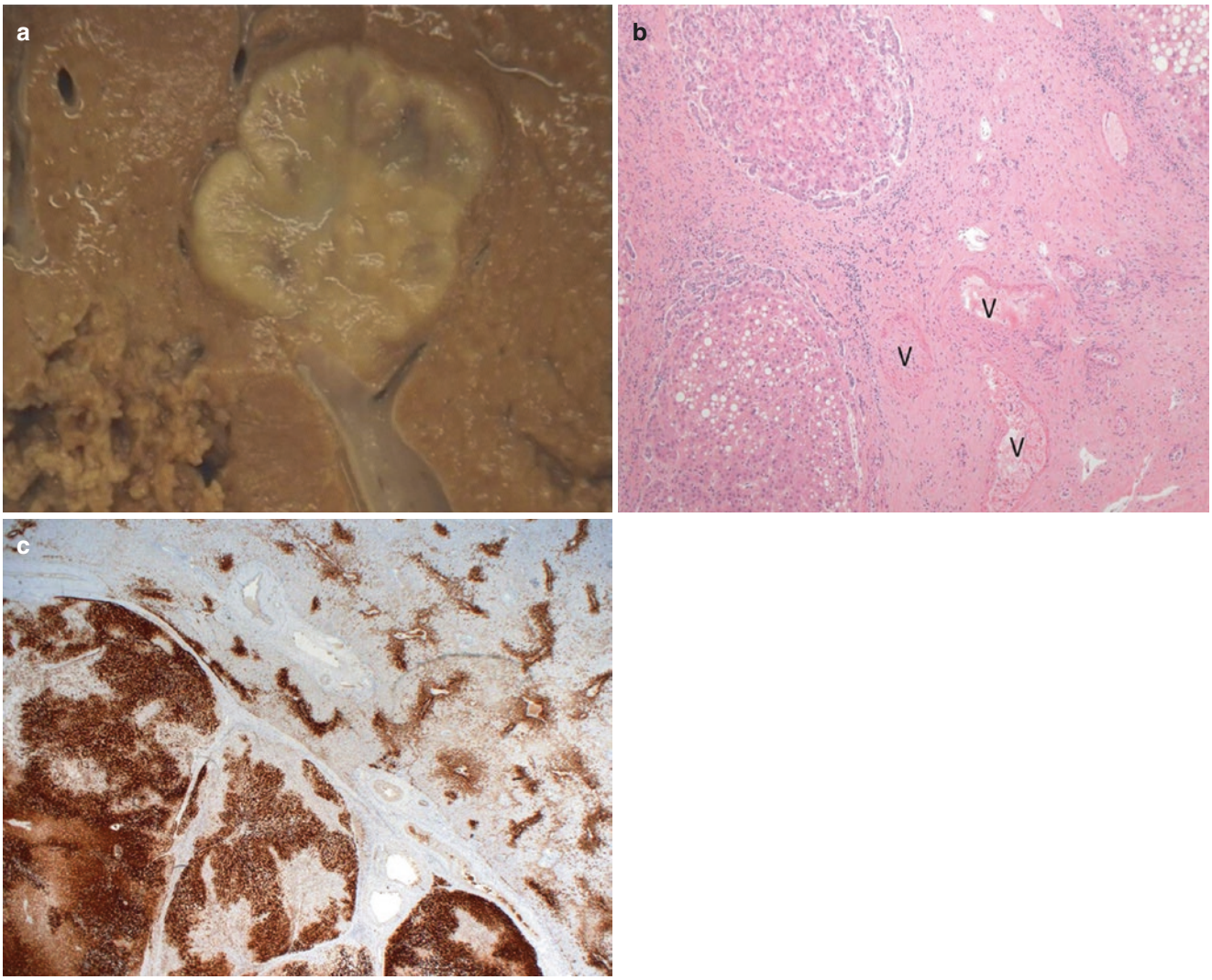

Fig. 4.5 (**a**) A resected lesion shows the macroscopic central scar of focal nodular hyperplasia. (**b**) Original magnification ×40 shows nodules of hepatocytes separated by fibrous septa containing prominent vessels 'V' unaccompanied by bile ducts. Ductules are present around the hepatocyte nodules. Features can mimic cirrhosis. In **c** the lesion is in the bottom left of the image, a 'map-like' pattern of positivity is seen with glutamine synthetase immunohistochemistry

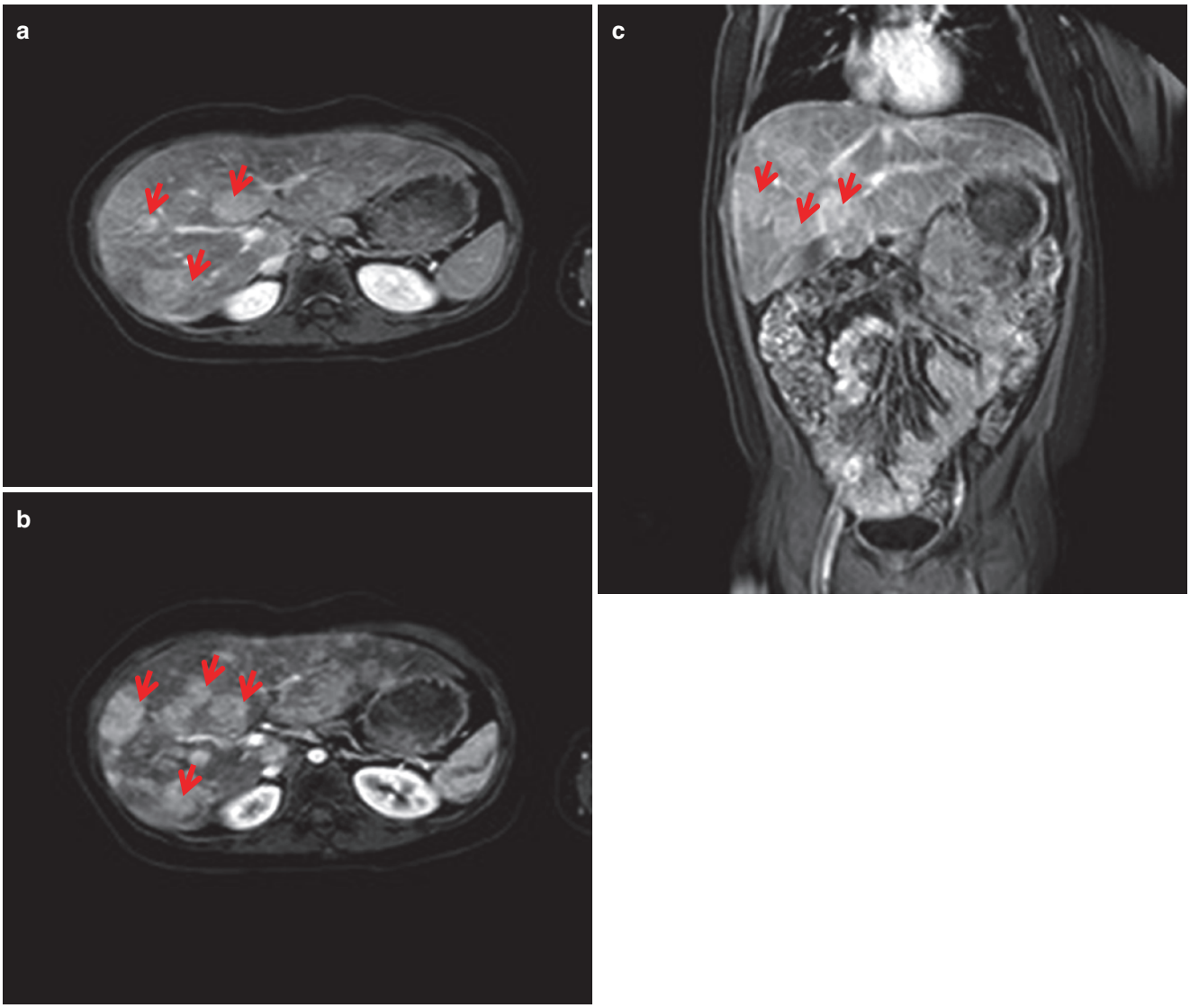

Fig. 4.6 (**a**–**c**) MRI scan multi-focal-T1 post gad fat sat VIBE axial and coronal sequences reveal progressive peripheral to central enhancement of multiple hepatic lesions (arrows marking multiple nodules) suggestive of multiple FNH

4.3 Hemangiomas

Haemangiomas and vascular lesions are the most common benign tumor of infancy affecting 4–5% of infants. They are grouped into two clinically and biologically distinct forms, congenital hemangiomas which are present at birth (some of these are diagnosed ante-natally) and infantile hemangiomas which evolve after birth.

4.3.1 Congenital Hemangiomas

Congenital hemangiomas evolve during fetal life and are fully developed at birth. These lesions are focal, have equal sex distribution and are rarely associated with accompanying cutaneous infantile hemangioma (Fig. 4.7a–d).

They have been identified on magnetic resonance imaging as a well-defined, solitary, spherical tumor that is hypointense

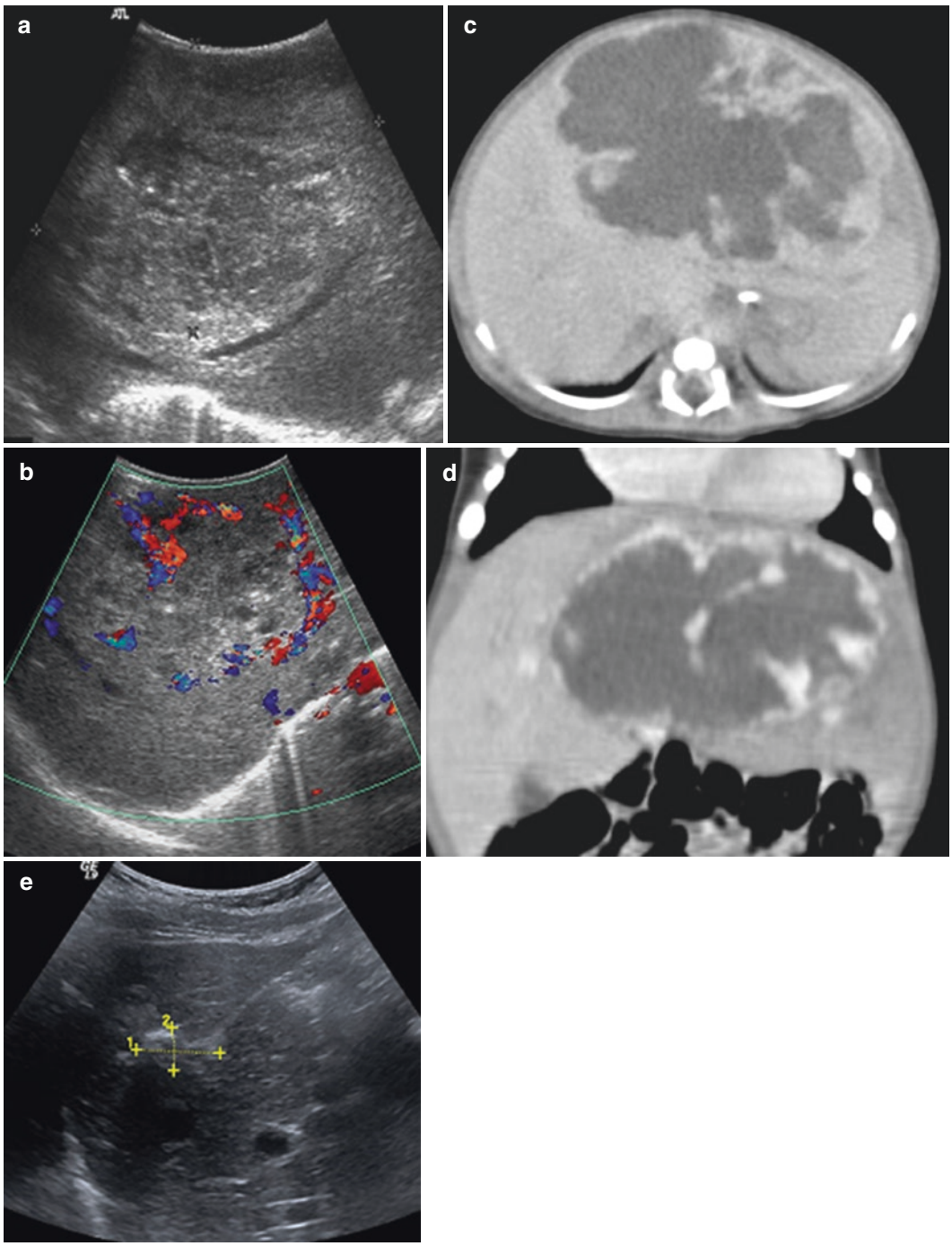

Fig. 4.7 Congenital hemangioma (**a**) US scan large cystic mass in the left and middle areas of the liver with mixed echogenicity. (**b**) Doppler US flow is seen predominately around the mass. (**c**) CT scan show a low density lesion in the left lobe of the liver. (**d**) The edge of this lesion enhances avidly with contrast medium, with no significant infilling on the delayed scan. The rest of the liver appears unremarkable. Follow-up US showing small, calcified mass on conservative management (**e**)

relative to liver on T1-weighted sequences and hyperintense on T2-weighted sequences (Fig. 4.8). The typical tumor demonstrates centripetal enhancement on gadolinium contrast-enhanced sequences. Areas of central necrosis, thrombosis, or intra-lesional hemorrhage are heterogeneously enhanced. The solid non-thrombosed (non-involuted) areas of the lesion exhibit intense homogeneous enhancement.

Some focal lesions are associated with mild anaemia or thrombocytopenia. Immunoexpression of GLUT-1 is not observed (Fig. 4.9).

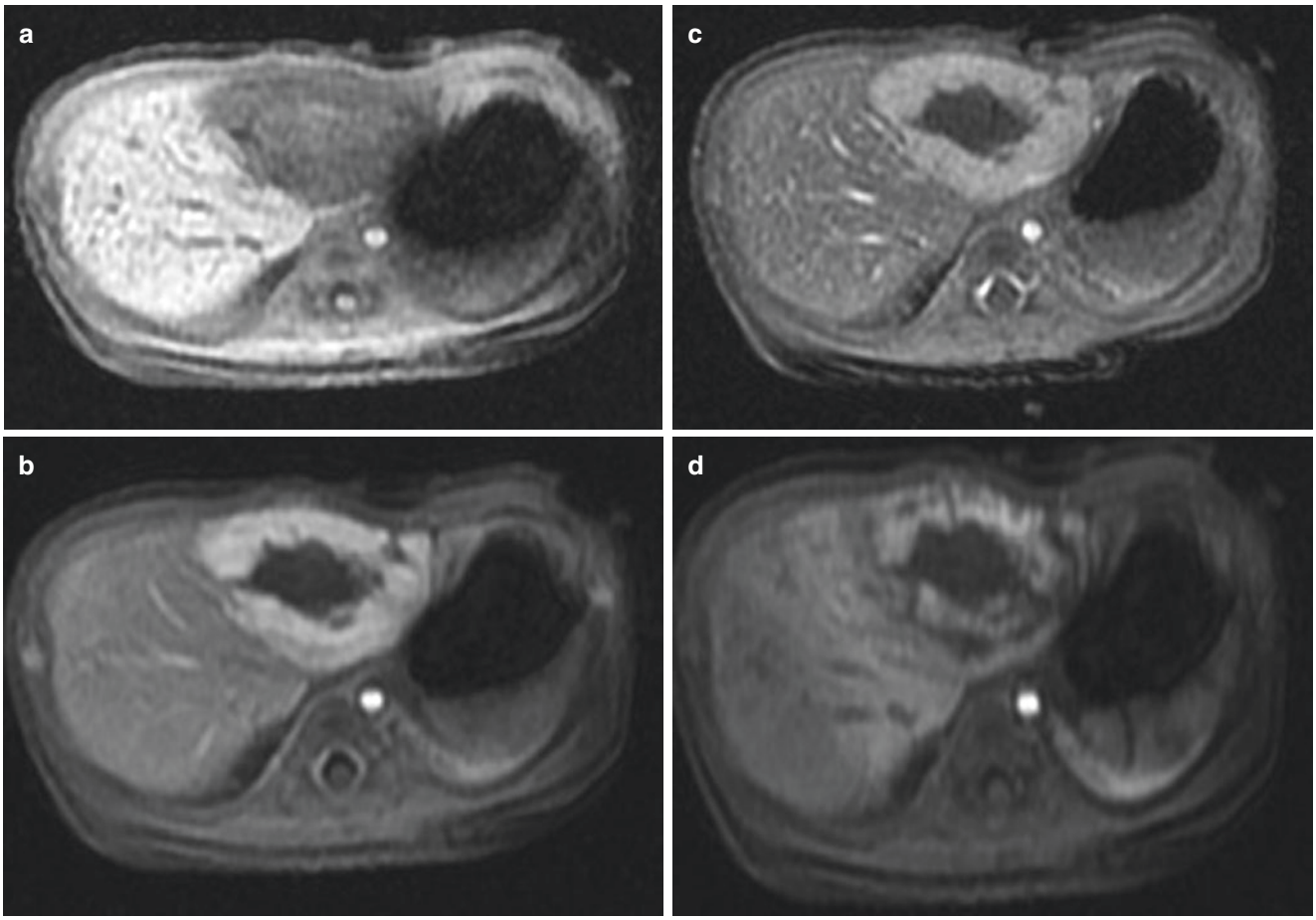

Fig. 4.8 (**a**–**d**) MRI Congenital Hemangioma: T1 VIBE fat sat images following intravenous gadolinium injection reveal progressive peripheral to central enhancement of a lobulated left lobe liver lesion in keeping with a congenital haemangioma

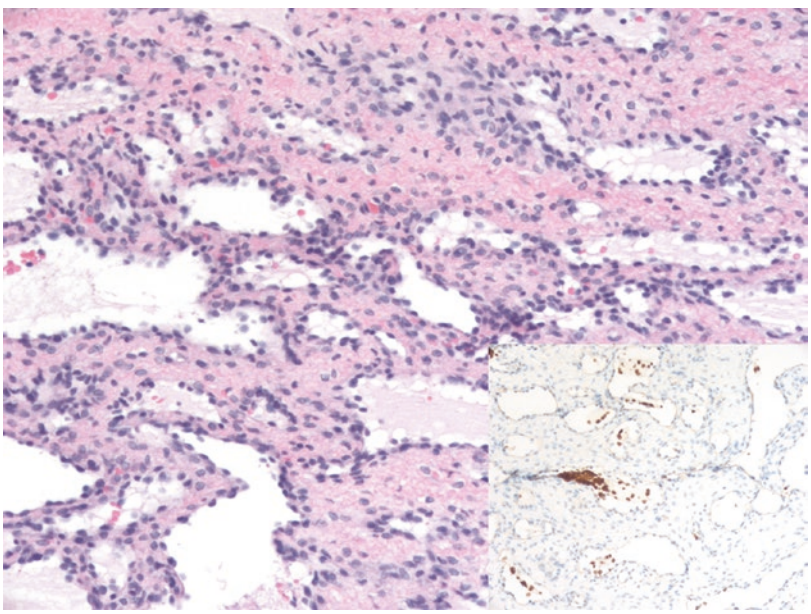

Fig. 4.9 Histological features: In the top left hand panel (H&E ×20) there is an ill-defined proliferation of small capillary sized blood vessels, these are also seen adjacent to biliary ductules in the top right hand panel (H&E ×100). In the bottom left hand panel the endothelium lining the vessels is positive with a vascular endothelial marker, CD34. Glut 1 is positive in a few red blood cells within the lumen of the vessels but, critically, the endothelium lining the vessels is negative. This distinguishes congenital haemangiomas from infantile haemangiomas

4.3.2 Infantile Hemangiomas

Infantile hemangiomas are either not present or are very small at birth. These lesions grow progressively and are associated with cutaneous hemangioma. It is possible that the majority remain undetected because they are clinically silent. Some lesions are incidentally diagnosed on routine postnatal imaging for other conditions (Figs. 4.10 and 4.11).

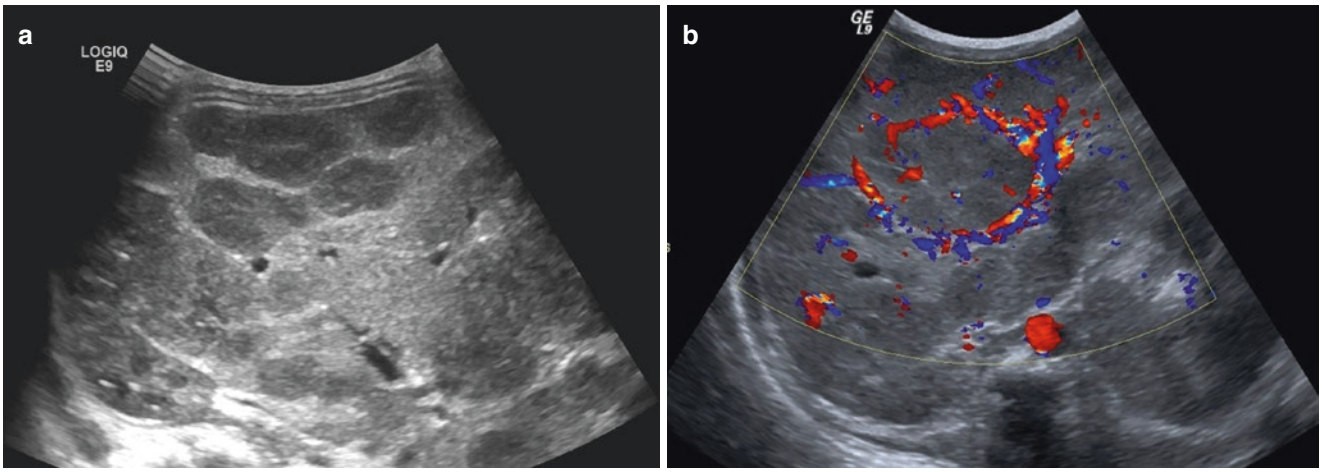

Fig. 4.10 Infantile Heamangioma: (**a**) mass in the liver which is hypervascular on Doppler US (**b**) reveal multiple hypo-echoic liver lesion which are suggestive of infantile Hemangioma

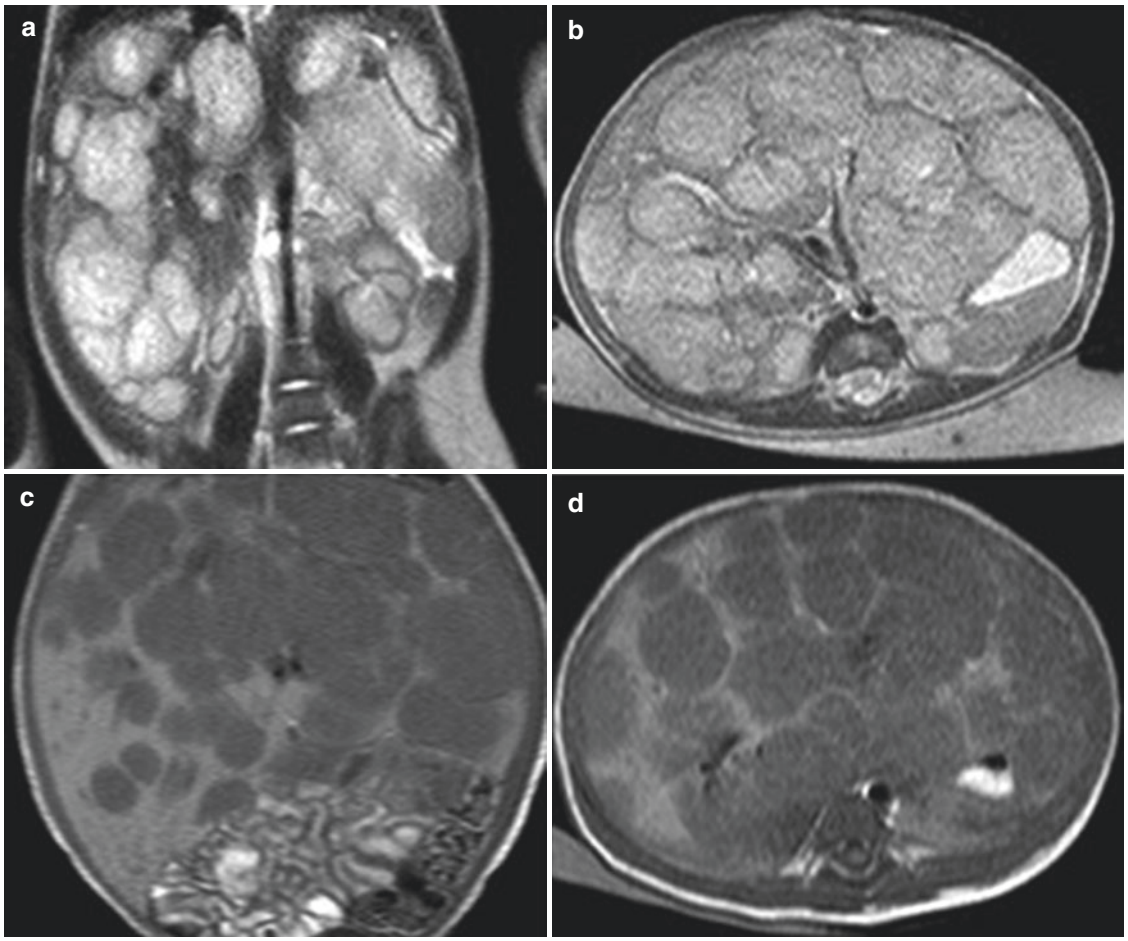

Fig. 4.11 (**a**–**d**) T1 and T2 axial and coronal images of the liver reveals hepatomegaly with presence of multiple well defined rounded lesions within liver which are hypo-intense on TWI and variably hyper-intense of T2WI

Management of hepatic vascular lesions. Most hepatic hemangiomas, congenital and infantile, do not require therapy because they are asymptomatic or involute spontaneously. If there are symptoms or the development of cardiac failure, embolization is required (Fig. 4.12a, b).

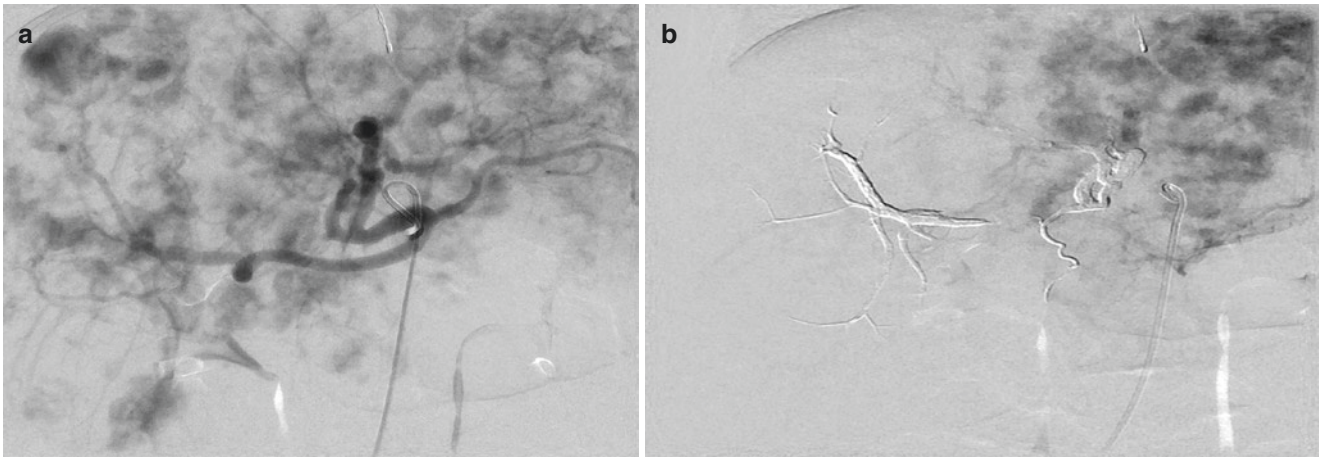

Fig. 4.12 (**a**) Reveals the vascular recruitment of multiple liver lesions on hepatic artery angiogram. (**b**) Reveals the ablation of vascular recruitment of the multiple lesions in the right lobe of liver following embolization

4.4 Malignant Tumours

The most common malignant liver tumors which present with abdominal distention include Hepatoblastoma, Hepatocellular carcinoma (HCC) and Embryonal/un-differentiated Sarcoma.

4.4.1 Hepatoblastoma

Hepatoblastoma is the most common malignant tumours in childhood with a peak age of presentation under the age of 18 months. They are rare after the age of 3 years. There is a male predominance of 3:2. The commonest presenting feature is a palpable abdominal mass with abdominal distension, but other features include anorexia, weight loss, pain, vomiting, and jaundice. The diagnostic work-up includes detection of biological markers e.g. alpha feto-protein and Beta HCG, radiological imaging includes abdominal US scan, MRI abdomen.

Hepatoblastoma may be associated with syndromes such as Beckwith–Wiedemann syndrome, hemi-hypertrophy and precocious puberty. Tissue diagnosis is recommended before planning management (Fig. 4.13a, b).

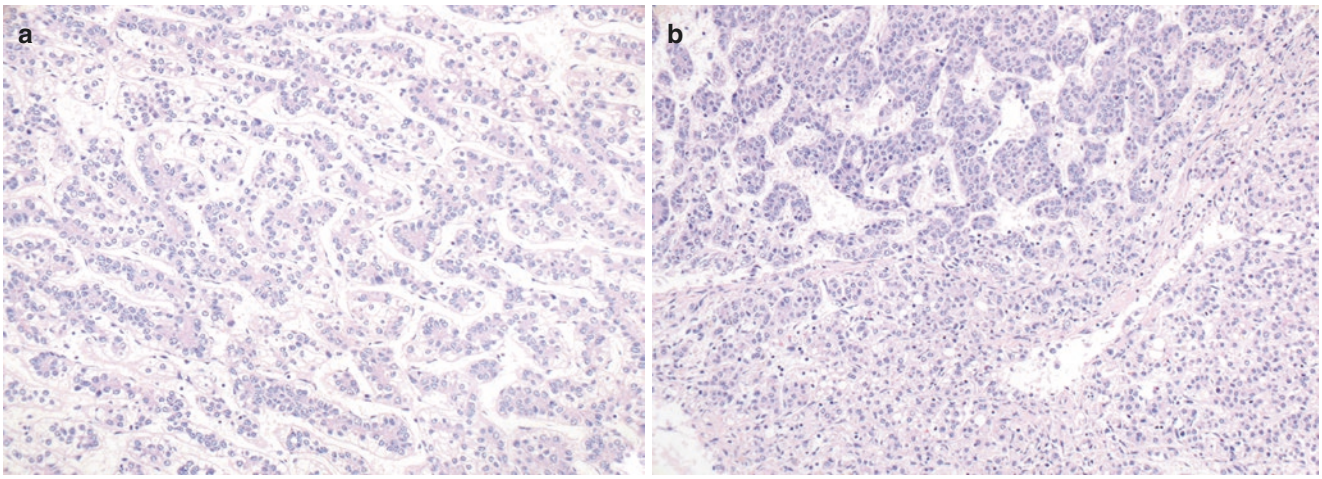

Fig. 4.13 Hepatoblastoma. (**a**) (H&E ×200). Fetal hepatoblastoma comprises cells resembling normal hepatocytes, in this example there is a trabecular arrangement, the cells have 'polarised' cytoplasm with one half appearing clear and the other half eosinophilic, this is quite a common change. (**b**) (H&E ×200). In this image fetal hepatoblastoma is seen in the bottom right, in the top left embryonal cells are seen, note these are smaller and appear dark due to an increased nuclear to cytoplasmic ratio

Management includes defining the extent of disease as described by The International Society of Pediatric Oncology (*Société Internationale d'Oncologie Pédiatrique,* SIOP). The staging system is based on preoperative assessment and the location of the tumor called Pre-T-ext of diseases (Figs. 4.14 and 4.15) (Reproduced with permission from Derek J Roebuck and Springer-Verlag 2006).

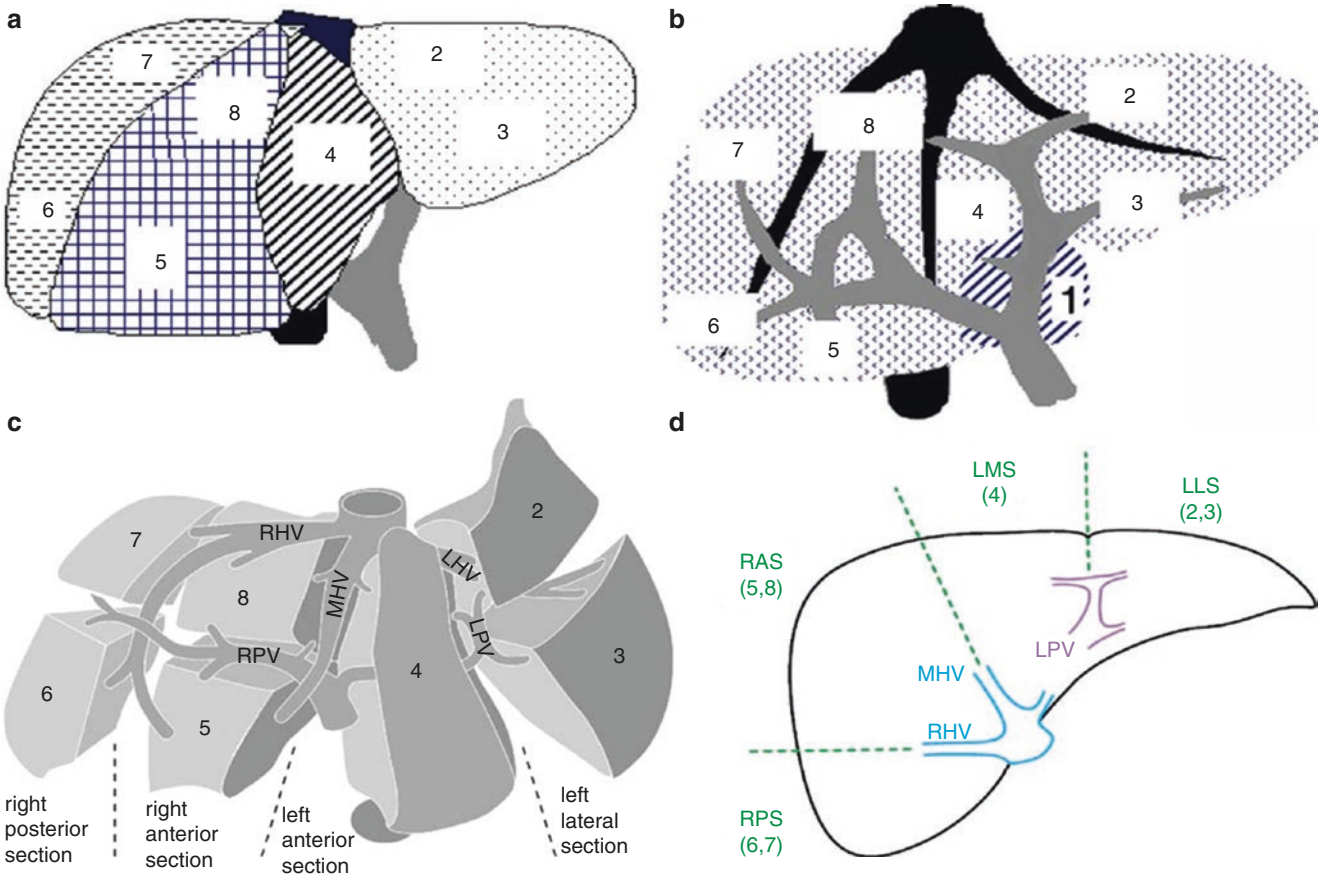

Fig. 4.14 Schematic representations of the segmental anatomy of the liver. (**a**) Frontal view of the liver. The numerals label Couinaud's segments 2–8. (**b**) The hepatic veins (black) and the intrahepatic branches of the portal veins (grey) are shown. (**c**) Exploded frontal view of the segmental anatomy of the liver. The umbilical portion of the left portal vein (LPV) separates the left medial section from the left lateral section (LLS). (**d**) Transverse section of the liver shows the planes of the major venous structures used to determine the PRETEXT number. The hepatic (blue) and portal (purple) veins define the sections of the liver (2–8). This schematic diagram shows how the right hepatic (RHV) and middle hepatic (MHV) veins indicate the borders of the right anterior section (RAS) with the right posterior (RPS) and left medial (LMS) sections. Note that the left portal vein (LPV) actually lies caudal to the confluence of the hepatic veins and is not seen in the same transverse image. The left hepatic vein (LHV) runs between segments 2 and 3 and is not used in PRETEXT staging

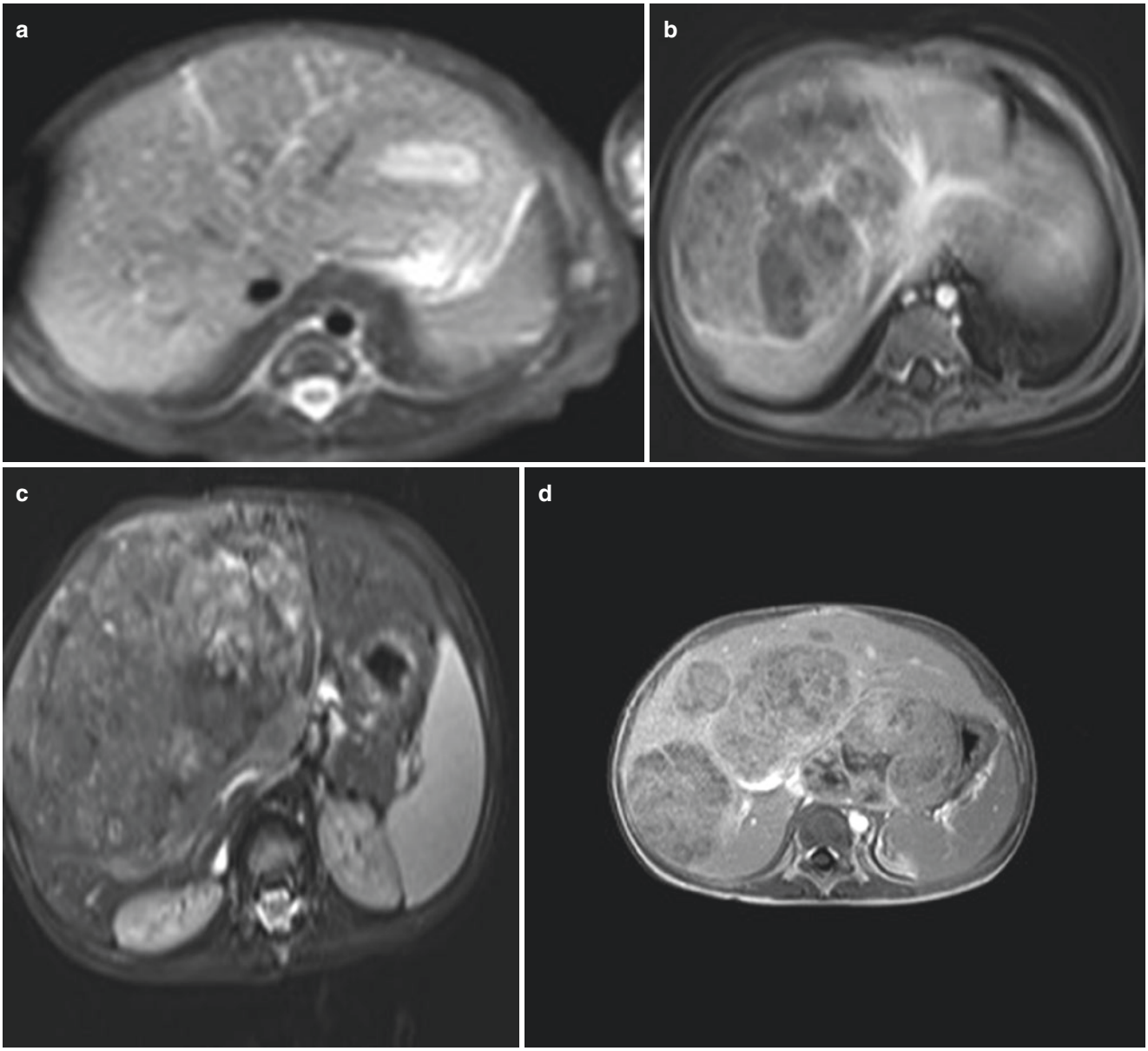

Fig. 4.15 (**a**) T1 post intravenous gadolinium enhanced axial section revealing tumour involving part of segment 2, 3 (Pretext 1). (**b**) T1 post intravenous gadolinium enhanced axial section of the liver reveals a large variably enhancing lesion involving segment 5, 6, 7 and 8 (pretext 2). (**c**) T1 post intravenous gadolinium enhanced axial section of the liver reveals a large variably enhancing lesion involving segment 5, 6, 7, 8 and 4 (pretext 3) (**d**) Pretext IV multifocal hepatoblastoma with all sector involved

4.4.2 Hepatocellular Carcinoma (HCC)

HCC presents in an older age group than hepatoblastoma and is rare in infancy. The clinical features are similar to those seen with hepatoblastoma, but it may arise in children with established liver disease, especially tyrosinemia, PFIC-2 (see Chapter 1) or Hepatitis B (see Chapter 7). A search for signs of underlying liver cirrhosis (splenomegaly due to portal hypertension, spider nevi, etc.) should be sought. The diagnosis is made by radiology and histology (Figs. 4.16 and 4.17).

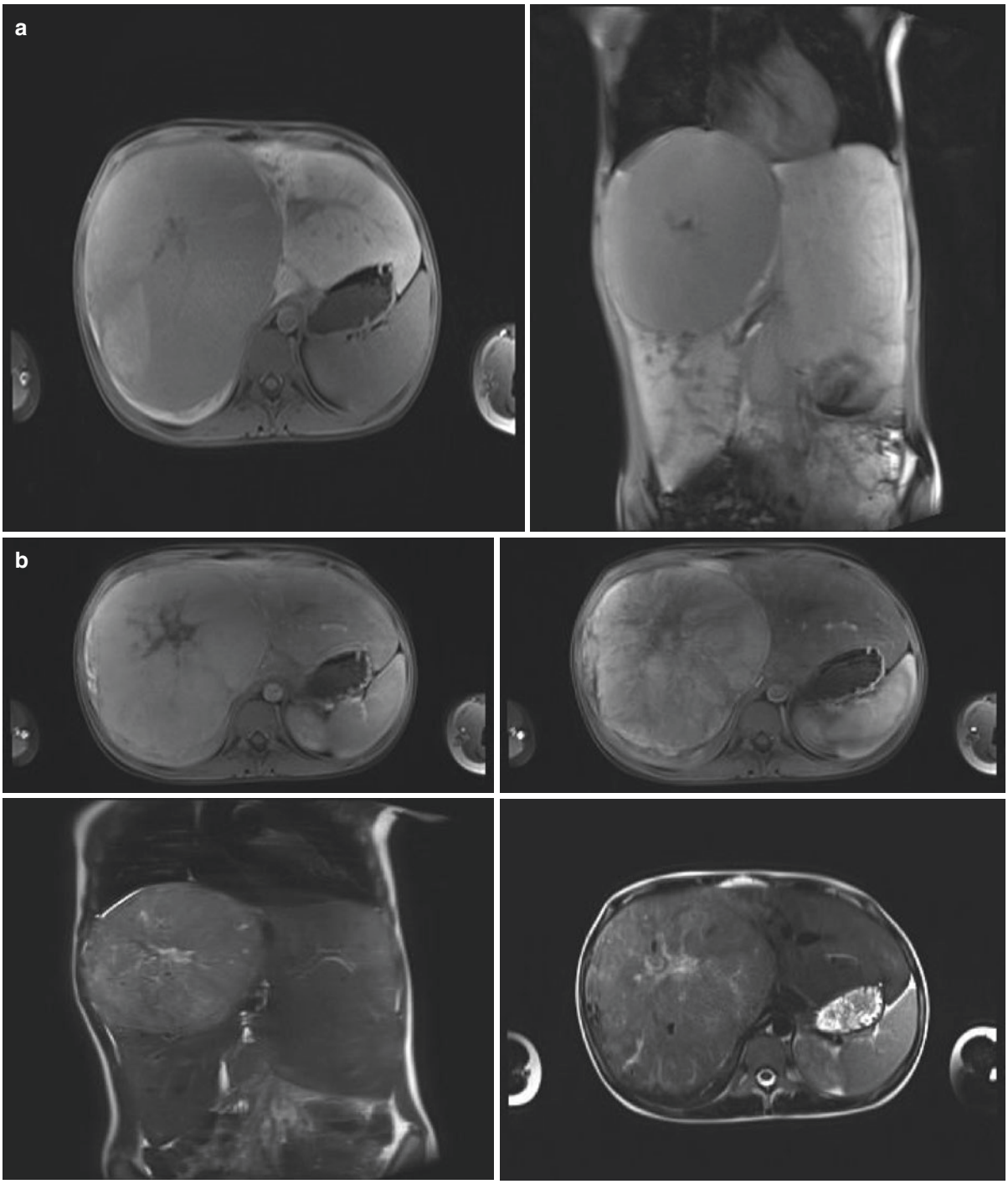

Fig. 4.16 (**a**) Axial DWI and ADC shows restricted diffusion of the large lobulated right lobe of liver mass typical of HCC. (**b**) T1 fat sat intravenous gadolinium enhanced axial and coronal images reveal relative non enhancement of the right lobe liver lesion in comparison with normal surrounding liver parenchyma. (**c**) T1 fat sat intravenous Primovist enhanced axial image reveal relative non uptake of the right lobe liver lesion in comparison with normal surrounding liver parenchyma

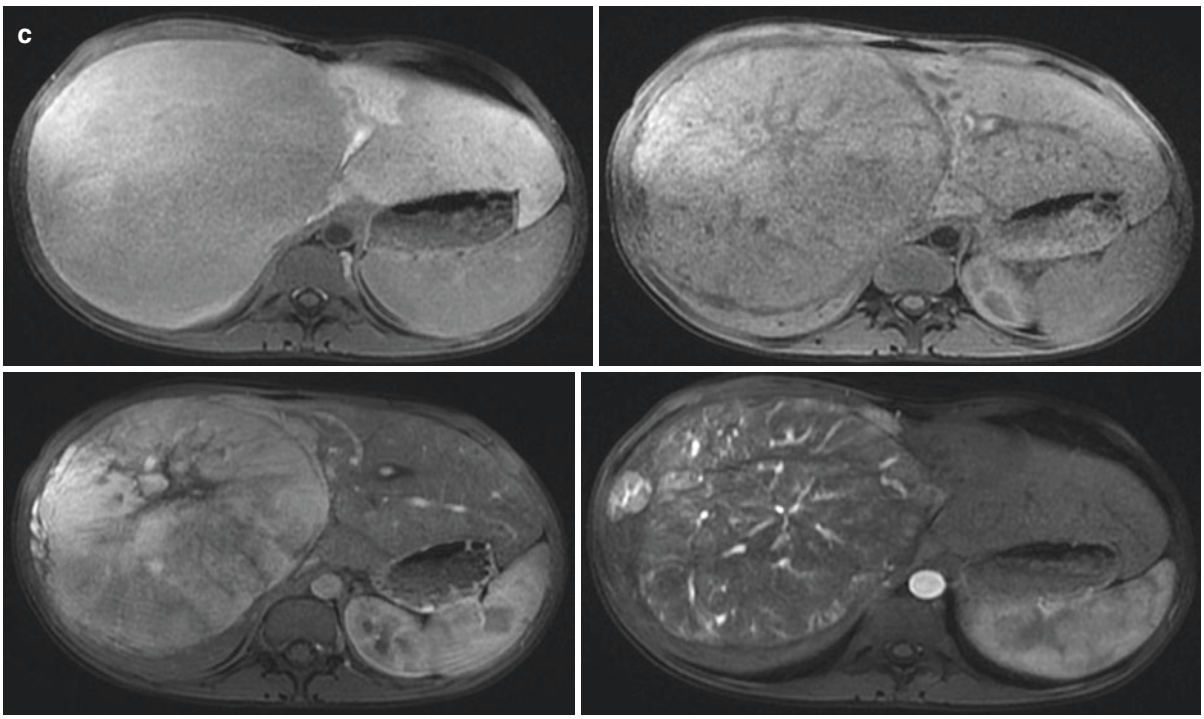

Fig. 4.16 (continued)

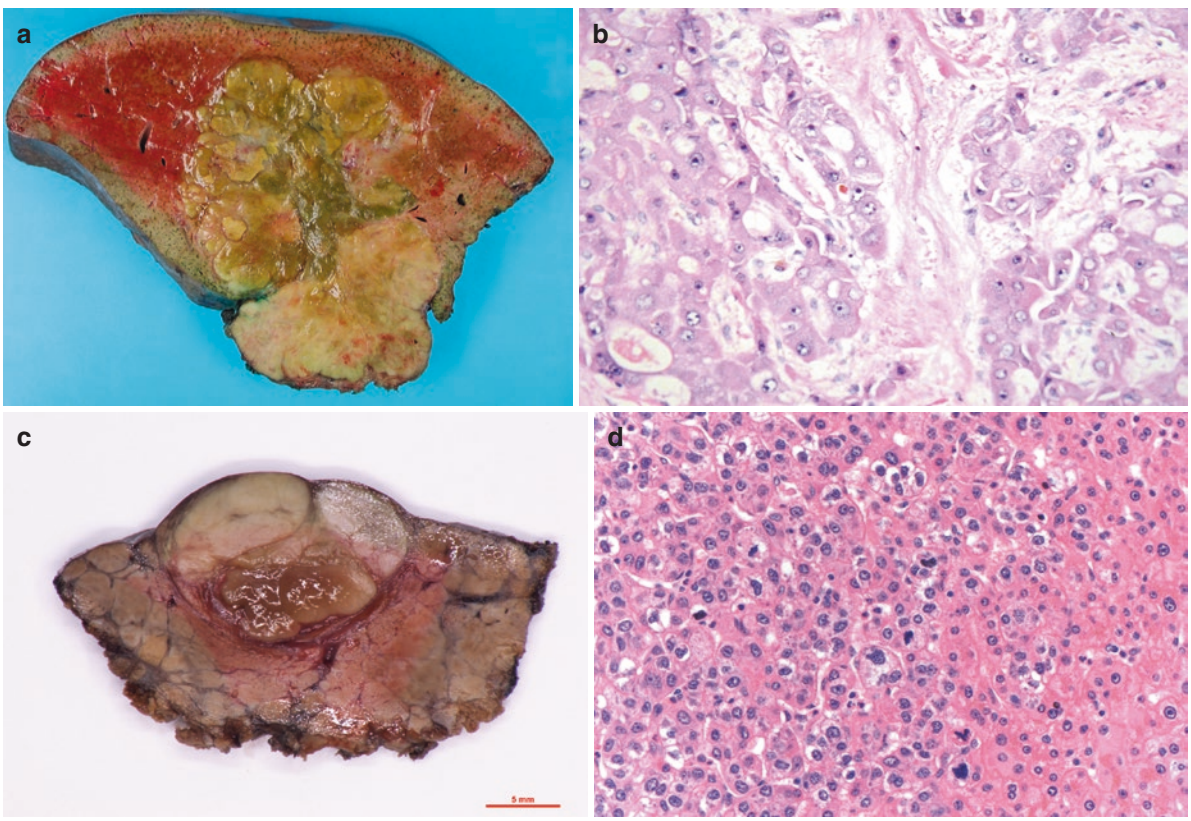

Fig. 4.17 Hepatocellular carcinoma. Panel **a** is a slice through a resection specimen, the carcinoma has a yellow/green appearance, note the central scar. Microscopically (**b** H&E ×400.) this is confirmed as fibrolamellar hepatocellular carcinoma, the tumour cells are very large with brightly eosinophilic cytoplasm secondary to the accumulation of mitochondria. The nuclei typically have prominent nucleoli. The tumour cells are separated by a sclerotic fibrous stroma. Panel **c** is a slice through a resection showing a hepatocellular carcinoma appearing as a dominant nodule in a background of cirrhosis. Microscopically (**d**, H&E ×400) the tumour cells still resemble hepatocytes but nuclear pleomorphism and mitotic figures are distinguishing features

The rare ***fibrolamellar type of HCC*** (Fig. 4.18a) is found in an older age group (median age 26.4 years) and occurs in non-cirrhotic livers. Abdominal mass is the commonest presentation and systemic symptoms are unusual.

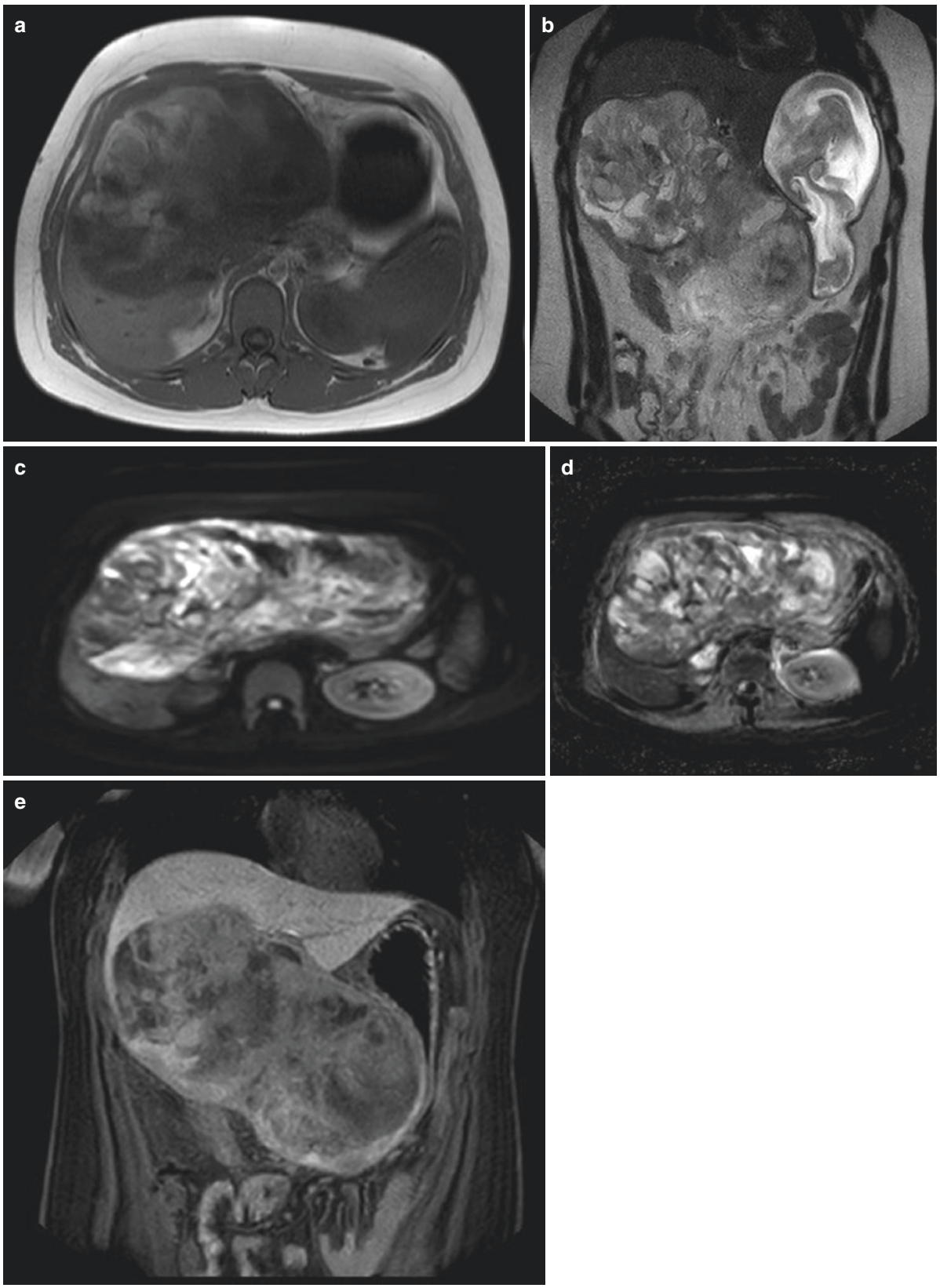

Fig. 4.18 Embryonal sarcoma Large lobulated lesion involving the entire right lobe of liver, heterointensity on T1WI (**a**) and T2WI (**b**), restricted diffusion on DWI (**c**) and ADC (**d**) with variable contrast enhancement on intravenous gadolinium enhanced fat sat T1WI (**e**)

4.5 Hepatic Sarcomas

Undifferentiated embryonal sarcoma of the liver has been considered an aggressive neoplasm with an unfavorable prognosis, but recent reports suggest that modern chemotherapy lead to significant tumor mass reduction, allowing radical surgery. The diagnosis is with radiology (Figs. 4.18 and 4.19) and histology (Fig. 4.20). Surgical resection is required (Fig. 4.21).

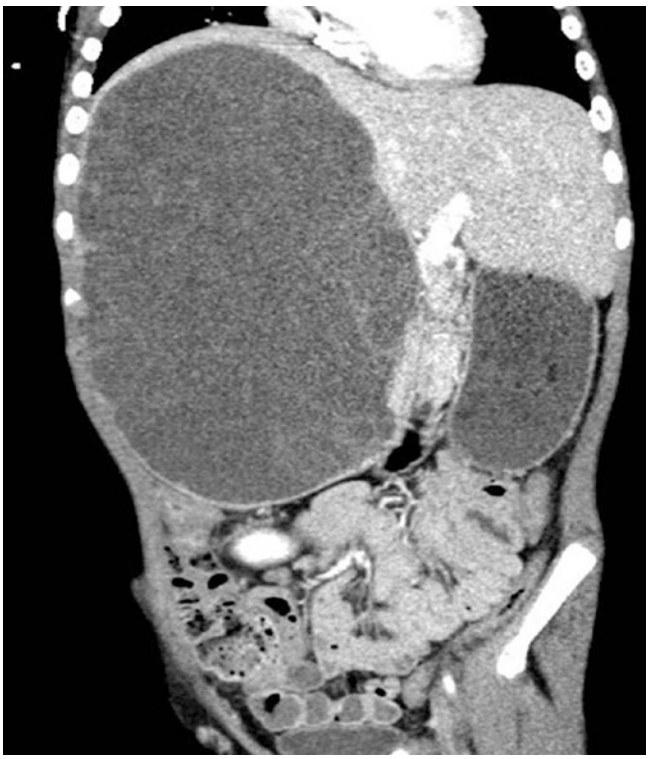

Fig. 4.19 Undifferentiated Sarcoma. A large tumour is occupying the right lobe of the liver which is both cystic and necrotic

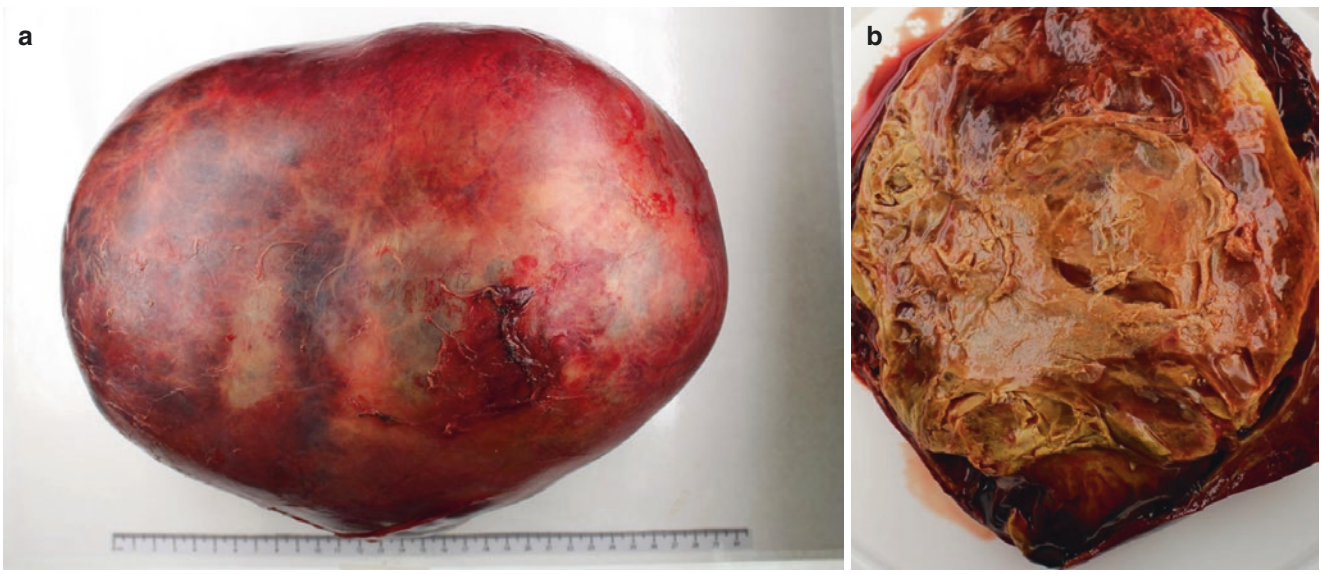

Fig. 4.20 Macro and **microscopic** of Undifferentiated Sarcoma. (**a**) The tumour can reach a large size and (**b**) often has a soft and necrotic cut surface. (**c**) Microscopically (H&E ×400) tumour is characterised by highly pleomorphic large cells. Eosinophilic globules (marked by the arrow in a cluster) can be further highlighted by PASD staining in examples where they are not so immediately apparent

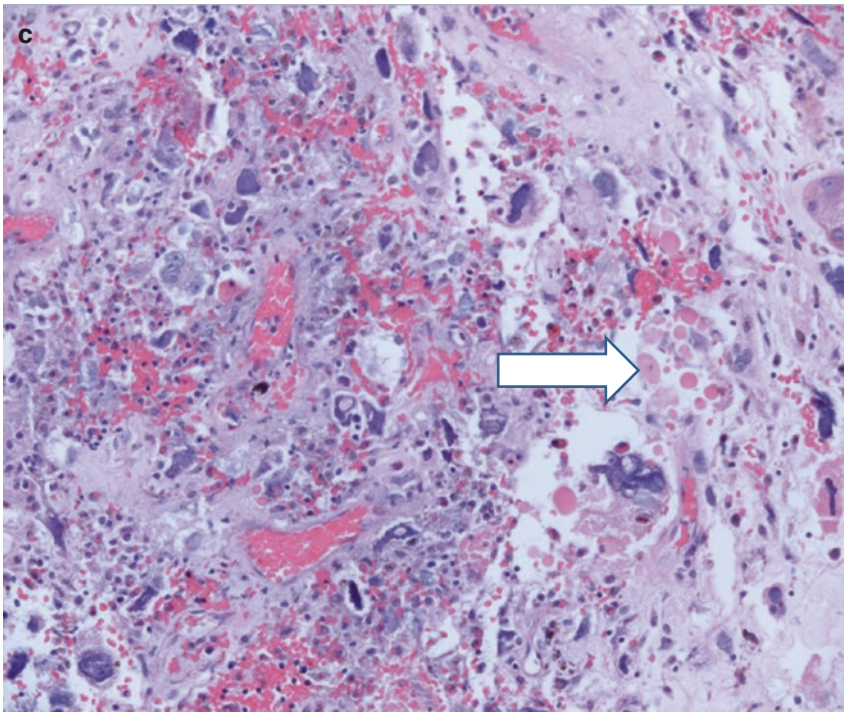

Fig. 4.20 (continued)

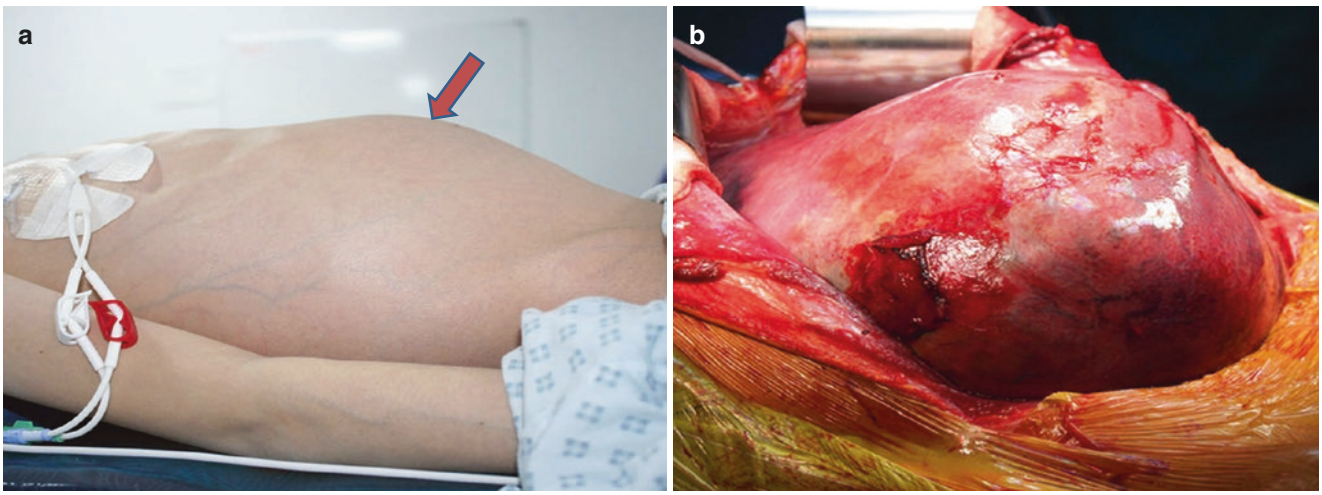

Fig. 4.21 This child had a visible mass caused by an undifferentiated sarcoma which was successfully resected. (**a**) arrow showing bulge on abdominal wall (**b**) large tumour visible on opening the abdomen

4.6 Pancreaticoblastoma

Pancreatic tumours are rare in children. However they are the most common malignant pancreatic tumours in children between 1 and 8 years. These tumours may develop in any part of the pancreas, but commonly affect the head. Common presenting symptoms include abdominal pain, distention, vomiting and jaundice. The diagnosis is with radiology and histology. Small tumors are resected followed by adjuvant chemotherapy. In children with big tumours, chemotherapy should be given first followed by surgery.

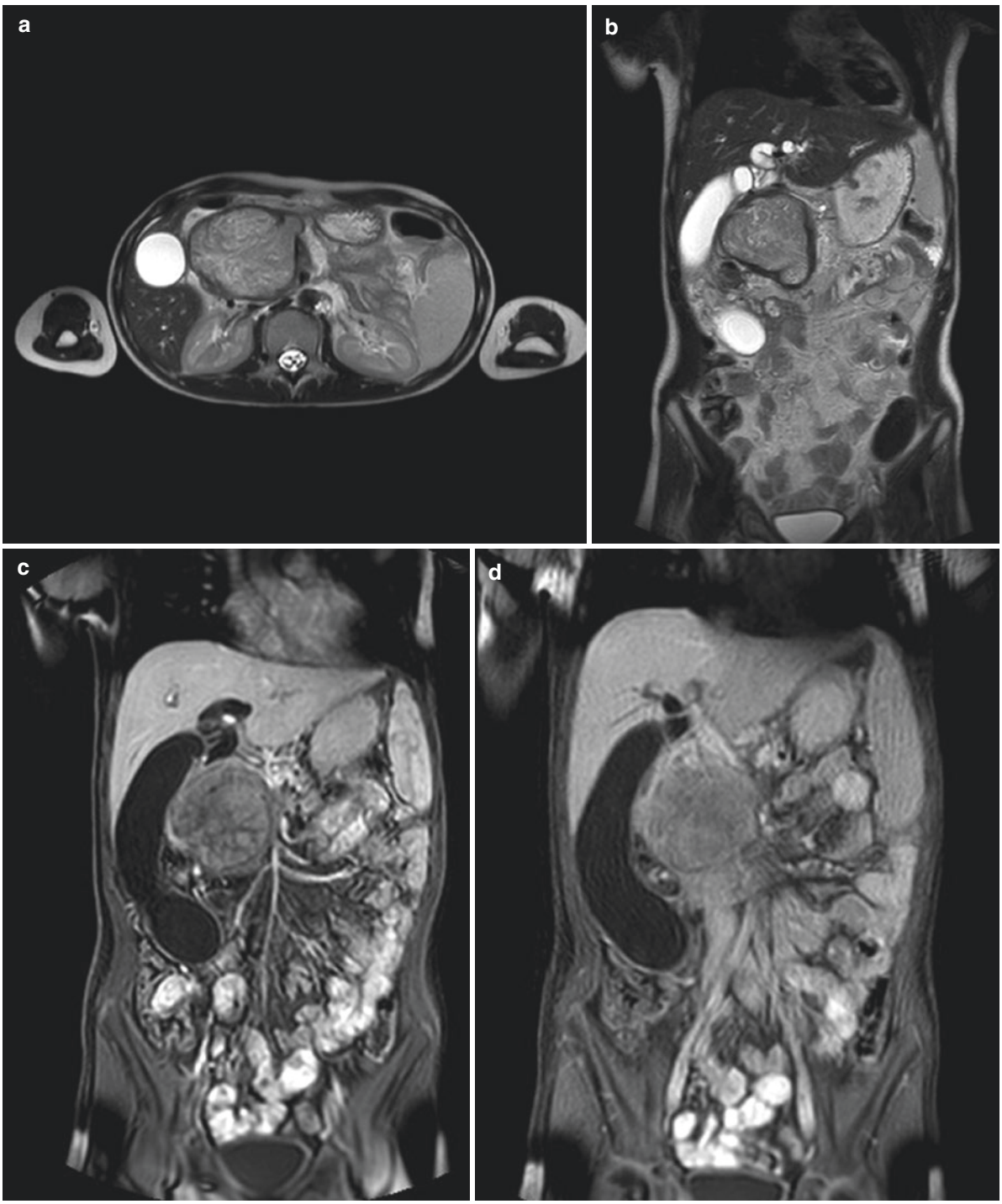

Fig. 4.22 Axial and coronal T2WI sections (**a**, **b**) reveals hyper intense mass in the head of pancreas causing dilatation of the common bile duct and pancreatic duct. Fat sat intravenous gadolinium enhanced arterial (**c**) and portal venous phase (**d**) reveals invasion of hepatic artery and portal vein by the mass in the head of pancreas

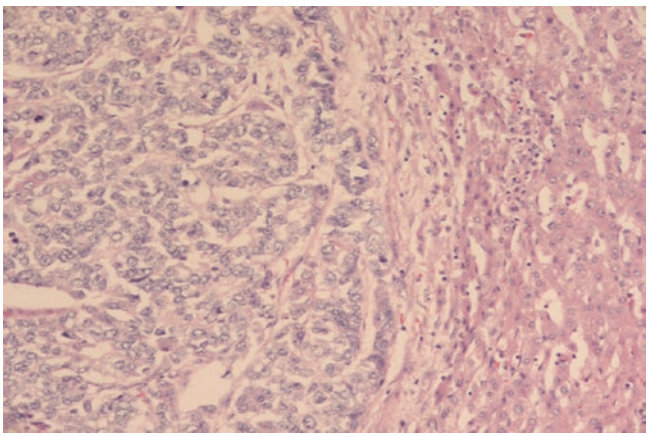

Fig. 4.23 Pancreaticoblastoma (H&E ×200). In this case there has been a metastasis to the liver. Normal hepatocytes, slightly compressed, are seen in the right of the image, pancreaticoblastoma is seen on the left as a small round blue cell tumour. Squamous morules, not demonstrated here, are sometimes seen

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The Acutely Ill Child

5

Deirdre Kelly

The main causes of liver disease in an acutely unwell older child are viral infection, drug injury or metabolic liver disease (Table 5.1). A thorough history may help distinguish from drug or toxin induced liver injury.

Table 5.1 Aetiology of acute liver disease

Aetiology of acute liver disease	Investigations	Clinical presentation and outcome
Viral illness	Serology for hepatitis A, B, C, E, EBV, CMV, HHV6 and adenovirus	Prodromal illness, vomiting, jaundice. Most recover spontaneously
Seronegative hepatitis	Diagnosis of exclusion but typical clinical course	Aplastic anaemia Poor prognosis, usually requires transplantation
Toxins/drugs	Drug levels Toxicology screening	Usually recovers once drug is withdrawn
Wilsons disease	Serum copper and caeruloplasmin, 24 h copper urine collection, typical liver histology, high copper levels in liver tissue, mutations in ATP7B	Chronic liver disease Neurological features Haemolytic anaemia
Autoimmune hepatitis	Raised serum immunoglobulin IgG Positive ANA, SMA, or LKM autoantibodies Typical histology	Chronic liver disease Cirrhosis and Malnutrition Coeliac disease
Budd Chiari	CT angiogram Typical histology Coagulation screen for Protein C,S, lupus anti coagulant	Acute liver failure Enlarged caudate lobe Ascites

Most metabolic disease presents in infancy, however hereditary fructose intolerance does not present until fructose is introduced into the diet (see Chapter 2).

Autoimmune hepatitis and Wilson's disease may present with acute liver disease, chronic liver disease or acute decompensation of previously unrecognised chronic disease.

Acute liver failure develops when hepatic synthetic function cannot be maintained leading to jaundice, coagulopathy, hypoglycaemia and encephalopathy.

The most common cause of acute liver failure worldwide is viral hepatitis (A, B, E) but in developed countries, seronegative hepatitis (Hepatitis non A–E) is the commonest and has a poor outcome.

Acute viral hepatitis is usually due to hepatitis A, but unless the child becomes cholestatic or develops acute liver failure, rarely requires hospitalisation.

Diagnosis is based on serology (Table 5.1) liver biopsy is rarely required but shows acute hepatitis with 'parenchymal disarray' (Fig. 5.1).

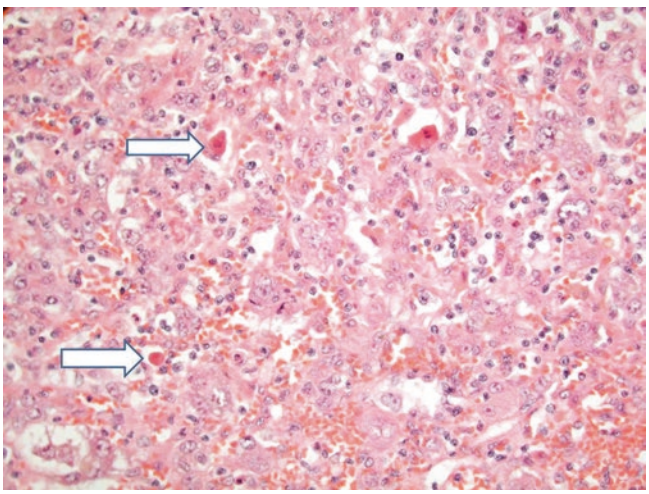

Fig. 5.1 (H&E original magnification ×200). Viral infection is a cause of acute hepatitis which shows a disorderly arrangement of hepatocytes, lymphocytes are present and there are apoptotic hepatocytes also referred to as 'acidophil bodies' two examples are marked with arrows

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D. Kelly et al. (eds.), *Atlas of Pediatric Hepatology*, https://doi.org/10.1007/978-3-319-69529-7_5

Abdominal ultrasound typically shows an enlarged liver with an oedematous gall bladder, but no evidence of chronic liver disease (Fig. 5.2). Spontaneous recovery is usual, but 10% may develop prolonged cholestasis or fulminant hepatitis.

This child presented at 8 years of age with lethargy, poor feeding and jaundice (Fig. 5.3). Despite supportive therapy she became progressively more encephalopathic and her clotting became more abnormal. Her MRI clearly showed cerebral oedema but no irreversible brain injury (Fig. 5.4). A provisional diagnosis of seronegative hepatitis was made as no underlying aetiology was identified. She received a successful super urgent liver transplant which has a 70% 1 year survival. The explanted liver showed submassive necrosis typical of seronegative liver failure (Fig. 5.5). Aplastic anaemia may be associated and require separate treatment, including bone marrow transplantation.

Drug Induced Liver Disease (DILI) is uncommon in children, but is an important cause of acute or chronic liver failure

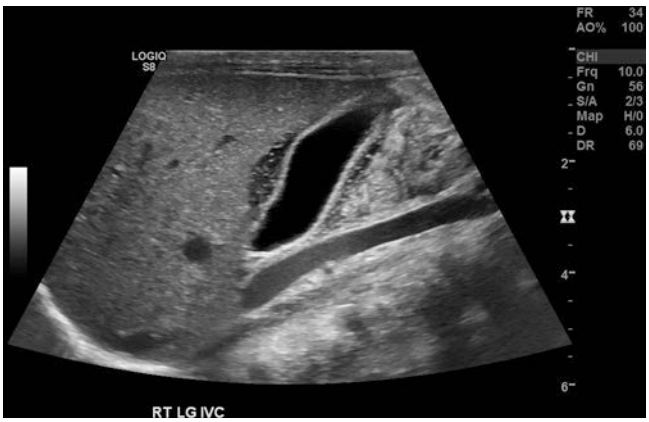

Fig. 5.2 Ultrasound of liver reveals an oedematous thick walled gall bladder. The adjacent liver has normal echogenicity and architecture, with no evidence of chronic liver disease

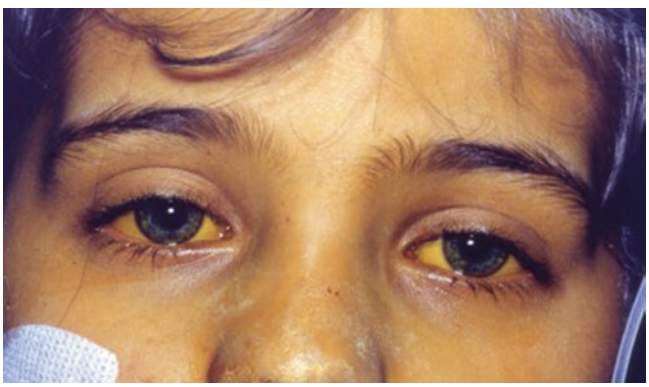

Fig. 5.3 This girl presented with acute liver failure due to seronegative hepatitis

(see also Chapter 6). DILI may be due to dose-dependent hepatotoxicity (e.g. paracetamol) but is more commonly due to idiosyncratic reactions. Underlying disorders, such as mitochondrial dysfunction may increase susceptibility to hepatotoxicity. The commonest DILI in childhood are listed in Table 6.2 in Chapter 6.

Acute Liver failure due to Isoniazid (INH) is common, particularly in those who are 'rapid acetylators". Clinical symptoms include jaundice, coagulopathy, and encephalopathy in a patient on INAH. It is essential to discontinue the drug, but liver failure may progress requiring transplantation. Histology demonstrates acute hepatitis and necrosis (Fig. 5.6) Anti-tuberculosis treatment is required post-transplant.

Acute liver failure also occurs with recreational drugs such as ecstasy, and the clinical history is important in the diagnosis. Presentation is with collapse within 6 h of ecstasy ingestion with hyperthermia, hypotension and convulsions. Death is likely unless transplantation is possible. Histology shows hepatocellular injury (Fig. 5.7).

Budd Chiari syndrome is due to thrombosis of the hepatic veins resulting in obstruction to the outflow of blood from the liver. The cause is either a congenital web or thrombosis due to an inherited coagulation disorder (Table 5.1).

This boy presented with acute liver failure at 11 years (Fig. 5.8) His abdominal ultrasound confirmed the narrowing of the hepatic veins but also showed that the portal venous and hepatic artery flow were compromised by the severe acute outflow obstruction (Fig. 5.9a, b). When a transjugular intrahepatic portosystemic shunt (TIPS) was inserted, (Fig. 5.9c, d) flow through all vessels was restored and the liver failure resolved. In this case no procoagulant condition was identified, but he remained on warfarin for six indefinitely.

If TIPS is unsuccessful then liver transplant will be necessary. This slide is from an explanted liver showing the severe congestion of the liver (Fig. 5.10).

Lysosomal acid lipase deficiency (LAL-D) is a rare disorder which presents in infancy as well as in older children. It causes cholesterol ester and tryglyceride accumulation. It can cause severe multi system disease with lipid accumulation, hepatomegaly, malabsorption, anaemia and adrenal calcification as seen on this plain abdominal X-ray (Fig. 5.11b).

The liver typically looks bright on ultrasound due to the accumulation of lipids (Fig. 5.11b). The diagnosis is made by dry blood spot analysis for the LAL enzyme. Liver histology typically shows). Liver histology typically shows a mixed micro and macrovesicular steatosis (Fig. 5.12a–c).

Enzyme replacement therapy with sebelipase alfa ameliorates the disorder and prolongs life.

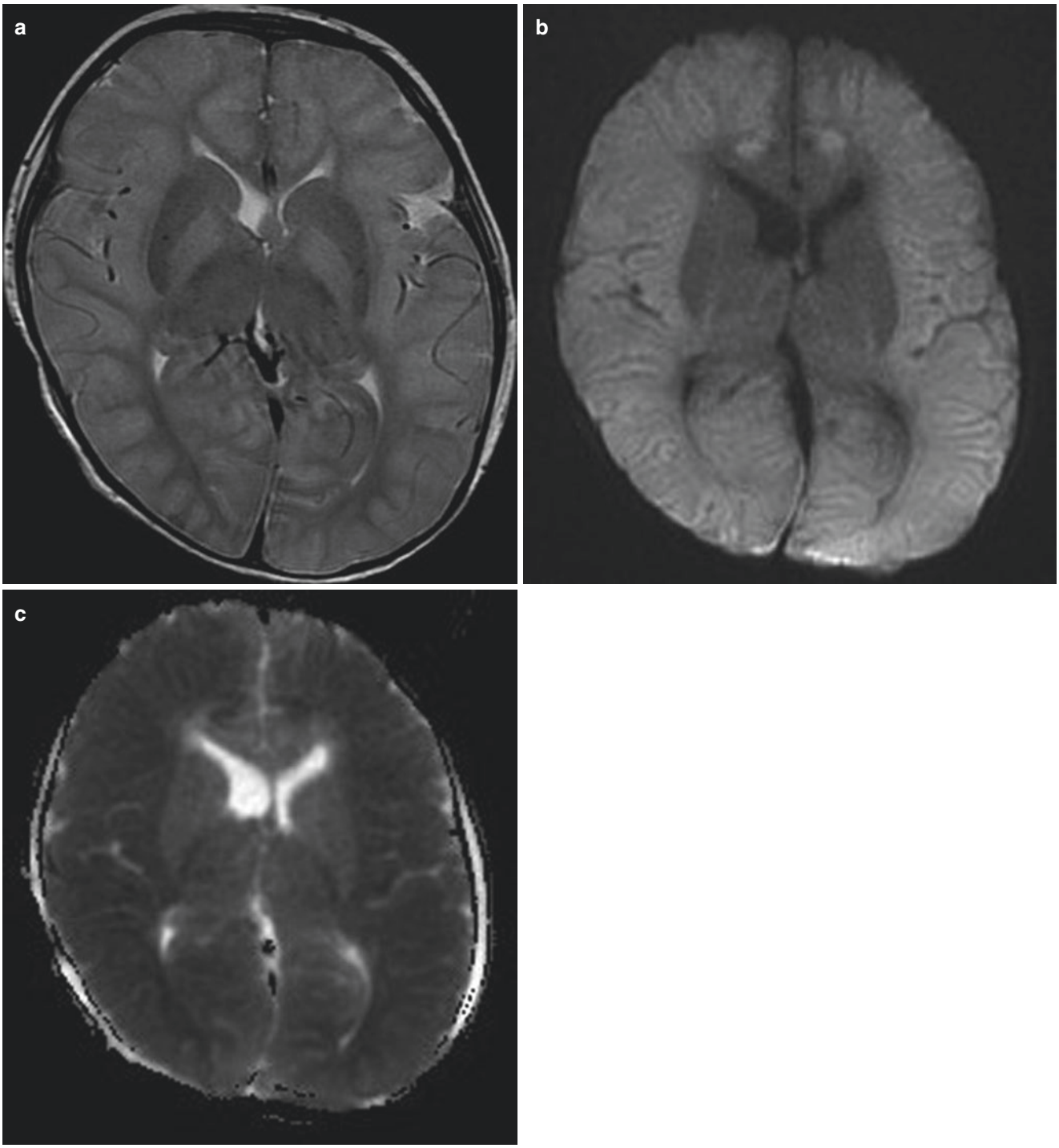

Fig. 5.4 Axial T2 MRI (**a**), diffusion weighted (**b**) and ADC (**c**), of the brain at the level of the frontal lobe reveals bilateral cerebral cortex and basal ganglia T2 high signal with restricted diffusion in keeping with cerebral oedema

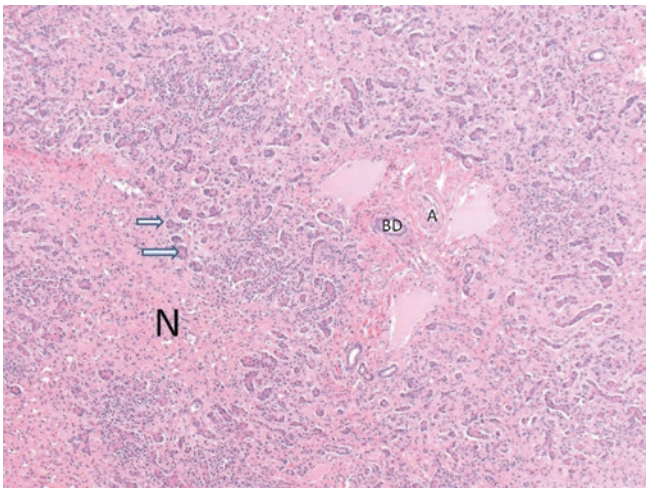

Fig. 5.5 (H&E original magnification ×100). There are no viable hepatocytes in this image, they are replaced by areas of necrosis (N) and regenerative type ductules (marked with arrows). A normal portal tract is present containing a bile duct (BD) and artery (A)

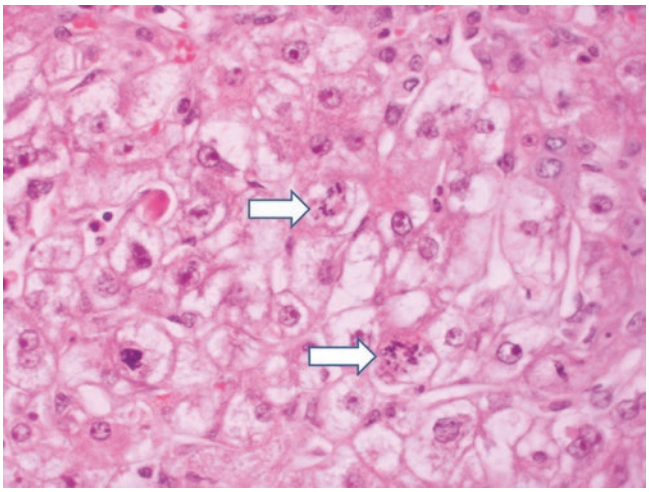

Fig. 5.7 (H&E original magnification ×400). Ecstasy can cause both cholestatic and hepatocellular injury with necrosis. In this example damaged hepatocytes have a swollen 'ballooned' appearance. An apoptotic cell is present on the left, two arrows mark mitotic figures rarely seen in normal liver

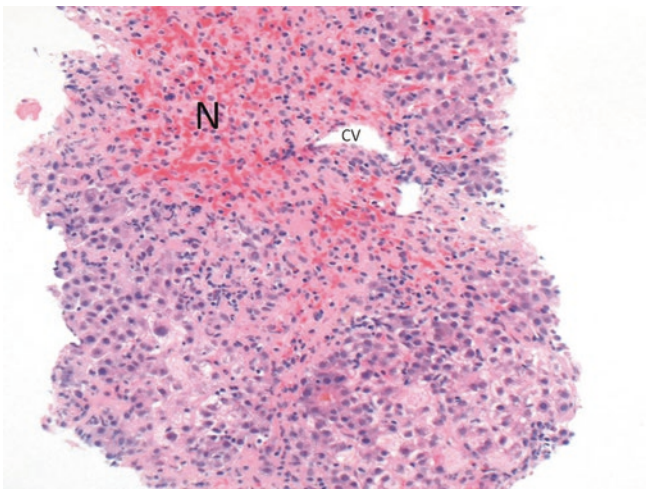

Fig. 5.6 (H&E original magnification ×200). Isoniazid can induce a hepatitic pattern of damage with acute hepatitis and necrosis (N) around the central vein (CV)

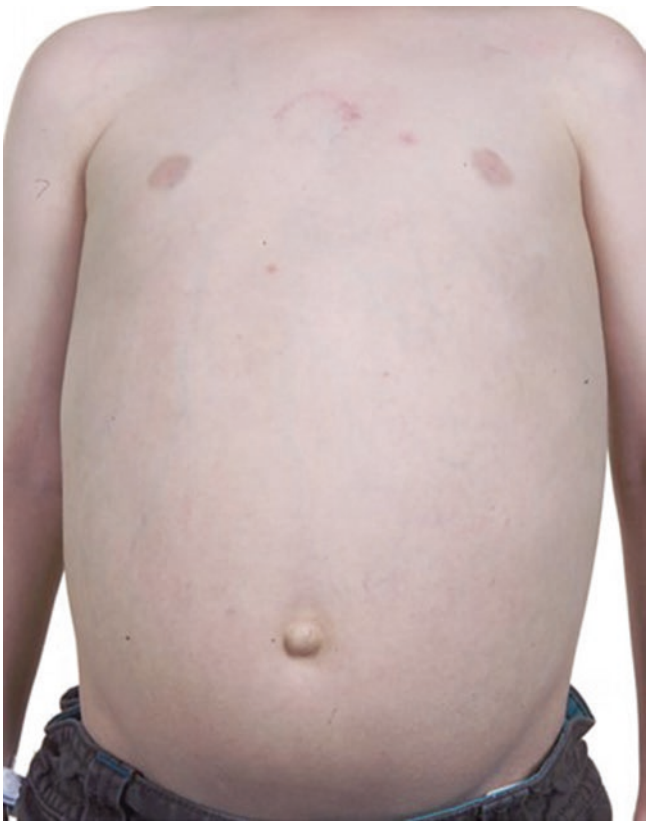

Fig. 5.8 This boy has abdominal distension from heptomegaly and ascited because of hepatic vein obstruction (Budd- Chiari Syndrome)

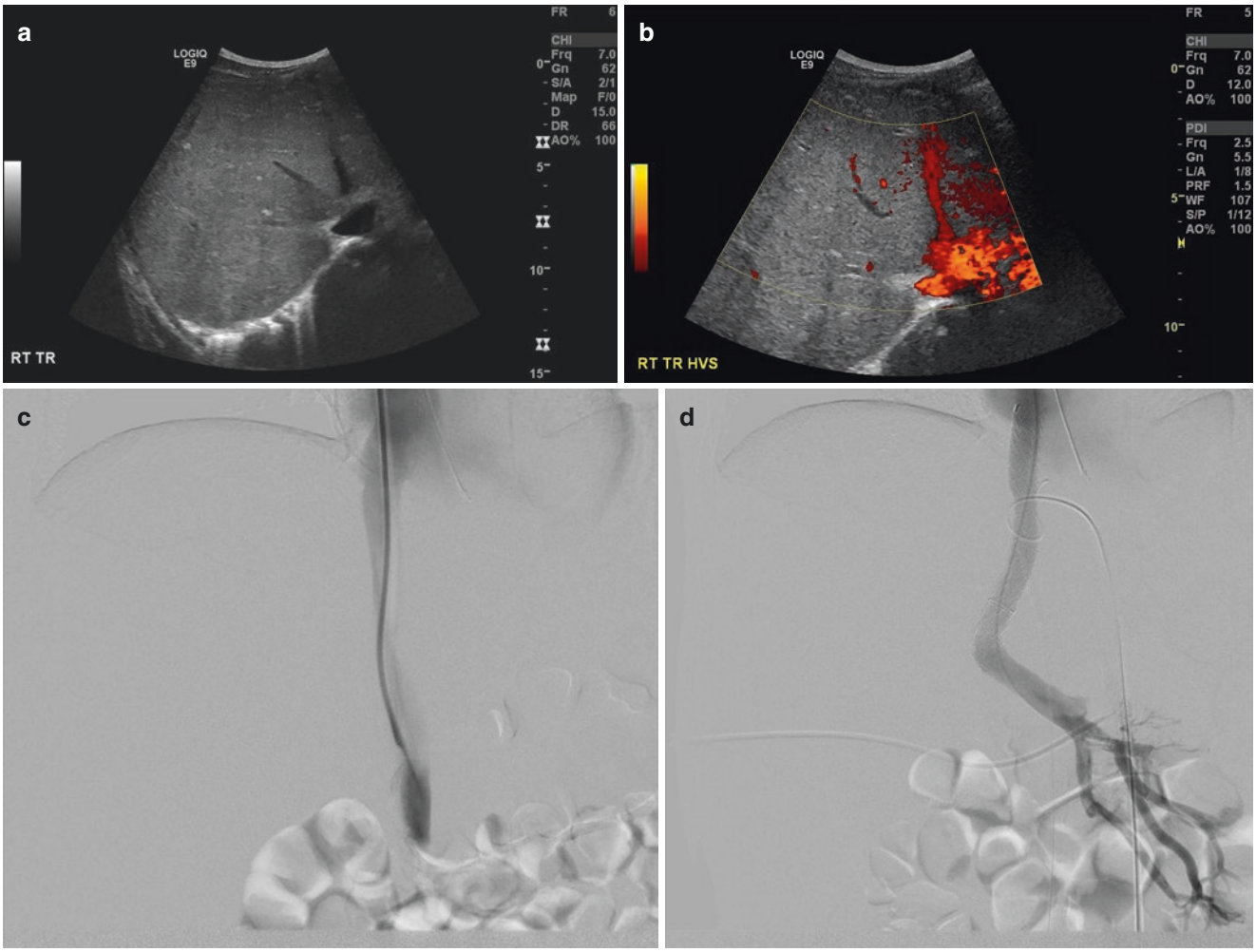

Fig. 5.9 (**a**) Ultrasound of liver shows lack of visualization of right and middle hepatic vein with narrowing of left hepatic vein while (**b**) Doppler confirms lack of color flow in right and middle hepatic vein with reduced flow in left hepatic vein. (**c**) Liver venography reveals IVC opacification with non opacification of all the hepatic veins which were re-connected following insertion of a transjugular intrahepatic porto-systemic shunt using a metallic shunt (**d**)

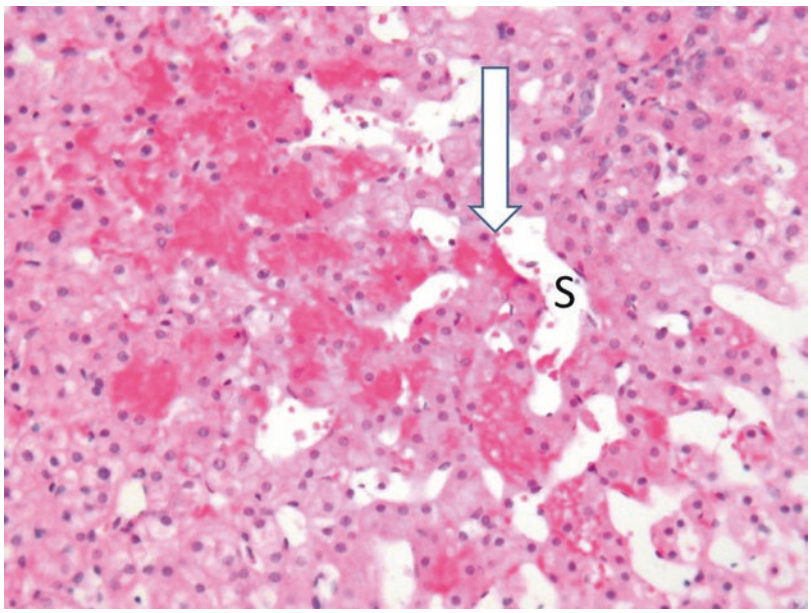

Fig. 5.10 (H&E original magnification ×200). The vascular congestion observed in Budd Chiari syndrome is illustrated here, sinusoids (S) are relatively empty, red blood cells are pushed out into the space of Disse, marked with an arrow

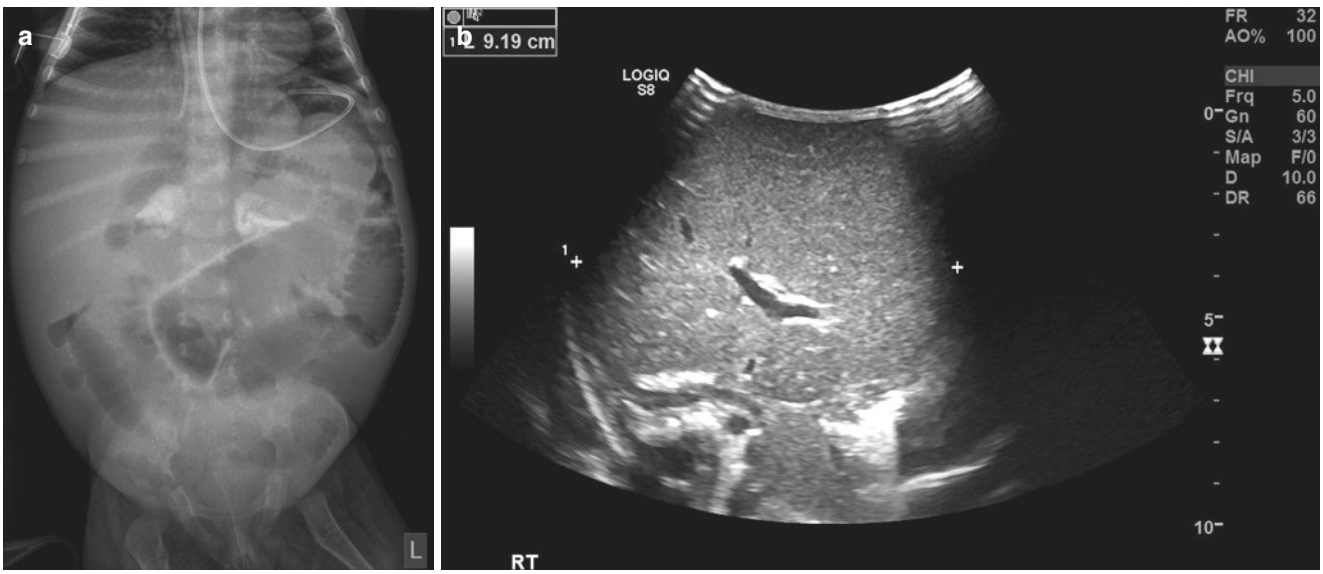

Fig. 5.11 (**a**) Abdominal X-ray reveals bilateral dense adrenal calcification while (**b**) ultrasound of the liver reveals diffuse increase in echogenicity in keeping with fatty liver which is seen with LAL-D

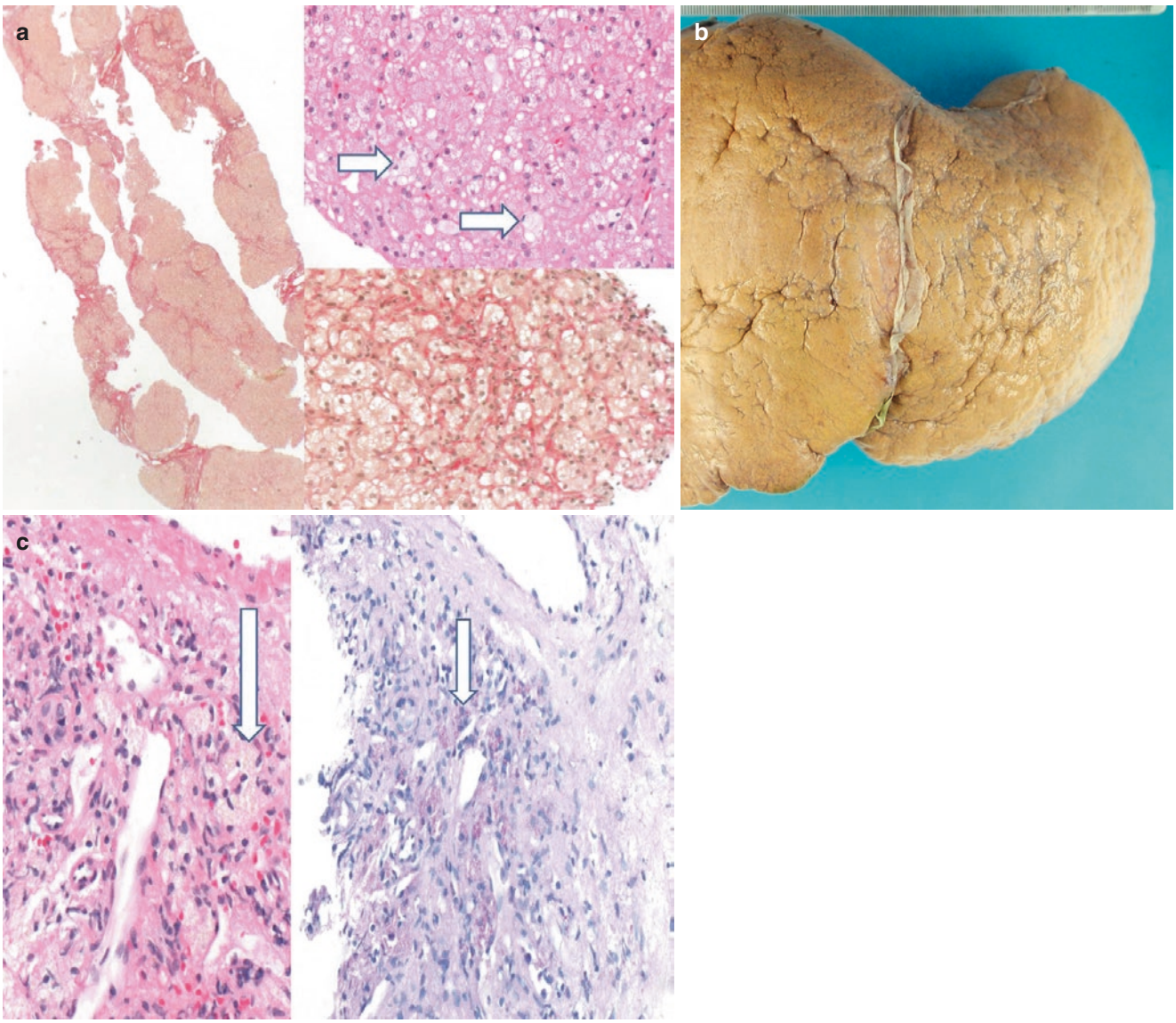

Fig. 5.12 Lysosomal acid lipase deficiency is associated with significant fibrosis. The panel on the left (**a**) (Van Giesen original magnification ×20) shows abundant fibrous septa and nodules indicative of established cirrhosis. The panel on the top right (H&E ×200) shows some small droplet steatosis in the background, clusters of storage cells are marked with arrows. These can be inconspicuous on H&E examination. Pericellular fibrosis as demonstrated on Van Giesen staining (magnification ×200) at the bottom right can alert the pathologist to the presence of storage cells. (**b**) End stage liver disease in lysosomal acid lipase deficiency may require liver transplantation, this liver demonstrates the typical bright yellow colour. (**c**) Storage cells also accumulate in portal tracts in lysosomal acid lipase deficiency. They have a light brown colour in H&E sections (left hand panel, original magnification ×400, marked by an arrow) and are also visible due to the presence of diastase resistant PAS positive material as seen in the right hand panel

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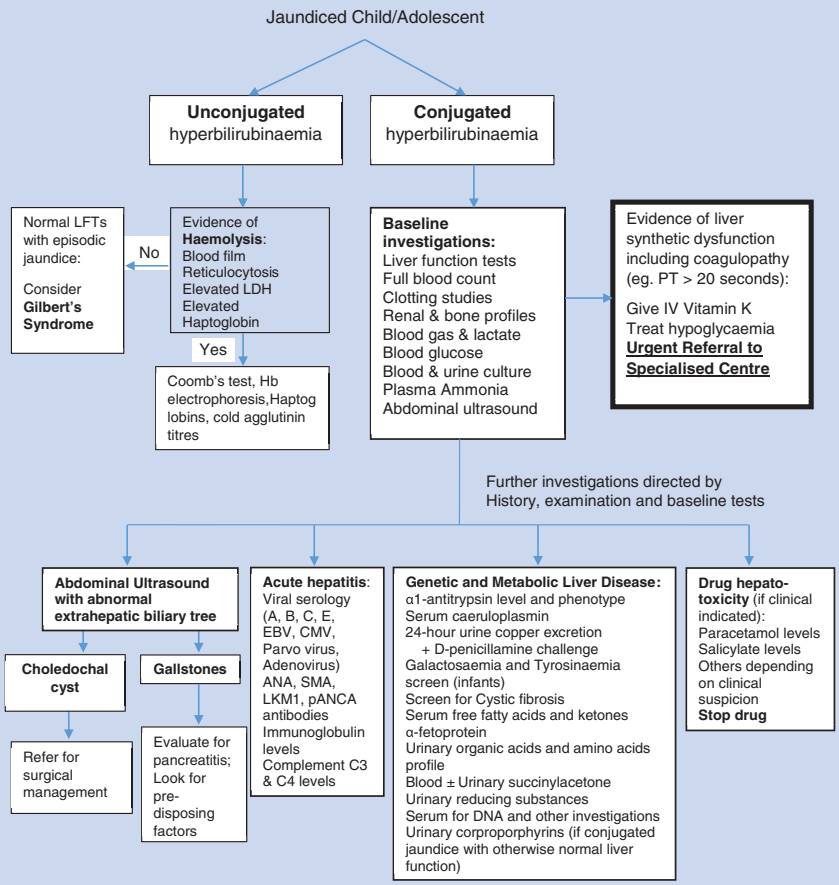
Jaundice in an Older Child

6

Deirdre Kelly

Jaundice is an important sign of acute and chronic liver diseases in older children and adolescents. The differential diagnosis is extensive and differs from neonatal liver disease. Jaundice may be a late feature in chronic liver disease while acute onset jaundice may be a sign of severe liver disease or acute liver failure. Prompt diagnosis and evaluation of liver synthetic function is essential in making the diagnosis (Box 6.1).

Box 6.1 Diagnostic algorithm for assessment of children and adolescents with jaundice



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D. Kelly et al. (eds.), *Atlas of Pediatric Hepatology*, https://doi.org/10.1007/978-3-319-69529-7_6

Viral hepatitis (Table 6.1), seronegative hepatitis, autoimmune hepatitis are the most common acute liver diseases to present with jaundice in older children (see also Chapter 5) in addition to drug-induced liver disease (Table 6.2), while sclerosing cholangitis, gallstones, haemolysis are the commonest chronic diseases.

Table 6.1 Causes of jaundice in children and adolescents and relevant investigations

CONJUGATED HYPERBILIRUBINAEMIA	
HEPATOCELLULAR INJURY PATTERN (Predominately elevated AST and ALT)	
Viral hepatitis A, B, C, E, Seronegative	Viral serology (A, B, C, E) or PCR (B, C, E, EBV, CMV)
Autoimmune hepatitis	ANA, SMA, LKM1, pANCA; Immunoglobulins (IgA, IgM, IgG); Complement C3 and C4 levels; Liver biopsy
Alpha-1 antitrypsin deficiency	α1-AT level and phenotype, liver biopsy (see Chapter 1)
Wilson's disease	24 h urinary copper excretion + D-penicillamine challenge, serum caeruloplasmin, liver biopsy (copper content), eye exam
CHOLESTATIC LIVER DISEASE (Predominantly raised ALP, GGT and conjugated bilirubin)	
Sclerosing cholangitis	ANA, SMA, LKM1, pANCA; Immunoglobulins (IgA, IgM, IgG); Complement C3 and C4 levels; Liver biopsy MR cholangiopancreatography; faecal calprotectin to detect IBD
Choledochal cysts	Ultrasound; TeBIDA; MRI of liver (Chapter 1)
Cholelithiasis	Ultrasound; TeBIDA; MRI of liver (Chapter 1 & 6) Assess for underlying cause (haemolysis, etc.); Serum amylase,
Cystic fibrosis	Sweat chloride, CFTR genetic testing (Chapter 8)
Dubin Johnson syndrome Rotor syndrome	LFTs, clotting analysis; Urinary corproporphyrin profile
MIXED OR VARIABLE PATTERN OF LIVER INJURY	
Drug induced liver injury (Table 6.2)	Specific assays depending on suspected toxin (e.g. Paracetamol and Salicylate levels); Urine drug screen
Tyrosinaemia type I	FBC, clotting studies, αFP; Blood (Porphobilinogen synthase inhibition) or urinary succinylacetone; Plasma amino acids; FAH mutation analysis; Urinary pH, phosphate, glucose, amino acids
Budd-Chiari syndrome Congestive cardiac disease Veno-occlusive disease	Abdominal ultrasound ± thrombophilia screen ± echocardiography (in specific clinical context)
UNCONJUGATED HYPERBILIRUBINAEMIA	
Haemolytic disorders	FBC and blood film, reticulocyte count, LDH, haptoglobin, Coomb's test, Hb electrophoresis, specific red cell assays
Gilbert's syndrome	Clinical diagnosis; Exclude haemolysis. Gene testing available if diagnostic uncertainty

Table 6.2 Patterns of drug-induced liver injury

Drug-induced liver injury	Medications
Hepatitis/Hepatic Necrosis: *Nausea, vomiting, anorexia and* abnormal *AST± ALT, jaundice may be late.*	Paracetamol, Halothane, Isoniazid, Phenytoin, Cyclophosphamide, Cisplatin, Ketaconazole
Cholestasis: *Jaundice, itch, raised conjugated bilirubin, ALP ± GGT; mildly elevated AST/ALT*	Carbamazepine, Oral contraceptive pill (oestrogen containing), flucloxacillin, 6-mercaptopurine, third generation cephalosporin (e.g. Ceftriaxone)
Microvesicular steatosis	Sodium valproate, Tetracycline
Fibrosis	Methotrexate, chemotherapy
Systemic syndrome (DRESS) *Rash, fever, lymphadenopathy, hepatitis, eosinophilia, multi-organ involvement (e.g. kidney, lung, heart)*	Anti-convulsants, sulphur-containing drugs, non-steroidal anti-inflammatory drugs
Acute Liver Failure: *Jaundice, raised conjugated bilirubin + AST/ALT, synthetic dysfunction*	Paracetamol, Halothane, Isoniazid, Valproate, Flucloxacillen, other antibiotics

6.1 Autoimmune Liver Disease (AILD)

Autoimmune hepatitis (AIH) is a chronic inflammatory disorder affecting children of any age from 6 months onwards. Type 1 AIH is associated with positive anti-nuclear antibody (ANA) and smooth muscle antibody (SMA) and Type 2 AIH has positive Liver-kidney-microsomal (LKM) antibodies. In >90% of patients, IgG is significantly raised, Complement (C3 and C4) are low.

Clinical presentation may be with acute or chronic hepatitis, cirrhosis and portal hypertension or acute liver failure. Other autoimmune phenomena are common, particularly with type I AIH and include immune thyroiditis, coeliac disease, inflammatory bowel disease, haemolytic anaemia and glomerulonephritis.

The young boy (Fig. 6.1) presented with haemolytic anaemia, a heart murmur and hepatosplenomegaly, secondary to Type 1 autoimmune hepatitis. The diagnosis was confirmed by liver biopsy which demonstrates a plasma cell infiltrate of the portal tract which spills into the surrounding parenchyma (interface hepatitis), varying degrees of parenchymal collapse and fibrosis (Fig. 6.2a–c).

Therapy. Most children respond to immunosuppression with prednisolone 2 mg/kg/day with azathioprine 0.5–2 mg/kg/day. Ciclosporin (2–4 mg/kg/day), tacrolimus (1–2 mg/day) or mycophenolate mofetil (20 mg/kg/day) are second line drugs Liver transplantation is required in 20% of children but relapse occurs in 25% unless steroids are maintained.

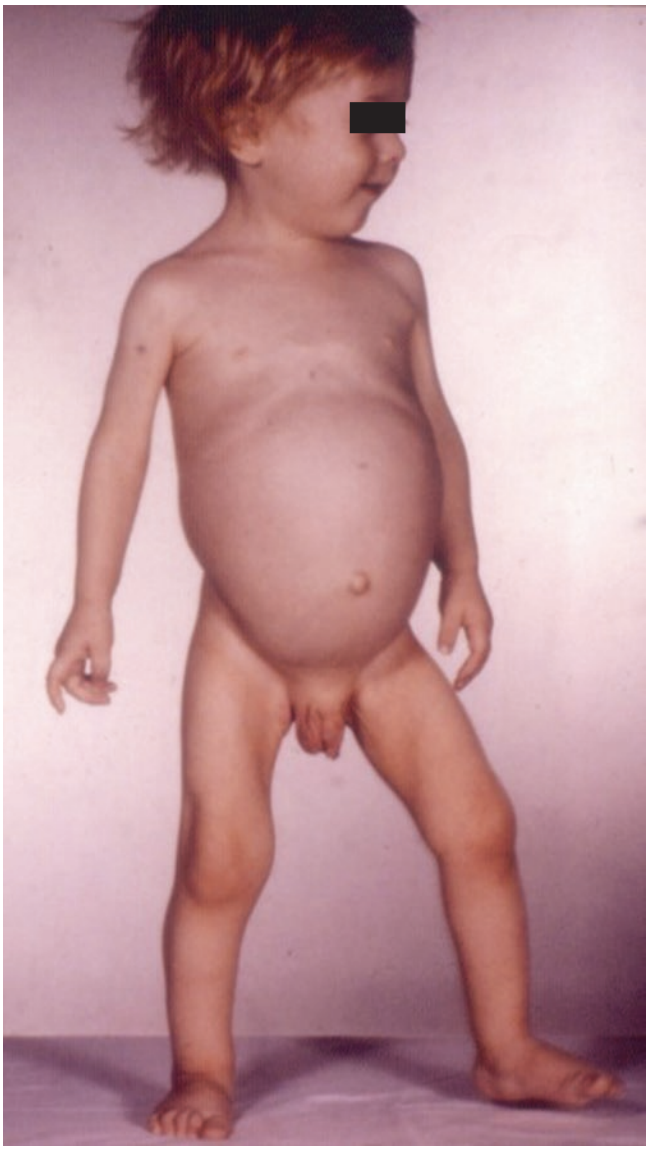

Fig. 6.1 This young boy presented with haemolytic anaemia, a heart murmur and hepatosplenomegaly. Note the distended abdomen and the pedal oedema. He was found to have Type 1 autoimmune hepatitis

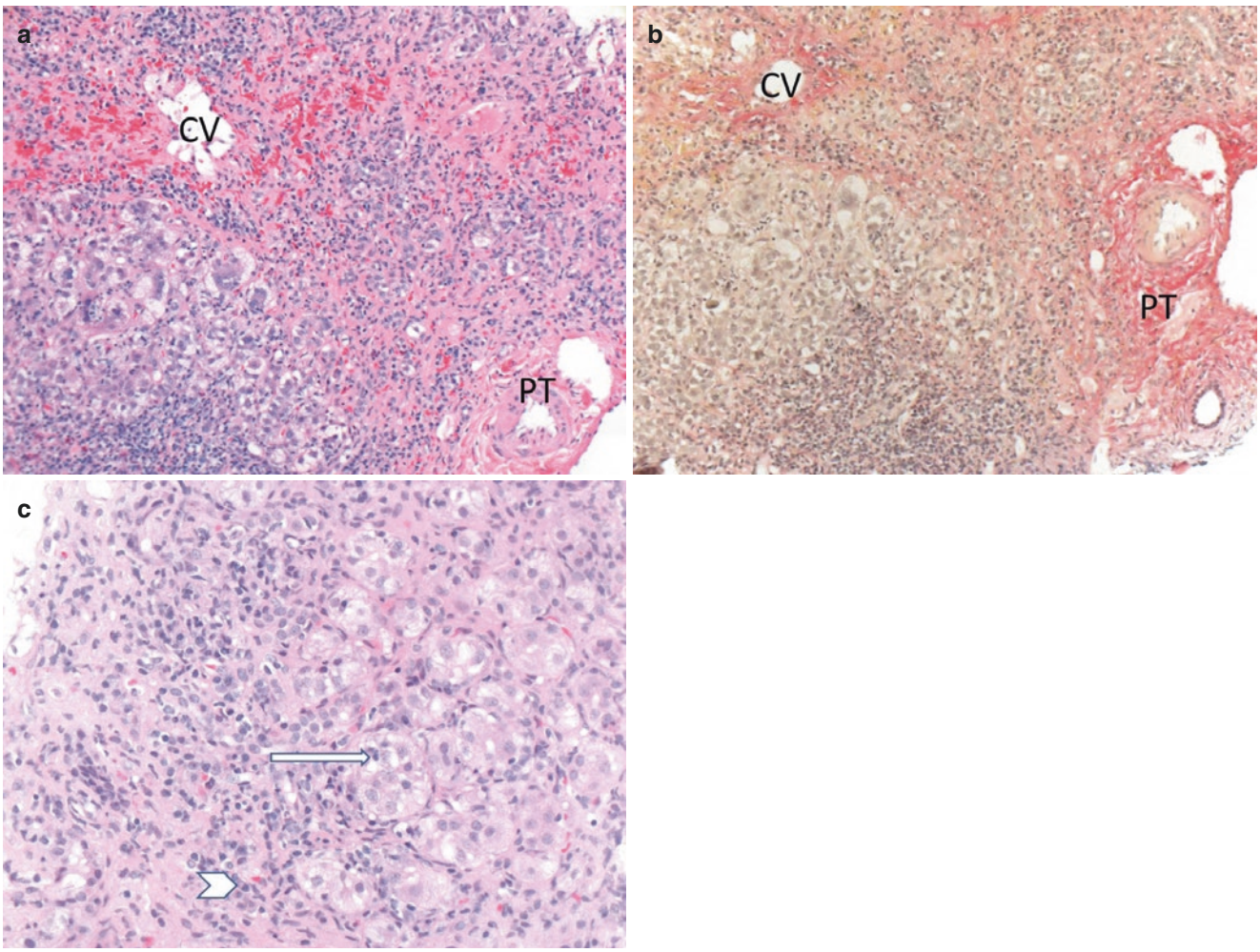

Fig. 6.2 The diagnosis was confirmed by liver biopsy which demonstrates a plasma cell infiltrate of the portal tract which spills into the surrounding parenchyma (interface hepatitis), with varying degrees of parenchymal collapse and fibrosis (**a**–**c**). (**a**) (H&E ×200). In this case of severe acute hepatitis bridging necrosis is present between the central vein 'CV' and portal tract 'PT'. Viable hepatocytes and inflammatory cells are seen in the bottom left hand corner, in the bridge between the two marked structures only biliary ductules, an attempt at regeneration, are seen. (**b**) (Haematoxylin Van Gieson ×200). This is an adjacent section to Fig. 6.1a. Mature collagen is dark red within the portal tract 'PT' and around the central vein 'CV'. The necrotic bridge shows only faint staining, this allows distinction between an acute necrotic bridge and a mature fibrous bridge which would have been an indicator of underlying mature fibrosis and chronic liver disease. (**c**) (H&E ×400). In this high power image the blue dots are inflammatory cells, the arrow is pointing to a plasma cell, there are many such cells present in this infiltrate. The arrow is pointing to a lymphocyte within a hepatocyte 'emperipolesis' in turn this hepatocyte is in a small nodule of hepatocytes or 'rosette', these are formed as a result of interface hepatitis where the 'interface' is between the portal tract and the parenchyma. Cases of acute hepatitis such as this with bridging necrosis and a plasma cell rich infiltrate imply an acute presentation of autoimmune hepatitis

6.2 Sclerosing Cholangitis (SC)

In children, SC is part of the spectrum of AILD with or without inflammatory bowel disease, but other causes include Langerhans Histiocytosis X (LCH) and immune deficiencies. In SC or Auto-immune sclerosing cholangitis (AISC), pANCA may be positive in addition to ANA and SMA. The diagnosis is based on radiology and histology. An abdominal ultrasound may show an enlarged gallbladder bur the irregular and dilated bile ducts are best seen on MRCP (Fig. 6.3). Liver histology typically demonstrates onion skin fibrosis around the bile duct (Fig. 6.4).

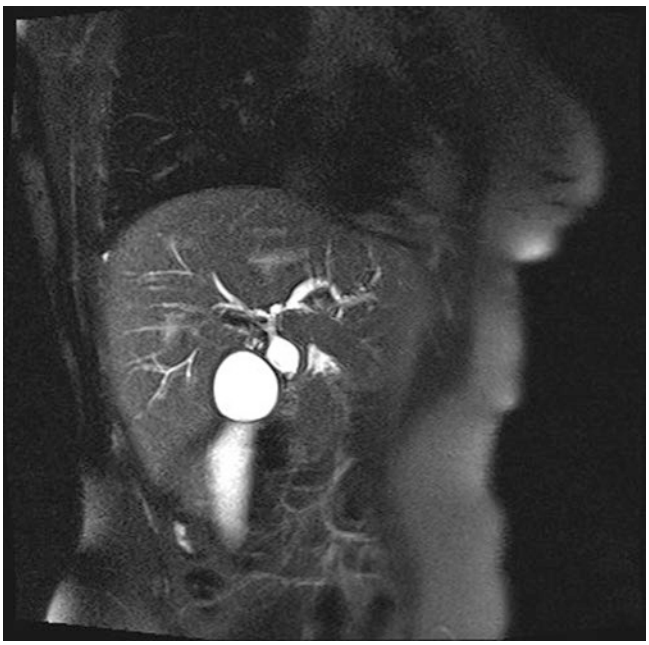

Fig. 6.3 In this teenager with biopsy proven sclerosing cholangitis, Coronal T2 MRCP of the biliary system reveals beaded narrowing of intrahepatic bile ducts and common bile duct and enlarged gall bladder

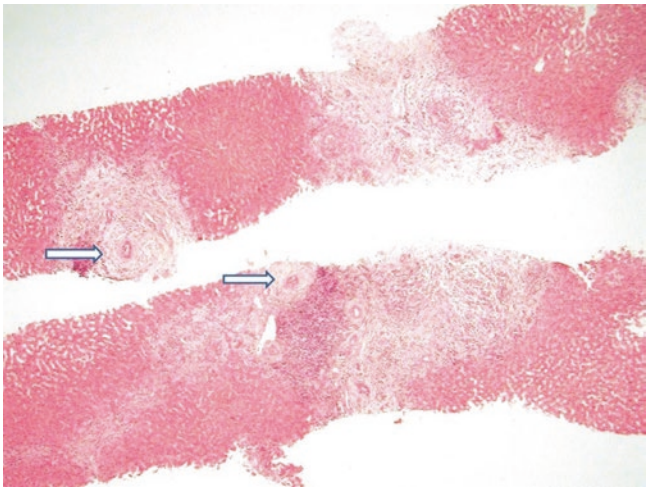

Fig. 6.4 (H&E ×40). This medium power image of two liver cores shows concentric fibrosis around bile ducts with an 'onion skin' pattern these are sclerosing bile duct lesions as seen in cases of sclerosing cholangitis, two examples are marked with arrows

6.3 Langerhans Cell Histiocytosis (LCH)

LCH is a rare multisystem disease which affects the biliary tree with sclerosing cholangitis which leads to biliary cirrhosis. Often the diagnosis is only apparent after transplantation unless there is multi-system involvement with bony lesions and pituitary insufficiency (Fig. 6.5). Her MRI of her brain demonstrated thickened and abnormally enhancing pituitary stalk (Fig. 6.6a, b). Histology of her explant (Fig. 6.7) shows biliary obstruction but it is unusual to find Langerhans cells.

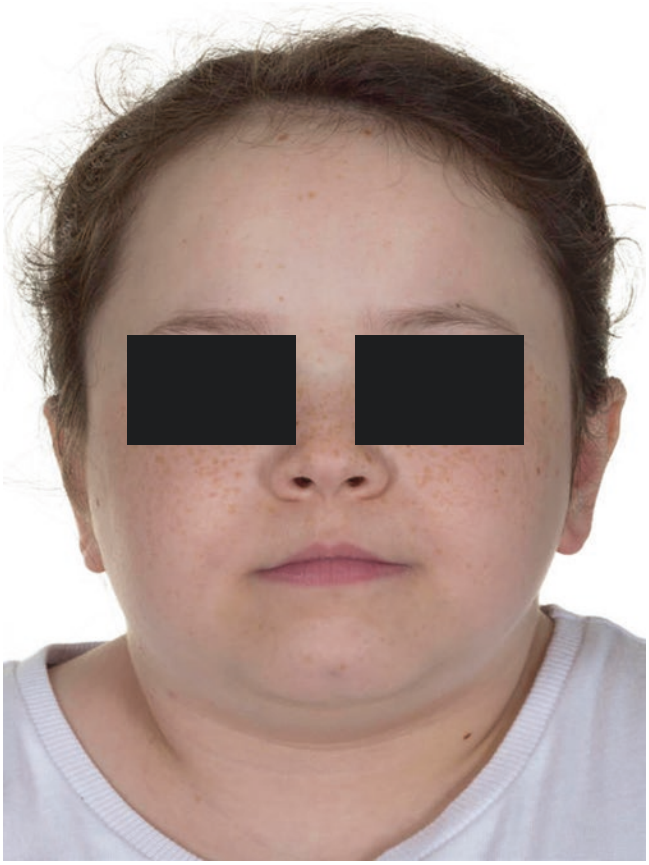

Fig. 6.5 This young girl presented with Diabetes insipidus (from pituitary involvement) and developed biliary cirrhosis. She had a successful liver transplant, but continues to need hormone supplementation

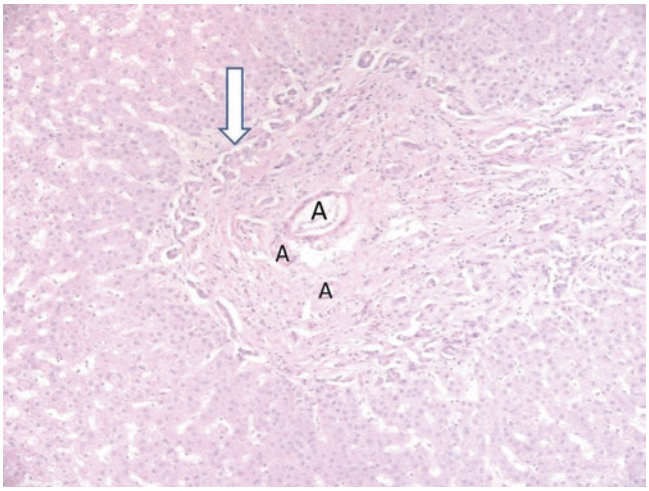

Fig. 6.7 Histology of her explant shows biliary fibrosis secondary to presumed large bile duct obstruction by Langerhans cell histiocytosis (LCH) it is unusual to find Langerhans cells themselves in peripheral liver. (H&E ×200). This portal tract has a 'biliary' appearance, ductules are present at the periphery of the portal tract as marked by the arrow. Centrally in the portal tract there are several hepatic artery branches 'A' but no accompanying bile duct. The peripheral liver in cases of Langerhans cell histiocytosis often shows this appearance as a manifestation of obstruction of the large bile ducts which is where the disease is manifested. No Langerhans cells are visible in this image

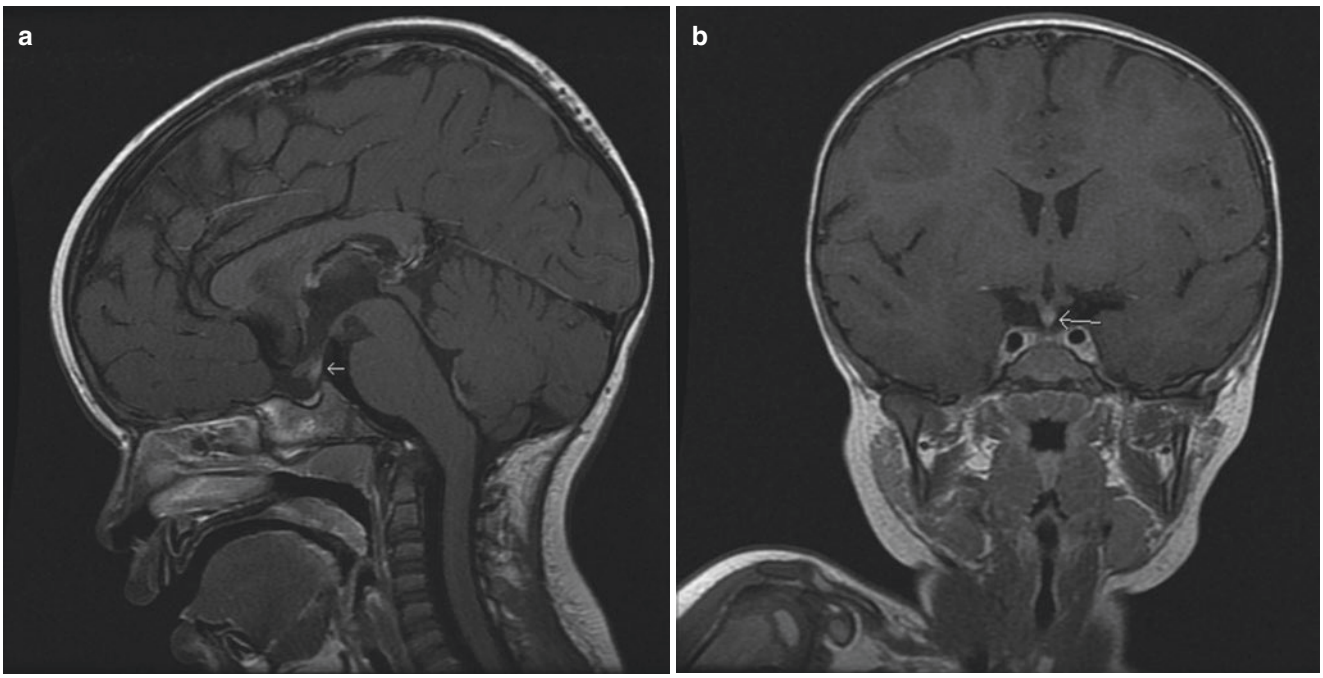

Fig. 6.6 Her MRI of her brain demonstrated thickened and abnormally enhancing pituitary stalk (**a**, **b**). T1 post contrast (gadolinium) enhanced sagittal and coronal sequence of the midline brain shows thickened and abnormally enhancing pituitary stalk in a child with biopsy proven Langerhans cell Histiocytosis

6.4 Drug Induced Liver Disease (DILI)

The liver is an important site of drug metabolism and although DILI is uncommon in children, it is an important cause of acute or chronic liver failure. DILI may be dose-dependent hepatotoxicity (e.g. paracetamol) but more commonly is due to idiosyncratic reactions. Underlying disorders, such as mitochondrial dysfunction may increase susceptibility to hepatotoxicity. The commonest DILI in childhood are in Table 6.2.

Clinical symptoms include abdominal pain, skin rash, nausea, jaundice, pruritus and dark urine. The diagnosis is by exclusion and depends on an accurate history, identification of eosinophils in blood and liver and improvement on discontinuation of the relevant drug, although in children with acute liver failure, progression of disease is likely despite discontinuation of therapy.

A maculo-papular skin rash is common, but is non-specific (Fig. 6.8). Liver histology may be helpful and includes hepatitis, cholestasis, fulminant hepatitis, fibrosis. In hepatotoxicity due to carbamazepine, a common anti-epileptic drug, a skin rash with cholestasis is common. Liver histology shows perivenular necroinflammation but granulomas may also be seen (Fig. 6.9). Sodium valproate and tetracycline both cause fatty liver with microvesicular fat in the hepatocytes, which is associated with hepatocellular dysfunction and may progress to acute liver failure.

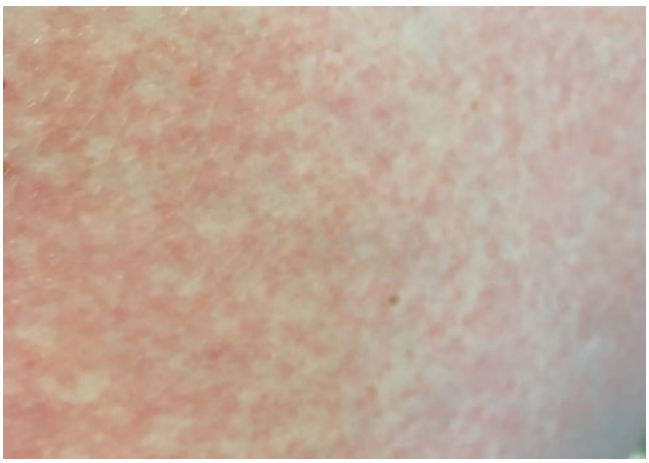

Fig. 6.8 A non-specific skin rash is common with drug-induced allergic reactions

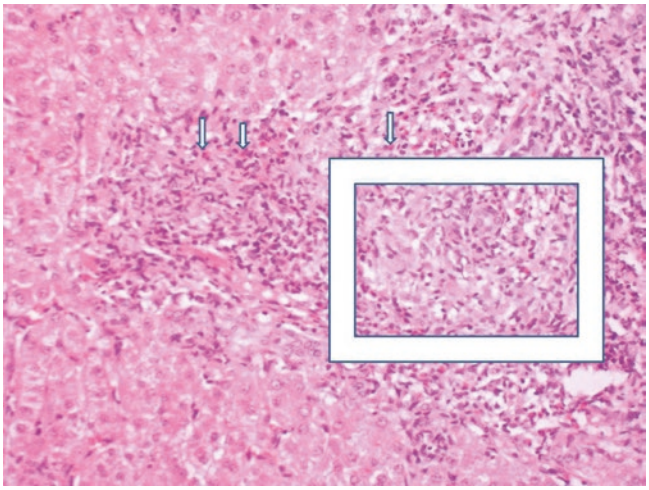

Fig. 6.9 (Haematoxylin and eosin ×200). This portal tract contains numerous eosinophils, marked with arrows. They are a useful indicator of drug induced liver disease although not specific. Within the rectangle the inflammation assumes a granulomatous quality comprising epithelioid histiocytes. Granulomas are seen in drug induced liver injury but are not specific

6.5 Wilson's Disease

Wilson's disease is an autosomal recessively inherited multisystemic disease caused by mutations of ATP7B, encoding an intracellular copper transporter in 1 in 30,000 individuals worldwide. Copper is deposited in the liver, central nervous system, and kidneys. The clinical presentation is varied and includes acute or chronic liver disease, acute liver failure, coombs-negative haemolytic anaemia, neuropsychiatric abnormalities (in older children), and Kayser-Fleischer rings (copper deposition at the corneal scleral junction) (Fig. 6.10). Characteristically there is a low serum alkaline phosphatase. Diagnosis is based on the clinical features and copper studies (see Table 6.1). MRI of the brain demonstrates copper deposition in the basal ganglia (Fig. 6.11a, b) while histology characteristically shows copper deposition (Fig. 6.12a, b). Liver copper is very high. Management includes therapy with penicllamine and or zinc. Liver transplantation may be required for acute liver failure or non-response to therapy. Family screening and treatment of affected siblings is essential

Fig. 6.10 Kayser- Fleischer rings represent copper deposition in the cornea, and are normally seen in Wilson's disease, but are unusual in children under 7 years

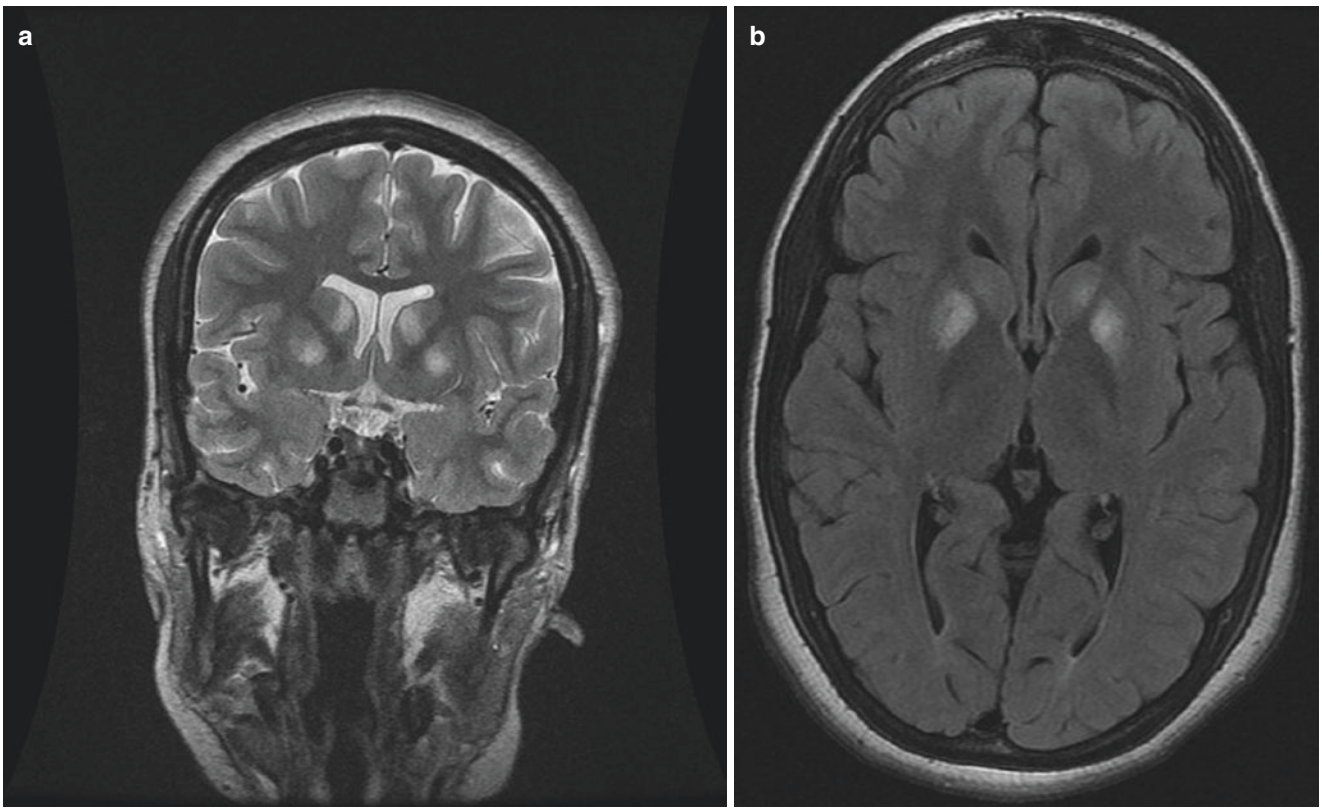

Fig. 6.11 (**a**, **b**) Coronal T2 weighted sequence (**a**) and axial FLAIR sequence (**b**) of the brain reveals hyper intensity of bilateral basal ganglia secondary to copper deposition in Wilson's disease

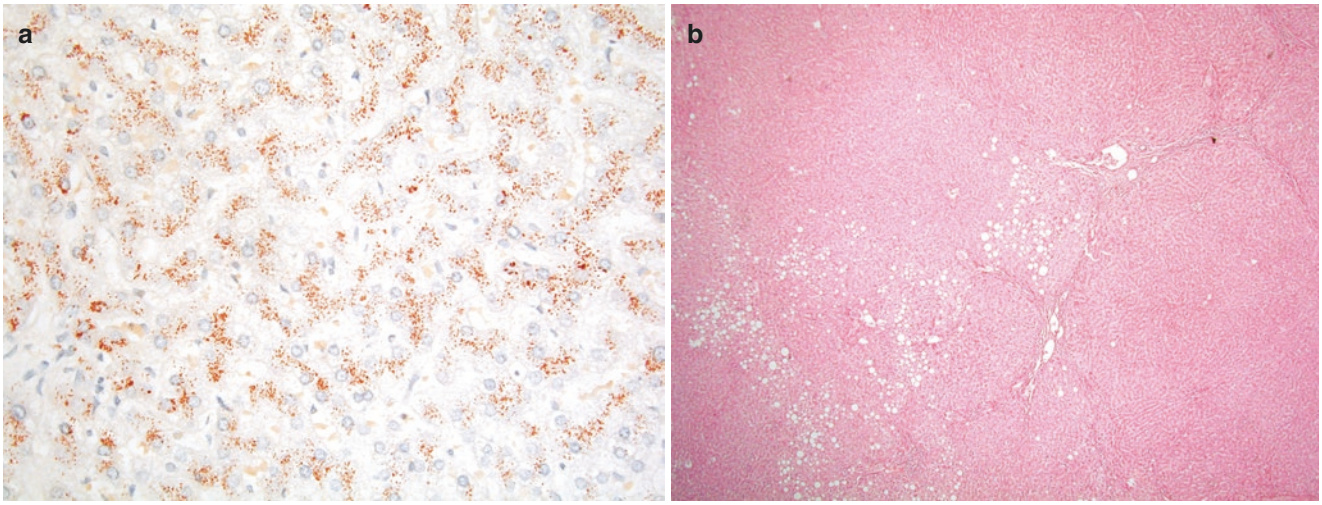

Fig. 6.12 (**a**) (Rhodanine stain ×400). Liver histology is variable in Wilson's disease, but red granules of copper are highlighted within hepatocytes in this child with Wilson's disease. (**b**) Haematoxylin and eosin ×25. Often the only histological clues to Wilson's disease are mild steatosis and fibrosis as in this case

Further Reading

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The Child with Chronic Liver Disease

7

Deirdre Kelly

7.1 Chronic Liver Disease

The main causes of chronic liver disease in children are: neonatal liver disease (see Chapter 1); alpha-1-anti-trypsin deficiency (see Chapter 1); autoimmune liver disease (see Chapter 6); cystic fibrosis (see Chapter 8), chronic viral hepatitis, non-alcoholic fatty liver disease liver disease (NAFLD) and metabolic liver disease (see Chapters 1 and 2) (Table 7.1).

Children may present with abnormal liver function tests, performed as a screen for a non specific symptoms (such as tiredness, intermittent abdominal pain) which require further investigation or with advanced liver disease.

Table 7.1 Chronic liver disease in children

Diagnostic features of chronic liver disease in older children (>2 years)	
Chronic liver disease	Diagnostic investigations
Chronic hepatitis	
Hepatitis B, C, D, Epstein Barr virus, Cytomegalovirus	Serology
Autoimmune hepatitis	
Primary sclerosing cholangitis	IgG >20 g/l, reduced C3, C4 complement Anti-nuclear antibodies and smooth muscle antibodies (type 1) Liver/kidney microsomal antibodies (type 2) ERCP/MRCP, liver biopsy with duct changes
Metabolic liver disease	
Wilson's disease	Serum copper Caeruloplasmin Urinary copper
a1-antitrypsin deficiency	Serum a1-antitrypsin and phenotype
Cystic fibrosis	Sweat test, liver biopsy, mutations
Tyrosinaemia type 1	Urinary succinylacetone, fumarylacetoacetate in fibroblasts, DNA for Mutations
Hereditary fructose	Fructose 1,6-phosphate aldolase intolerance, DNA for mutations, reducing sugars in urine
Other	
Fibropolycystic liver disease	Ultrasound/MRI/endoscopy liver biopsy shows ductular disarray
Non-alcoholic fatty liver disease	Fatty change in liver biopsy/on liver disease or ultrasound

ERCP endoscopic retrograde cholangiopancreatography, *IgG* immunoglobulin G, *MRCP* magnetic resonance cholangiopancreatography

7.1.1 Chronic Viral Hepatitis (HBV and HCV)

Children with either Hepatitis B (HBV) or hepatitis C (HCV) are asymptomatic with normal growth and development. In children, vertical transmission of HBV is common. 90% of infants born to HBV carrier mothers become infected without vaccination and the majority become chronic carriers. Vertical transmission is less likely and with 2–10% of infants becoming infected. The majority become chronic carriers. Diagnosis depends on identification of:

HBV: hepatitis B surface antigen (HBsAg) is usually positive >6 months; Hepatitis B e antigen (HBeAg) is positive and HBV DNA is elevated, indication chronic infection. Biochemical liver function tests are usually normal and do not reflect liver inflammation (Fig. 7.1) HBV typically causes a low grade hepatitis with HBsAg visible in hepatocytes on histology.

HCV: HCV IgG is usually always positive, even if infection is resolved, so diagnosis of active infection is by detection of HCV RNA. There are six genotypes. Histology usually demonstrates mild hepatitis with fatty change (Fig. 7.2).

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D. Kelly et al. (eds.), *Atlas of Pediatric Hepatology*, https://doi.org/10.1007/978-3-319-69529-7_7

Fibrosis is rare in childhood, but develops in most children and young adults with time (Fig. 7.3).

Lifetime monitoring to detect cirrhosis or hepatocellular carcinoma with annual ultrasonography and serum a-feto-protein (AFP) is advisable for both HBV and HCV.

Treatment for HBV is only partially successful and long term use of oral antiviral therapy (tenofovir or entecavir) to reduce HBV DNA is effective in 25% of children. The development of effective direct-acting (DAA) antiviral therapy in adults, currently licensed in >12 year olds, will eventually cure HCV.

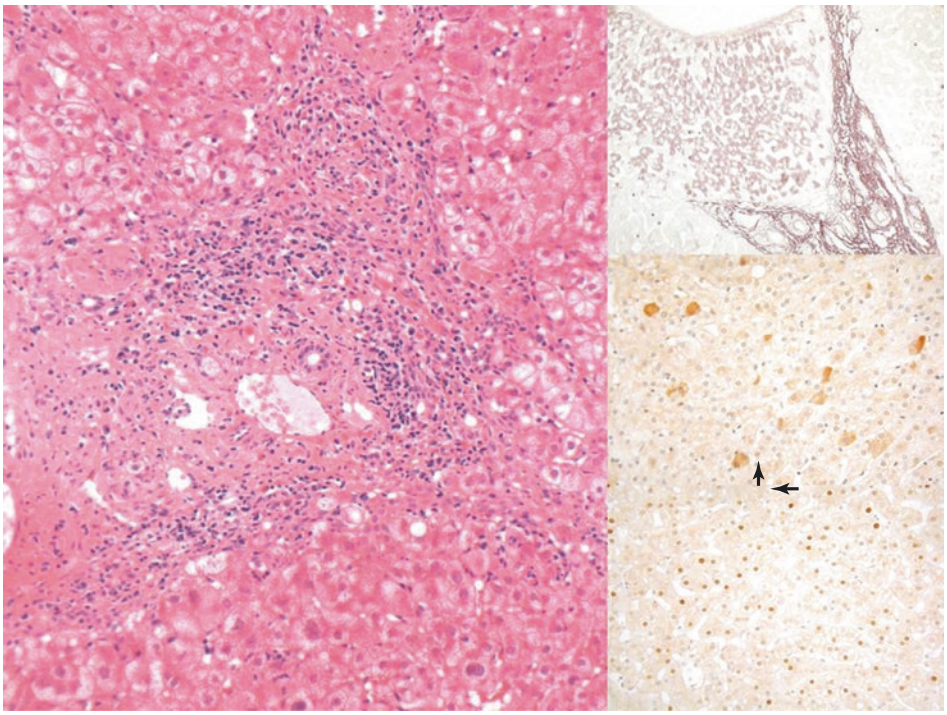


Fig. 7.1 Hepatitis B. In the H&E panel on the left, (original magnification ×200) there are features of chronic hepatitis. The HBsAg can be demonstrated histochemically on an orcein stain, top right, and also by immunohistochemistry; middle right panel demonstrating HBsAg and the bottom right panel nuclear HBcAg

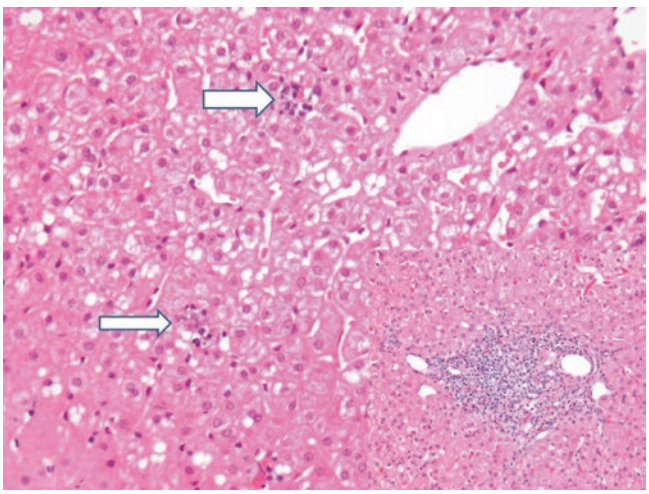


Fig. 7.2 Hepatitis C. In the panel at the bottom right there is chronic hepatitis similar to that seen with hepatitis B, in hepatitis C the lymphocytes can be more aggregated. In the main image the arrows are pointing to foci of spotty inflammation in the parenchyma. Some mild steatosis is also present

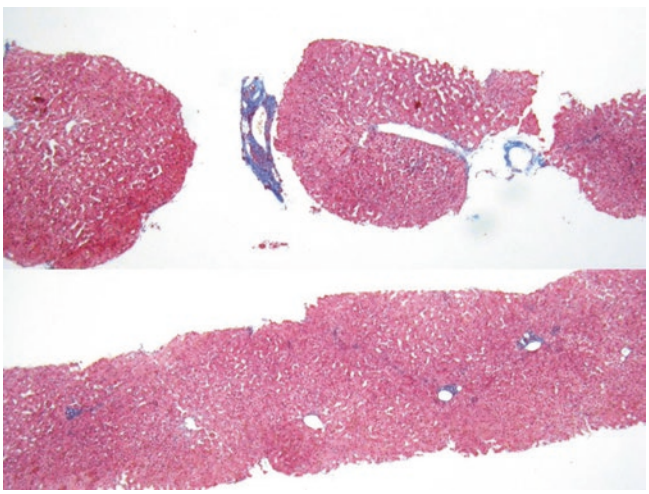


Fig. 7.3 Masson trichrome stain, (original magnification ×40). In the bottom core there is very little evidence of fibrosis, the collagen, stained blue, is confined to portal areas. In the top core however there is fragmentation and the fragments have a nodular appearance, this is due to the presence of a fibrous bridge. Bridging fibrosis is usually regarded as being of moderate severity

7.1.2 Non-alcoholic Fatty Liver Disease (NAFLD)

Non-alcoholic fatty liver disease (NAFLD) is a significant cause of chronic liver disease in both adults and children. It is related to the metabolic syndrome: obesity, insulin resistance and type 2 diabetes mellitus, hypertriglyceridaemia and cardiovascular morbidity.

Increased childhood obesity and recognition of insulin resistance in several inherited disorders has led to an increased diagnosis of this disorder in childhood (Table 7.2). However, NAFLD also in individuals of normal body weight.

Table 7.2 Inherited metabolic disorders associated with NAFLD

Alstrom syndrome
Bardet–Biedl syndrome
Polycystic ovary
Turner syndrome
Lipodystrophy

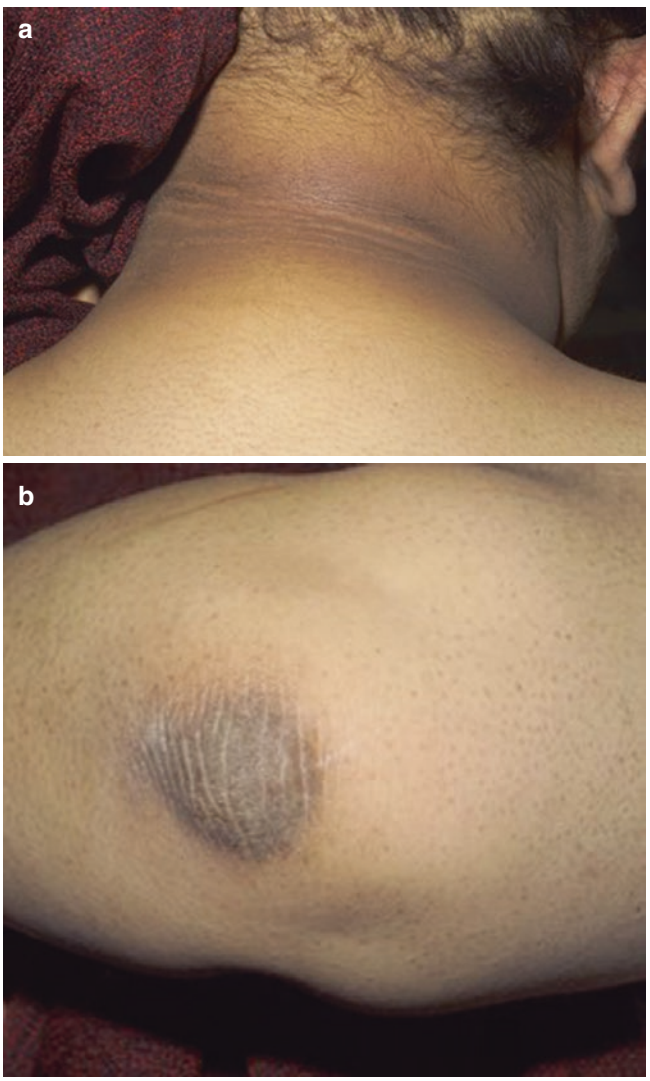


Fig. 7.4 (**a**, **b**) Clinical photo of acanthosis nigricans

Presentation is usually with abnormal liver transaminases in an obese child although it may present as part of the inherited syndrome (Table 7.2).Insulin resistance as evidenced by acanthosis nigricans is visible around the neck (Fig. 7.4a) or on the elbows (Fig. 7.4b).

In fatty liver disease the liver will appear bright as compared to the kidney parenchyma. The findings are not specific and need to be interpreted alongside clinical findings as a fatty liver may also be seen on ultrasound scan in metabolic conditions (Fig. 7.5).

Liver biopsy is still the only method to confirm diagnosis and identify evidence of steatohepatitis and fibrosis. In its mildest form, there is fatty infiltration (steatosis) of the liver. In non-alcoholic steatohepatitis (NASH,) steatosis is associated with inflammation and fibrosis and there is a risk of progression to cirrhosis and end-stage liver disease (Fig. 7.6a, b).

The long-term outcome is not determined, but the development of cirrhosis in childhood has been described. Children respond poorly to weight reduction and exercise. Metformin, vitamin E and UDCA have not proved effective and trials are underway to evaluate the weight-reducing effect of gastric bands.

Whilst NASH is currently a rare indication for liver transplantation in childhood, it is common in adults and may recur post-transplant in allografts. Furthermore NASH has recently been described as a cause of hepatocellular carcinoma, so long term follow up is required.

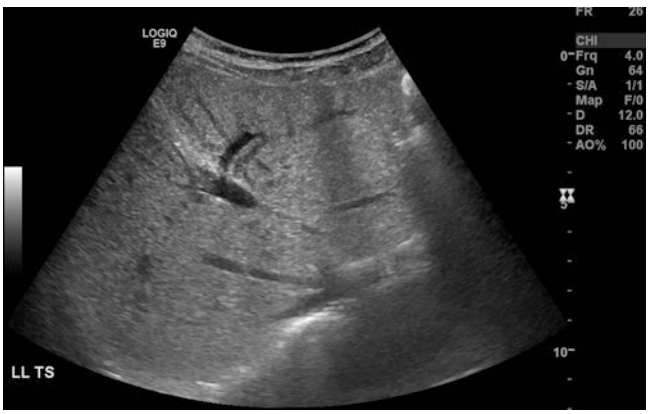


Fig. 7.5 Ultrasound axial sections of the liver reveal echogenic liver parenchyma with loss of echogenicity of the portal venous walls commonly seen in fatty liver

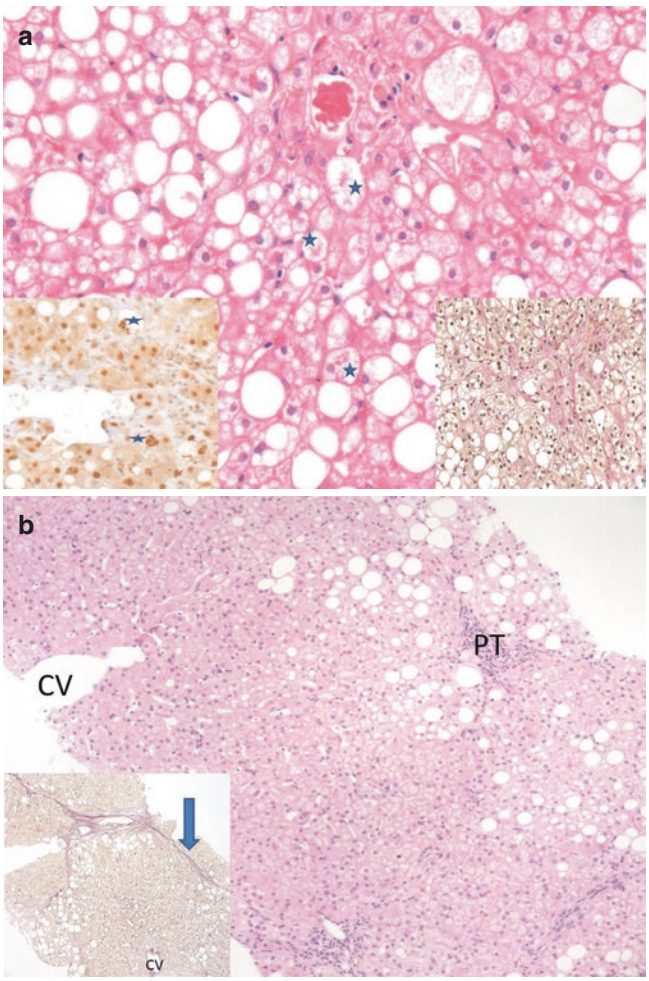


Fig. 7.6 (**a**) The main image here is H&E (original magnification ×200). In addition to steatosis, which appears as sharply punched out 'holes' there are ballooned cells with streaky cytoplasm. These contain Mallory Denk bodies, marked with a star and highlighted with ubiquitin immunohistochemistry in the bottom left panel. In the bottom right Van Gieson staining highlights red collagen in a pericellular and perisinusoidal pattern. These two features define/separate 'steatohepatitis', potentially progressive liver disease, from simple steatosis. (**b**) In usual, adult type, fatty liver disease the fat accumulates around the central vein 'CV'. In these images it can be seen that the fat has accumulated around the portal tract 'PT' (H&E original magnification ×100). In the panel at the bottom left an arrow marks a fibrous septum (red in a Van Gieson stain) originating from a portal tract. This pattern of portal-based fibrosis is more commonly seen in Paediatric non-alcoholic fatty liver disease and has sometimes been referred to as 'type II'

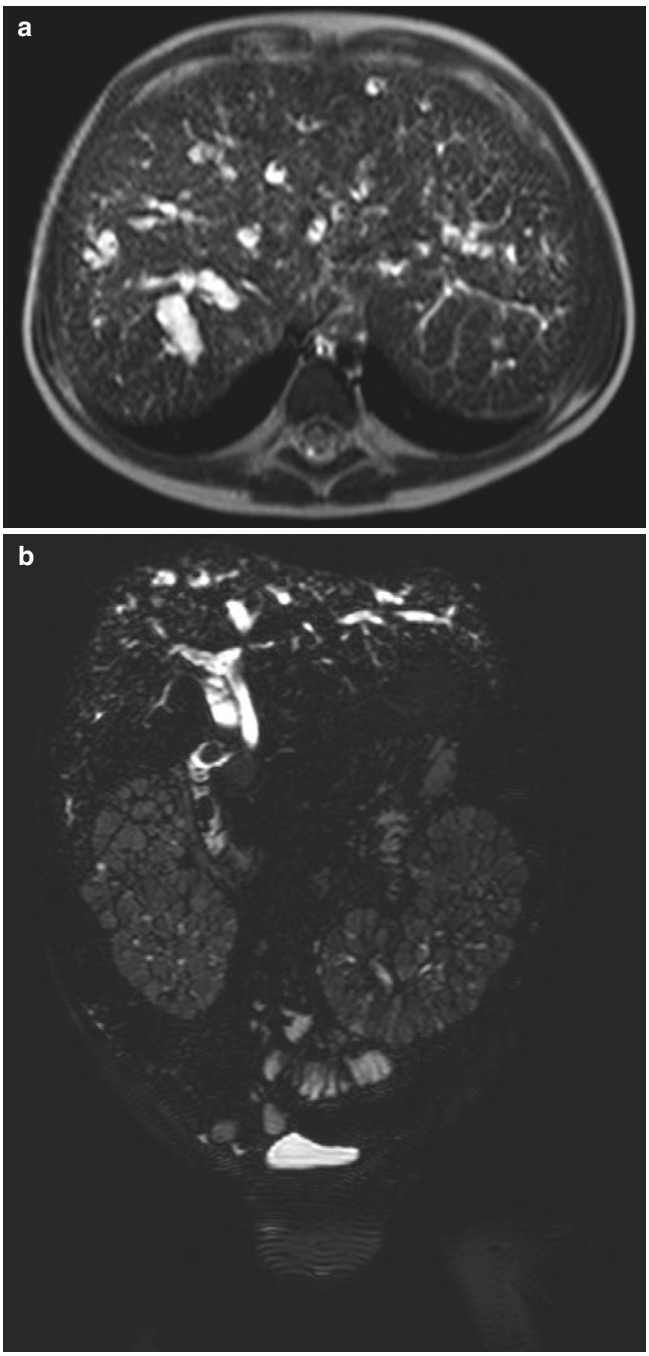


Fig. 7.7 (**a**, **b**) T2 space sequence (MRCP) of the liver reveals multiple intrahepatic cysts with variable bile ducts dilatation and multiple bilateral tiny renal cysts resulting in organomegaly

7.1.3 Congenital Hepatic Fibrosis

Fibropolycystic disease includes congenital hepatic fibrosis, polycystic kidneys with hepatic fibrosis/cysts, and congenital intrahepatic biliary dilatation (Caroli's disease) with or without renal cysts. Liver function is usually normal and the main concern is the development of portal hypertension or associated renal disease (see Chapter 13). The liver cysts are best visualized by MRCP confirms abnormal bile ducts and biliary cysts (Fig. 7.7a, b). Histology demonstrates hepatic fibrosis with abnormal bile ductules, but the hepatic parenchyma is normal (Fig. 7.8a, b).

Management of hepatic disease consists of treating portal hypertension. The prognosis depends on the severity of renal disease, portal hypertension and recurrent cholangitis. If both liver and renal failure develop, combined liver and kidney transplantation is indicated (see Chapter 13).

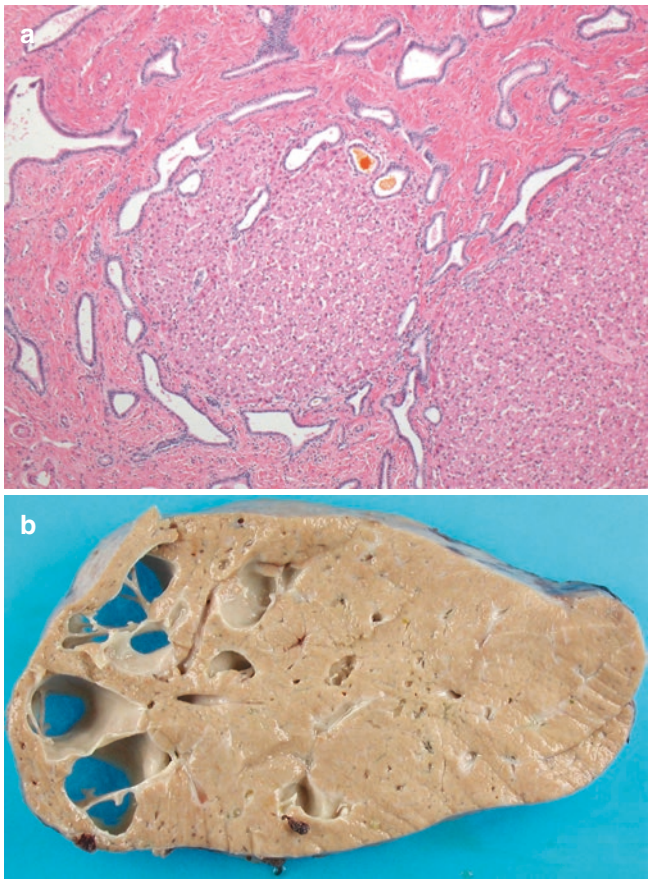


Fig. 7.8 (**a**) H&E (original magnification ×100). In this image multiple biliary ductules show variable dilatation and plugging with bile. Their configuration implies abnormal remodelling of the ductal plate 'ductal plate malformation'. This pattern is typical of any of the conditions under the heading of fibropolycystic syndrome. Note the completely normal appearance of the parenchyma (**b**). In some of the fibropolycystic syndromes the ductal structures become grossly cystically dilated as is seen here in a slice through an affected liver

7.1.4 Cirrhosis

Chronic liver disease usually leads to cirrhosis, which may be compensated (maintained hepatic function, growth and development) or decompensated (many complications and retarded growth and development) which usually requires transplantation.

Clinical features: Children with decompensated cirrhosis have palmar and plantar erythema (Fig. 7.9b), facial telangiectasia (Fig. 7.9a), malnutrition, hypotonia and hepatosplenomegaly with ascites (Fig. 7.9a–c). Jaundice may be absent. In younger children, rickets is common (Fig. 7.10) as in this child who had a pathological fracture.

Biochemical investigations: hepatic transaminitis

- low serum albumin (<30 g/l)
- low serum calcium and phosphate secondary to rickets
- anaemia
- prothrombin time >20 s

Diagnosis: Ultrasound demonstrates a nodular liver (Fig. 7.11a) with splenomegaly and varices (Fig. 7.11b). Histology shows extensive fibrosis and regenerative nodules (Fig. 7.12a, b).

Complications include the development of portal hypertension with

- Oesophageal and gastric varices on endoscopy (Fig. 7.13a, b). Bleeding oesophageal varices are managed medically (Table 7.3) or endoscopically using oesophageal band ligation (Fig. 7.14). Sclerotherapy is rarely used. Intractable bleeding may require insertion of a trans-jugular intrahepatic portosystemic shunt to reduce portal pressure (Fig. 7.15), but it may cause encephalopathy.
- Ascites is managed by fluid restriction and diuretic therapy (spironolactone, 3 mg/kg, or furosemide, 1 mg/kg).
- Encephalopathy demonstrated by slow, irregular low-frequency waves on EEG (Fig. 7.16) is treated with lactulose 2–4 ml/kg/day tds, or rifaximine 20–30 mg/kg/day. Sepsis is common and may precipitate encephalopathy. Treatment with appropriate broad-spectrum antibiotics is essential.

Management: Nutritional supplementation with a high-calorie protein feed (110–150% recommended daily allowance). Protein restriction is not advised unless encephalopathy is severe. Medium-chain triglycerides are supplemented to 50% of fat intake and fat-soluble vitamin supplementation is required if the patient is jaundiced. Pruritus is alleviated by rifampicin, 3 mg/kg, UDCA, 20 mg/kg, colestyramine, 0.5 g/kg/day, or topical evening primrose oil. Without transplantation, most children with advanced liver failure die before adolescence.

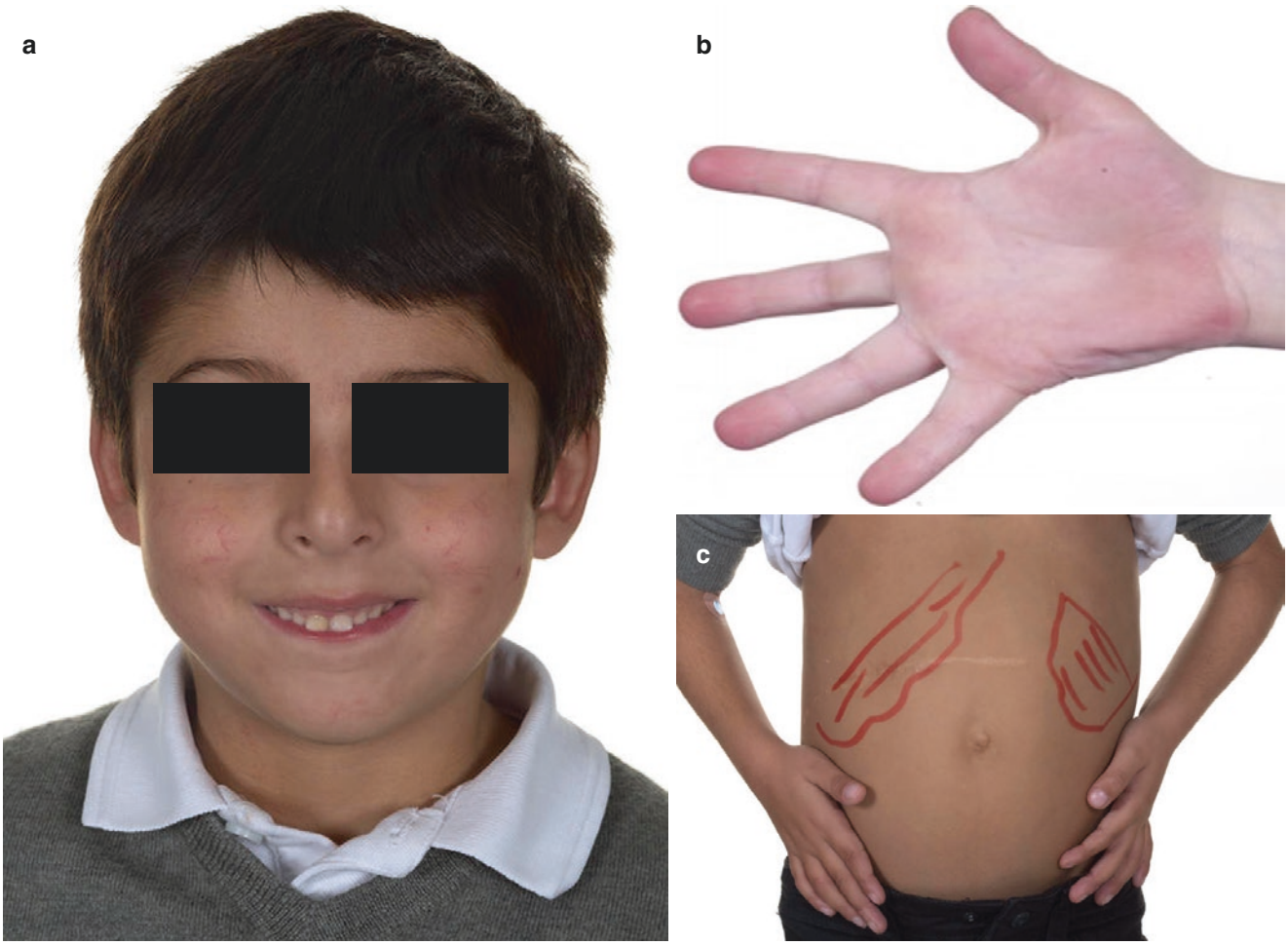


Fig. 7.9 (**a**) This young boy with compensated cirrhosis has obvious facial telangiectasia and palmar and plantar erythema (**b**) with hepatosplenomegaly (**c**)

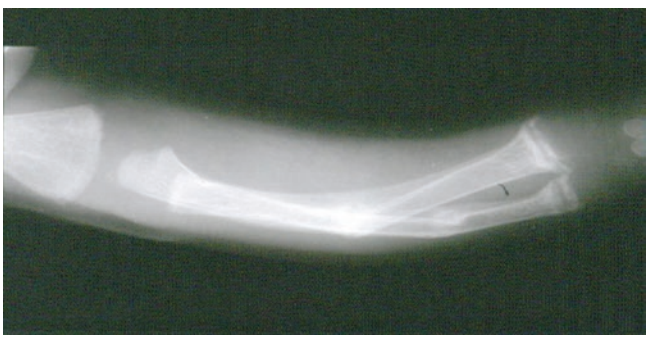


Fig. 7.10 Metabolic Bone disease with fractures

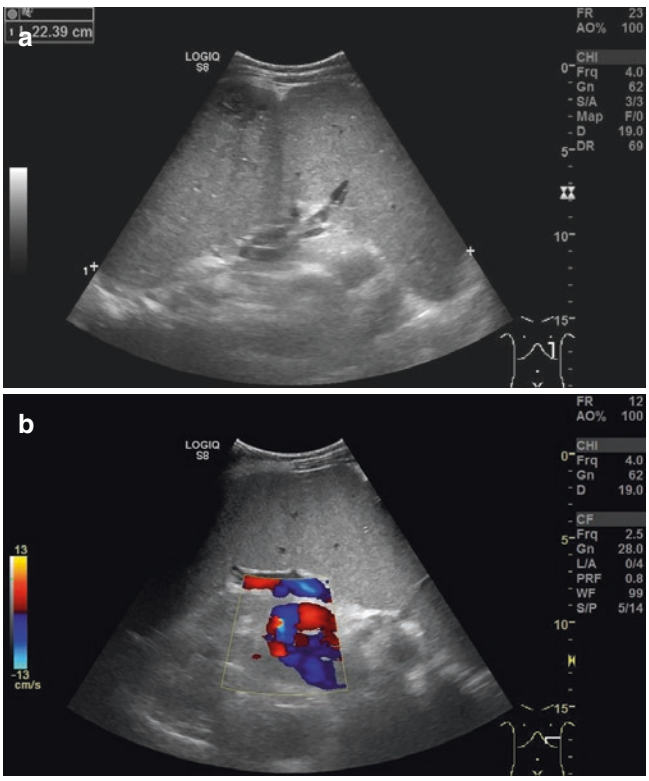


Fig. 7.11 (**a**) Ultrasound axial sections of the liver reveals irregular nodular surface of the liver with coarse echogenicity of the liver parenchyma. Ultrasound coronal section of the spleen (**b**) reveals splenomegaly with varices at the hilum

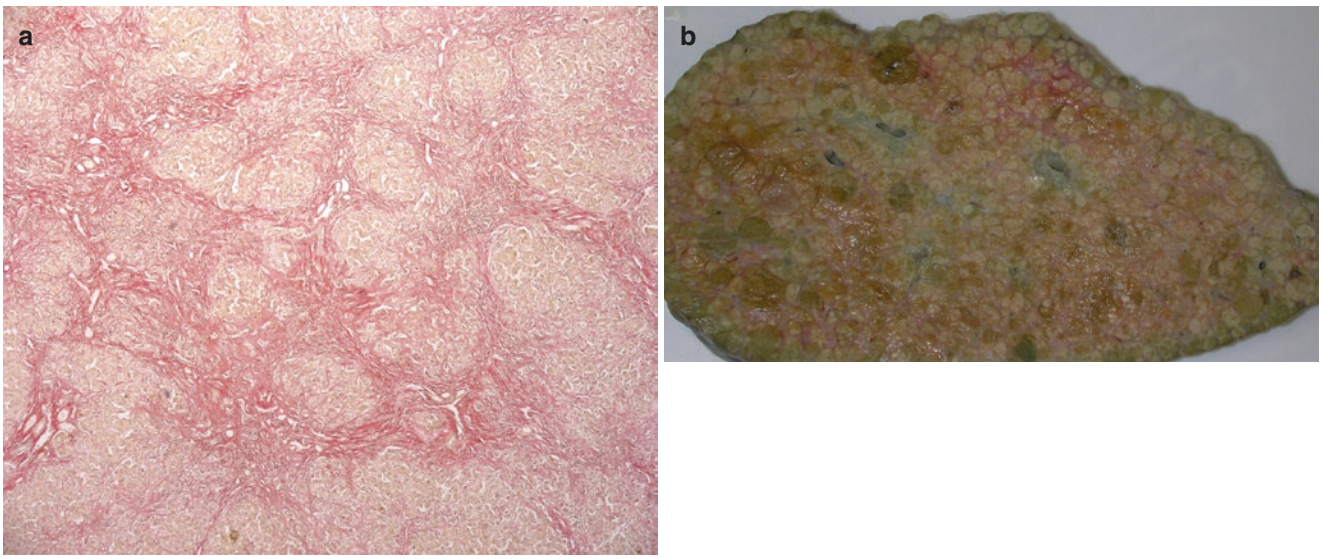


Fig. 7.12 (**a**) (Original magnification ×20). Collagen stains such as this show fibrous tissue (red) surrounding nodules diagnostic of cirrhosis. (**b**) Macroscopically the nodular appearance of cirrhosis is accompanied by a firm feeling liver. It should be noted that nodules outlined by necrosis can be seen in the acute setting, histological examination is necessary sometimes to make the distinction

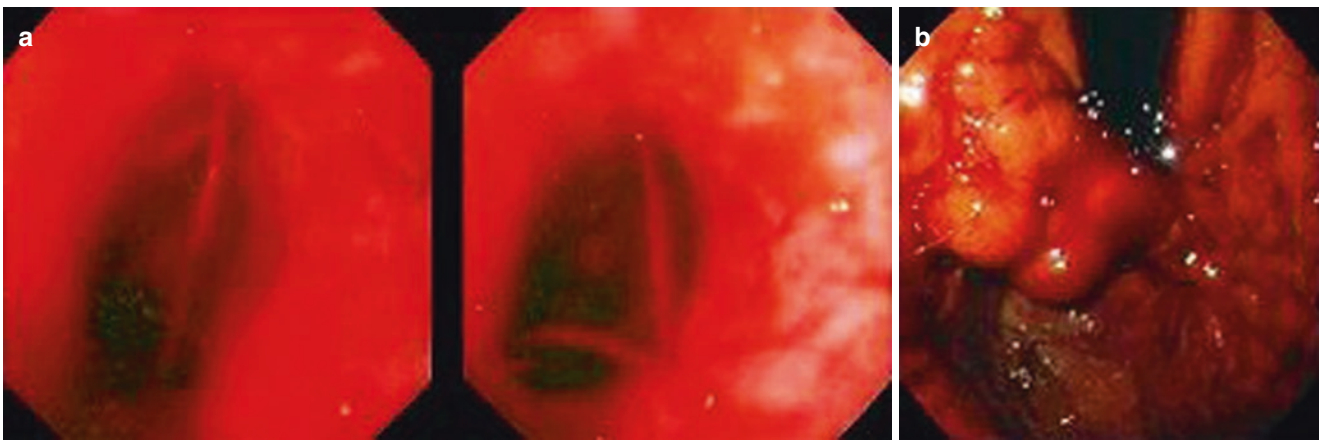
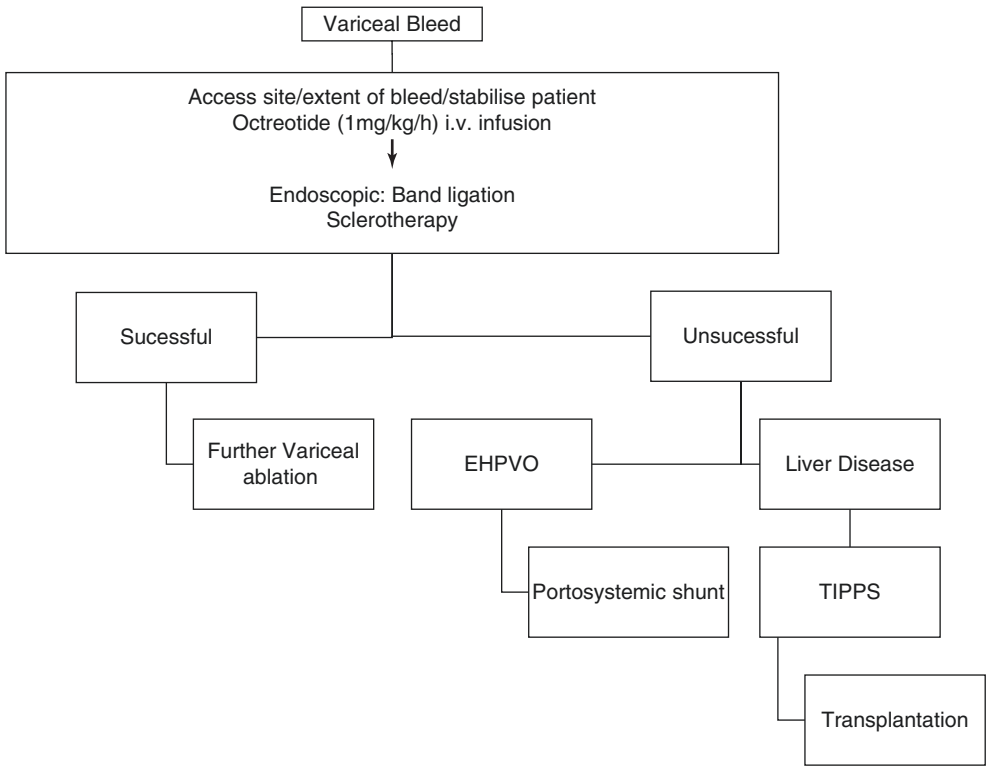


Fig. 7.13 (**a**, **b**) Bleeding Varices on Endoscopy. Endoscopic banding is usually effective in stopping the bleeding

Table 7.3 Management of a variceal bleed
EHPVO **extra-hepatic portal vein obstruction**



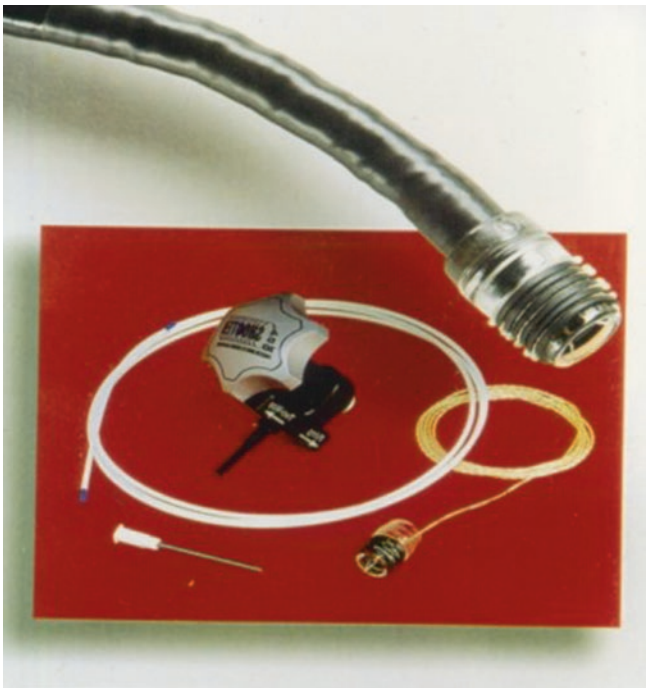


Fig. 7.14 Endoscope with banding equipment

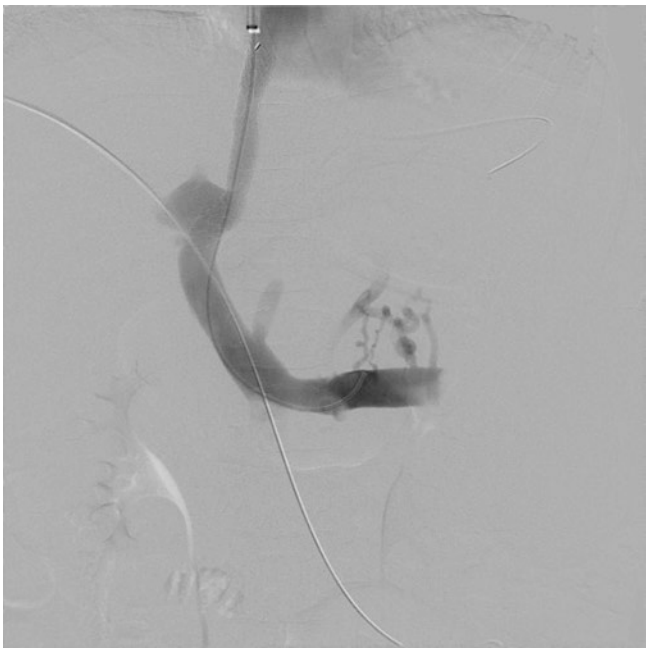


Fig. 7.15 A transjugular intrahepatic portosystemic shunt (TIPS) is a tract created within the liver using x-ray guidance to connect the hepatic vein with the portal vein. The shunt is kept open by a stent and is useful to reduce portal pressure in intractable variceal bleeding

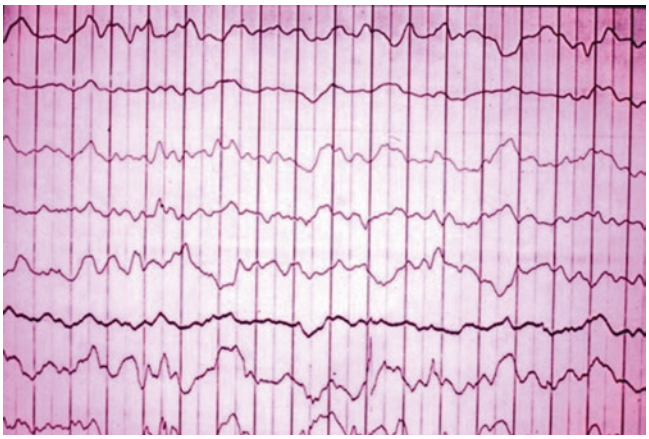


Fig. 7.16 EEG showing slow, irregular low-frequency waves typical of chronic Encephalopathy

Extra-Hepatic Portal Vein Obstruction

Portal Hypertension may arise secondary to portal vein thrombosis or obstruction, usually secondary to umbilical vein manipulation as a neonate, inherited coagulation disorder or other causes of thrombosis. A portal cavernoma develops (Fig. 7.17a–c). Although growth failure is sometimes described, the main complications are extensive collaterals as seen in this child's abdomen distended with ascites (Fig. 7.18a) and with finger clubbing (Fig. 7.18b) and variceal bleeding. If medical management is unsuccessful (Table 7.3), then a surgical shunt is required.

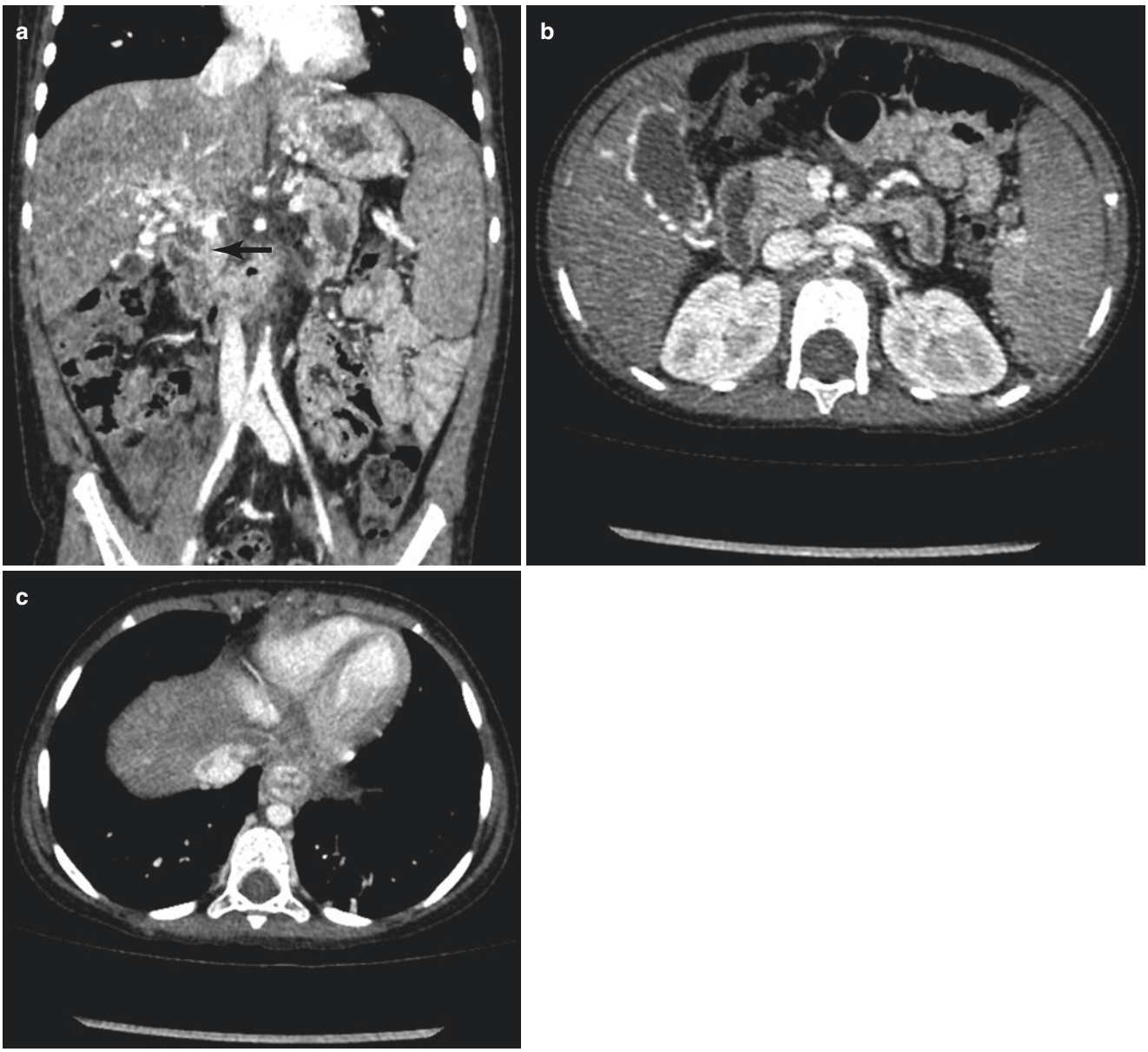


Fig. 7.17 (**a**–**c**) Post intravenous contrast enhanced MRI axial and coronal sections of the abdomen reveal cavernous transformation of portal vein at porta with extensive varices around the stomach, gall bladder, lower oesophagus with splenomegaly

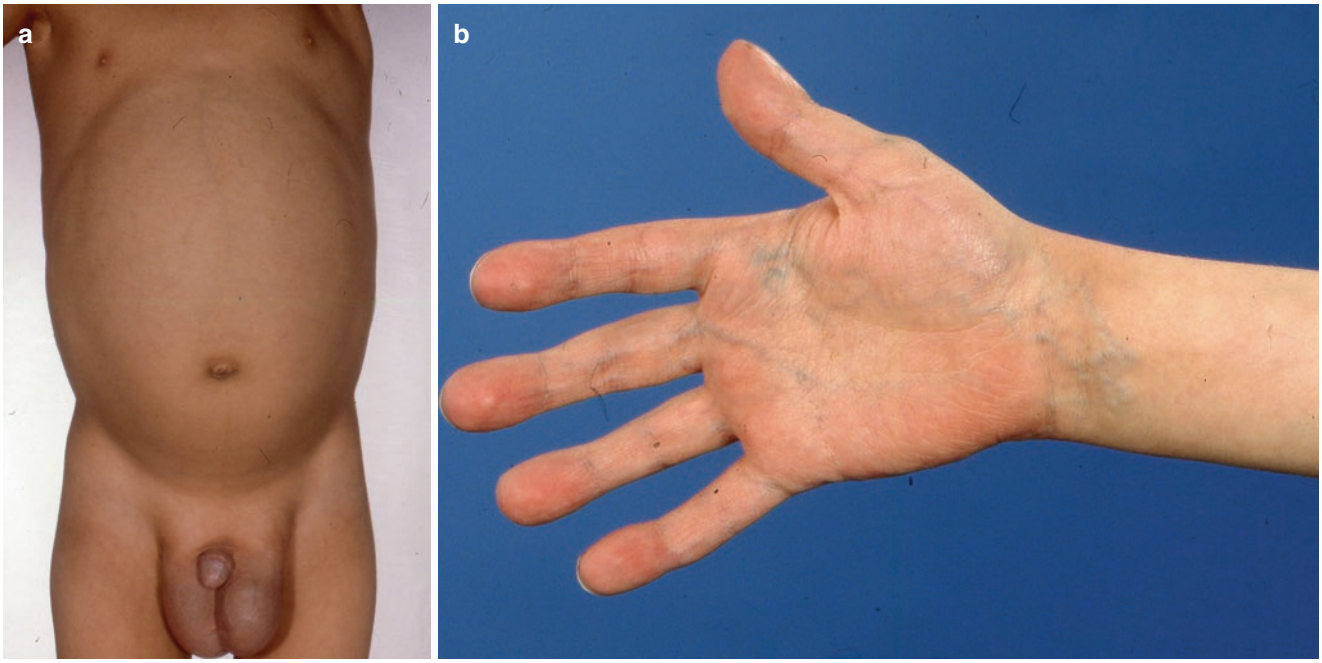


Fig. 7.18 (**a**) Extrahepatic portal vein obstruction is associated with extensive collaterals as seen in this child's abdomen and with finger clubbing (**b**)

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The Child with Cystic Fibrosis Liver Disease

8

Deirdre Kelly

Cystic fibrosis (CF) is the most common life limiting autosomal recessive disorder of Caucasians. The defect in the cystic fibrosis transmembrane regulator (CFTR) protein causes an inability to maintain normal hydration of luminal tracts which leads to thickened secretions and obstruction. As survival with lung disease improves, the recognition of liver, pancreas and bowel disease is increasing. Liver disease develops in a third of CF patients and causes 2.5% of CF deaths (Table 8.1). It is more common in male CF patients and those with meconium ileus as a neonate.

Table 8.1 Hepatobiliary manifestations in CFLD

Lesion	Clinical manifestation	Frequency (%)
Specific alterations due to the defect in CFTR	Neonatal cholestasis Sclerosing cholangitis Microgallbladder Cholelithiasis Cirrhosis Portal hypertension	Rare Rare 30 15 20–30 2–5

8.1 Presentation in the Neonate

8.1.1 Prolonged Jaundice

In the neonate it may cause prolonged jaundice (Fig. 8.1) (which resolves), neonatal hepatitis, fat soluble vitamin deficiency (especially vitamin K), or inspissated bile syndrome causing biliary obstruction. Infants may present with meconium ileus (Fig. 8.2) which may resolve with laxatives and N-acetyl cysteine or a Gastrografin enema but often requires surgery. Management of neonatal CF liver disease is supportive as described in Chapter 1.

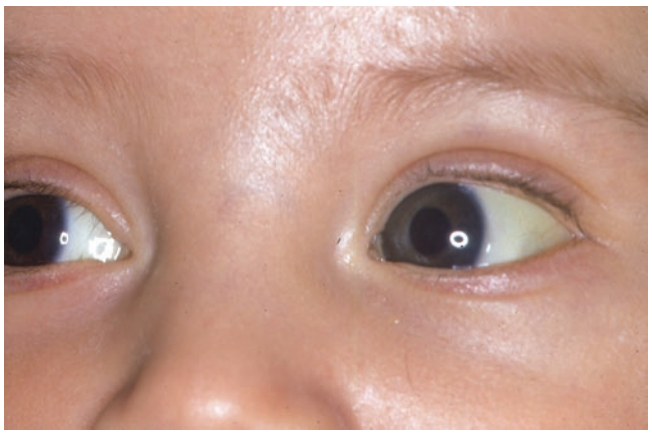

Fig. 8.1 Mild jaundice in an infant with cystic fibrosis

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D. Kelly et al. (eds.), *Atlas of Pediatric Hepatology*, https://doi.org/10.1007/978-3-319-69529-7_8

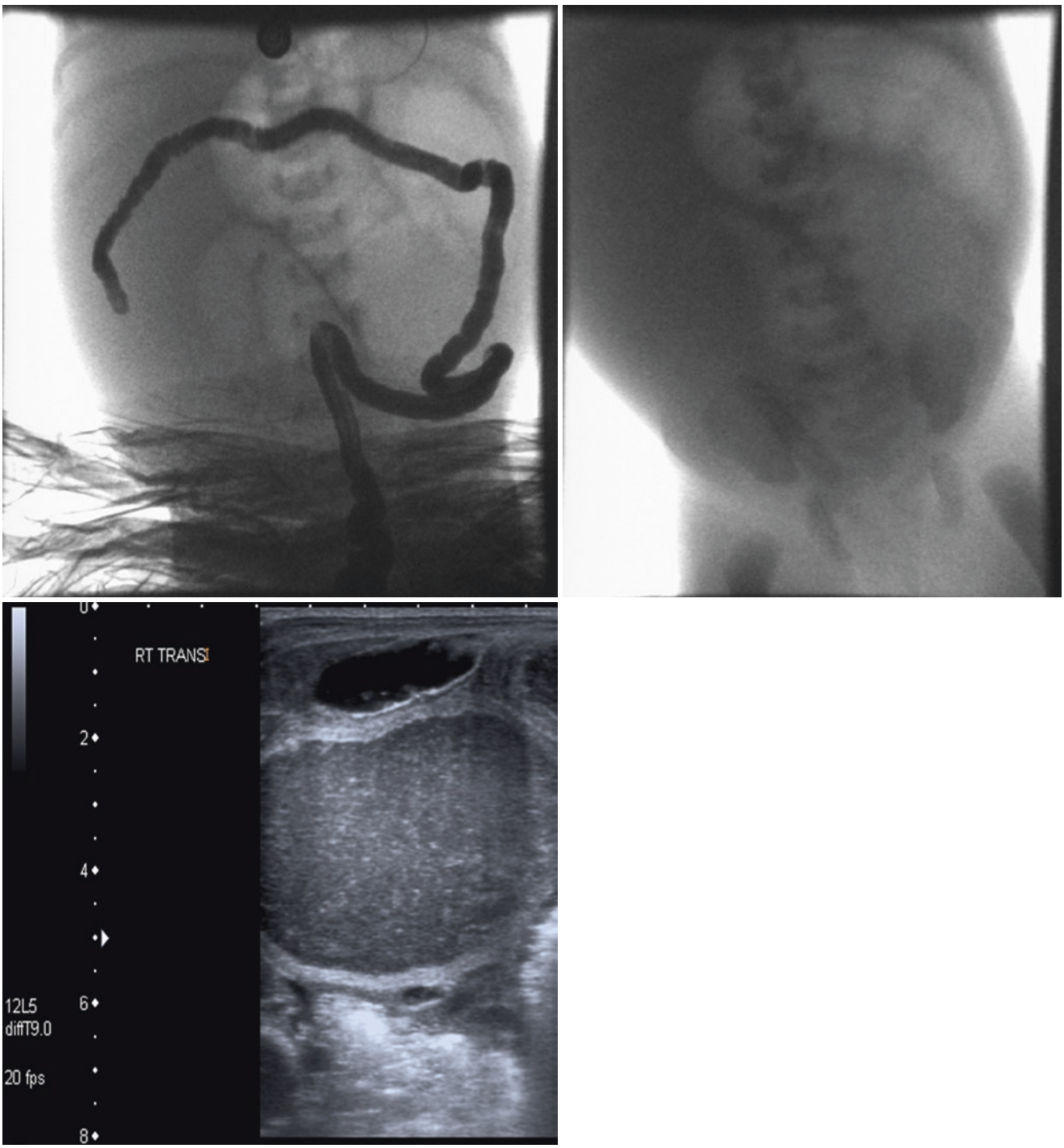

Fig. 8.2 Contrast enema of a child with cystic fibrosis and intestinal obstruction and failure to pass meconium at birth. It reveals a micro colon with multiple meconium plugs in colon and terminal ileum causing small bowel obstruction

8.2 Presentation in Older Child

In most children with CF, presentation is with failure to thrive, diarrhoea and chest symptoms. Liver disease develops later and may present with gall stones (Fig. 8.3) usually first seen on ultrasound (Fig. 8.3a) but shown here on MRCP (Fig. 8.3b). They are usually asymptomatic but Ursodeoxycholic acid (10–20 mg/kg) is usually prescribed.

In some children, pancreatic insufficiency due to chronic or recurrent pancreatitis is an issue and most children require pancreatic enzyme supplements, or when the pancreas becomes atrophic (Fig. 8.4) insulin is required for diabetes mellitus.

Management of CF lung disease requires specialised care focussed on physiotherapy, antibiotics and good nutrition.

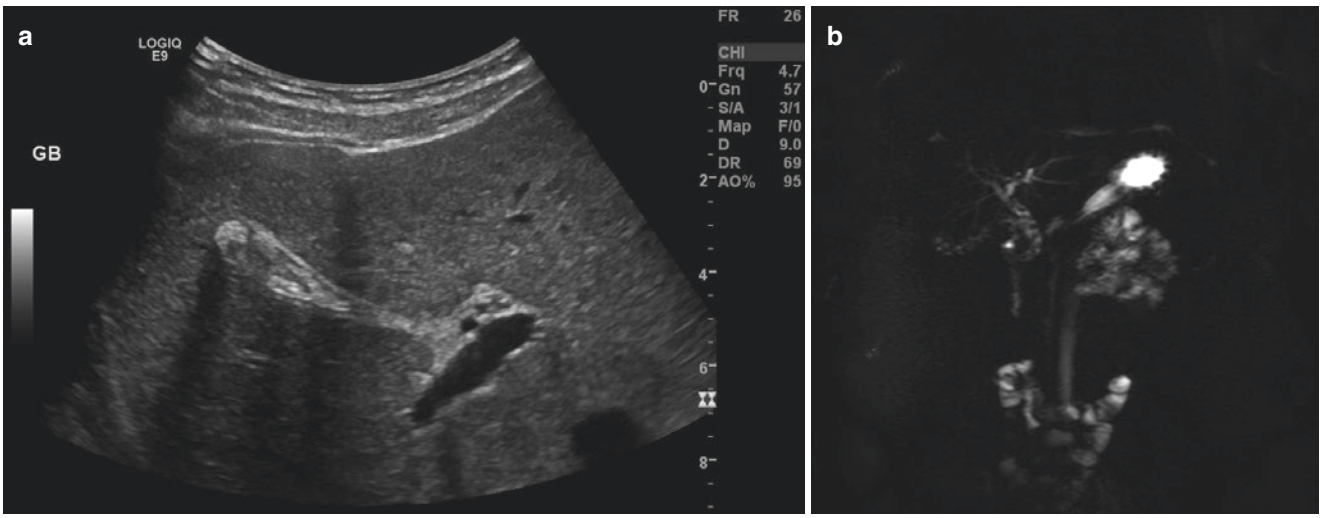

Fig. 8.3 (**a**) Abdominal ultrasound reveals multiple gall stones in the gall bladder and common bile duct which are also seen on the MRCP (**b**)

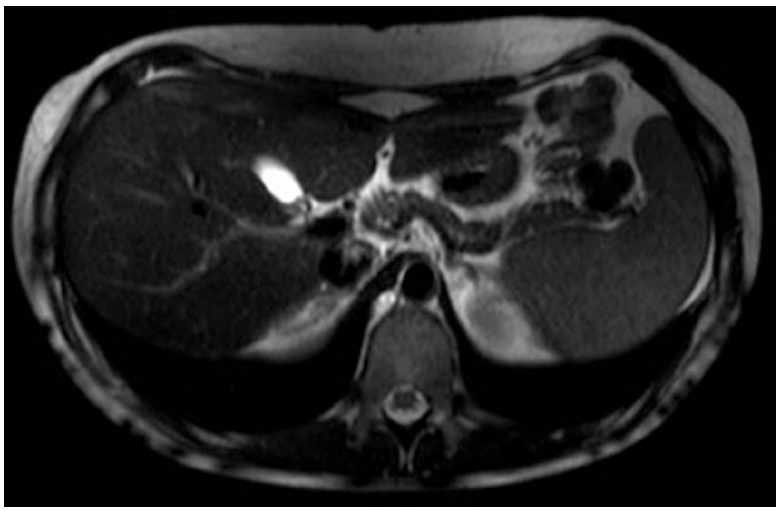

Fig. 8.4 MRI: T2 axial sections through body of pancreas reveals small and atrophic pancreas with pancreatic duct dilatation typical of Cystic Fibrosis

8.2.1 Malnutrition/Chronic Liver Disease/ Cirrhosis and Portal Hypertension

In older children CF presents with hepatomegaly and abnormal transaminases and may remain subclinical until malnutrition, cirrhosis and portal hypertension develop. Note the distended abdomen because of hepatosplenomegaly and the muscle wasting from malnutrition in the arms (Fig. 8.5). Liver function may be normal for years prior to hepatic decompensation.

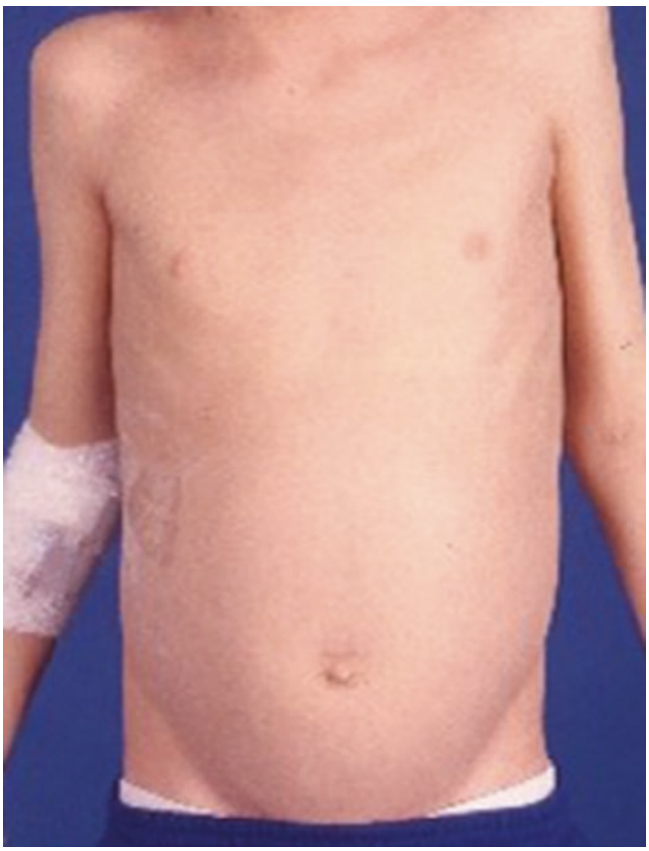

Fig. 8.5 Note the distended abdomen due to hepatosplenomegaly and the intravenous line in the right arm for antibiotics

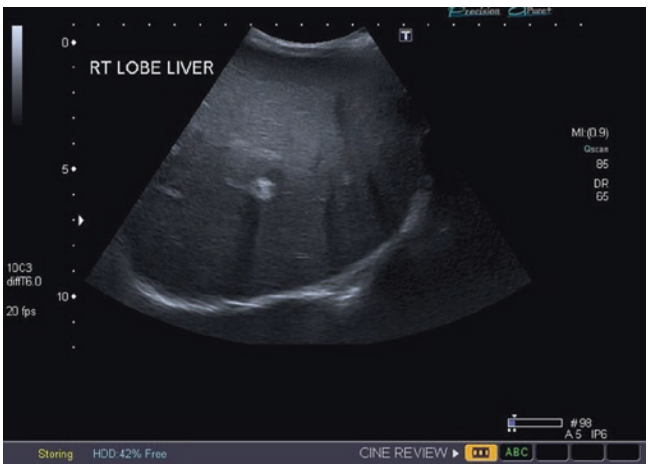

Fig. 8.6 Ultrasound of the right lobe of the liver is 'bright' because of steatosis typical of CFLD

Detection of liver disease is based on detection of abnormal hepatic transaminases (ALT and AST) and a raised Alkaline phosphatase on at least two occasions over 6 months. Abdominal ultrasound is the most useful initial investigation as it may demonstrate a fatty liver secondary to steatosis (Fig. 8.6) or identify cirrhosis with an irregular liver (Fig. 8.7a) and portal hypertension with splenomegaly (Fig. 8.7b).

Liver biopsy is required if there is doubt about the diagnosis or to stage the disease. Typical histological findings are steatosis (Fig. 8.8), and focal biliary fibrosis (Fig. 8.9a) which progresses to cirrhosis (Figs. 8.9b and 8.10).

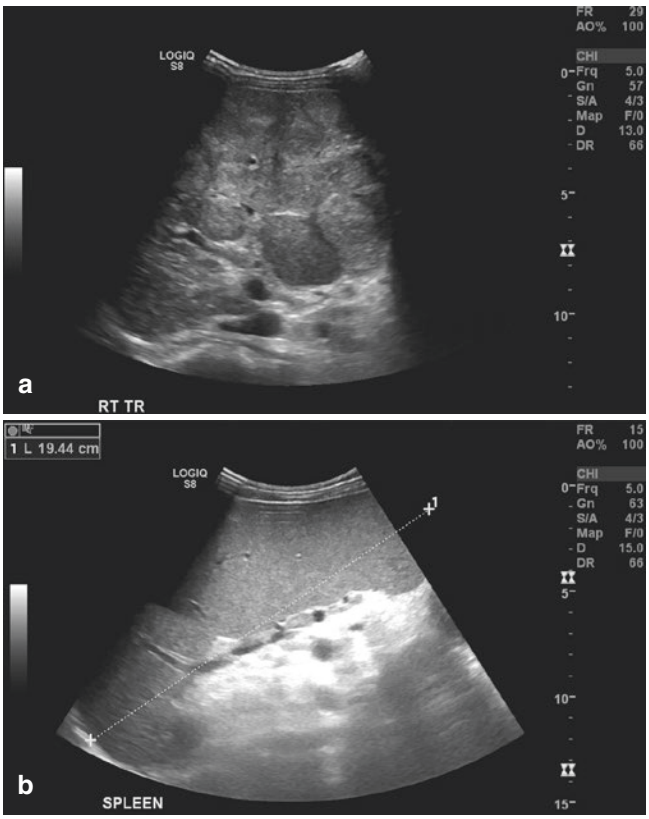

Fig. 8.7 (**a**, **b**) Ultrasound axial sections of the liver and coronal section of the spleen reveal irregular heteroechoic liver with nodular surface and splenomegaly in keeping with cirrhosis and portal hypertension in CFLD

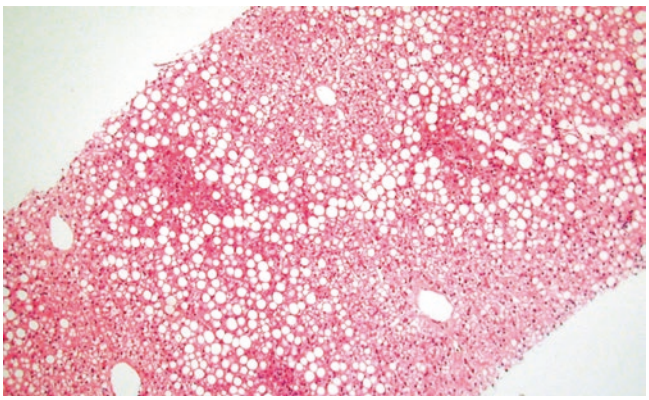

Fig. 8.8 (H&E original magnification ×100). Macrovesicular steatosis sometimes dominates the histological picture in CF

Follow up: It is usual to monitor with liver biochemistry and ultrasound to detect the progression of liver disease, alpha fetoprotein to detect the possible development of hepatocellular carcinoma. Upper gastrointestinal endoscopy is required to detect and treat varices in those with cirrhosis.

Management of CFLD is in the context of other multiorgan involvement. Nutrition is key, ursodeoxycholic acid (20 mg/kg/day) is used to improve bile flow, fat soluble vitamins and pancreatic supplements (Creon) are required.

In advanced portal hypertension, variceal bleeding requires treatment as discussed in Chapter 7. TIPSS should be considered for recurrent variceal bleeding when liver function is maintained, as long as there is no significant encephalopathy (Fig. 8.11).

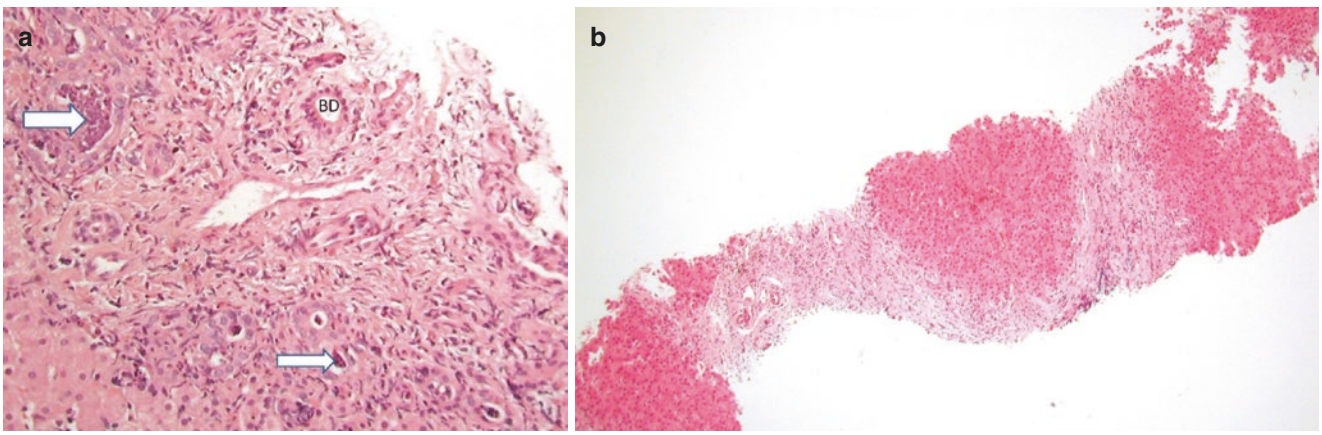

Fig. 8.9 (**a**) (H&E original magnification ×200). Fibrosis is accompanied by notoriously patchy biliary changes 'focal biliary fibrosis'. This image shows a preserved bile duct in the portal tract (marked BD) at the portal tract margin there are ductules which are plugged with eosinophilic inspissated secretion accompanied by neutrophil polymorphs. Two examples are marked with arrows. (**b**) (H&E original magnification ×40). Broad bands of fibrosis are dividing this liver core into nodules indicative of established cirrhosis

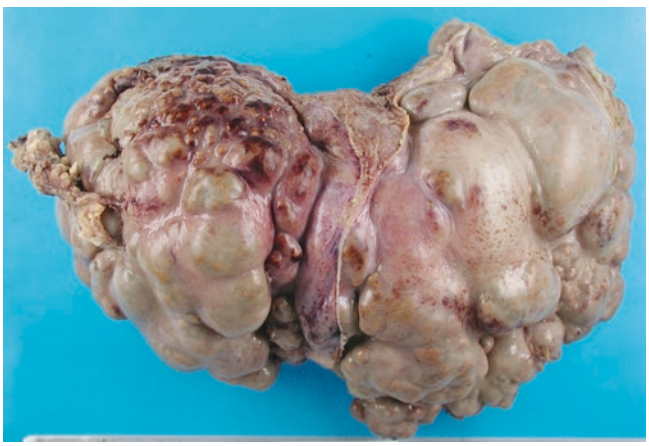

Fig. 8.10 This is a grossly distorted liver from a child with end stage CF related liver disease who underwent liver transplantation)

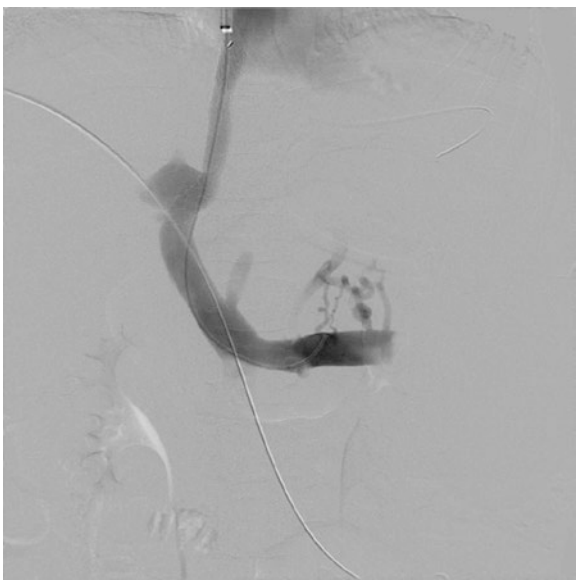

Fig. 8.11 Emergency TIPPS placed because varices ruptured during an endoscopic procedure. The stent connects the hepatic veins to the portal venous system and reduces the portal pressure and stops the variceal bleeding

8.3 Indications for Liver Transplantation

Liver transplant is indicated for hepatic decompensation, ascites and jaundice or intractable variceal bleeding. It should be carried out prior to significant deterioration of lung function (FEV1 < 50%). Results are initially very satisfactory with similar outcomes to other indications, although there is a higher incidence of diabetes. Lung function stabilizes post-transplant, but nutrition may take longer to normalise because of pancreatic and lung disease. Sadly, many successful transplant survivors die of respiratory causes in adult life.

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Children with Cancer Who Have Liver Disease

9

Deirdre Kelly

Children with haematological or solid organ malignancies may develop liver involvement due to cytotoxic treatment, an impaired immune system or as part of the complications of bone marrow or stem cell transplantation.

The clinical features are related to the drug therapy and include hepatic fibrosis and portal hypertension (see Chapter 7), hepatitis or necrosis or vascular damage.

Methotrexate hepatotoxicity is dose related, and liver biopsy may show steatosis and portal tract fibrosis in children who have received prolonged courses (Fig. 9.1). It may be reversible if the drug is discontinued.

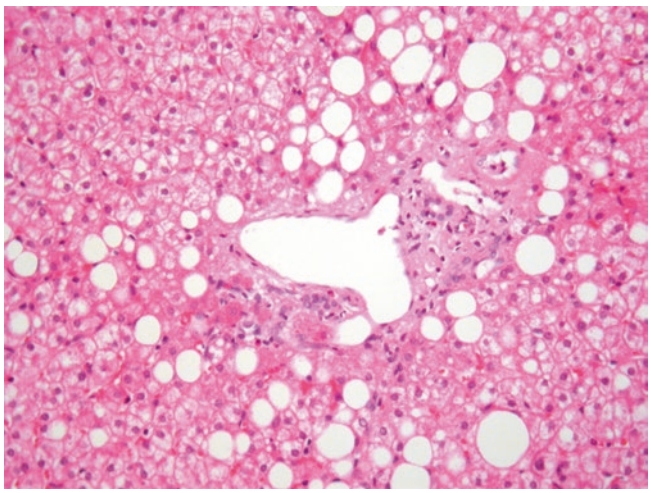

Fig. 9.1 (H&E original magnification ×200). Methotrexate typically induces fatty change in the liver. In this image the steatosis is seen around a portal tract, this is in contrast to the distribution in fatty liver disease where the fat accumulates around the central vein. Fibrosis may also develop

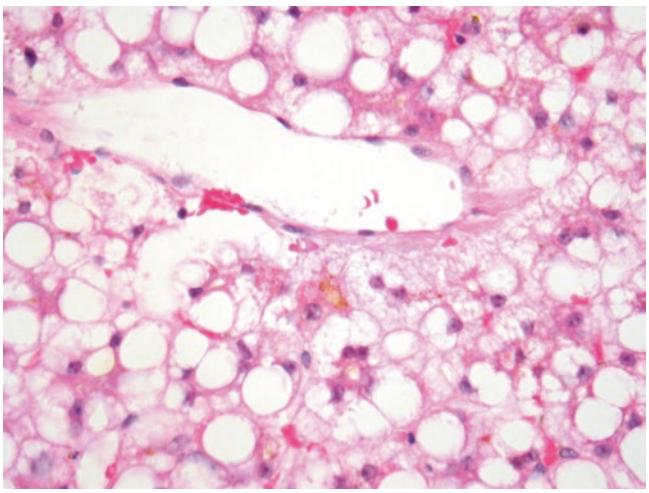

Fig. 9.2 (H&E original magnification ×400). In this child treated with Asparaginase there was diffuse and severe macrovesicular steatosis, illustrated here around a central vein. Yellow bile is also visible in canaliculi/parenchymal cholestasis

6-Mercaptopurine (6-MCP), used in maintenance treatment of acute lymphocytic leukaemia, is associated with hepatic necrosis and cholestasis as are similar drugs such as asparaginase, although liver toxicity is less common in children (Fig. 9.2) Fatalities have been reported. Patients on 6-MCP should have regular liver function tests as hepatic damage is reversible if treatment is stopped promptly. Actinomycin, used to treat Wilms' tumour, may cause subacute hepatic failure or fibrosis.

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D. Kelly et al. (eds.), *Atlas of Pediatric Hepatology*, https://doi.org/10.1007/978-3-319-69529-7_9

9.1 Veno-occlusive Disease (Sinusoidal Obstruction Syndrome)

Veno-occlusive disease (Sinusoidal Obstruction Syndrome) is associated with a number of chemotherapeutic agents, radiotherapy, busulphan therapy prior to Bone marrow transplantation or Stem cell transplantation.

Clinical presentation is with tender hepatomegaly, ascites (note the scrotal oedema), (Fig. 9.3) thrombocytopenia and splenomegaly .The diagnosis is based on:

- Abdominal ultrasound of the portal vein flow to identify retrograde flow and or an increase in hepatic resistance. (Fig. 9.4a, b) which is confirmed by CT Scan (Fig. 9.4c, d).
- Liver histology demonstrates narrowing or occlusion of the terminal hepatic venules, sinusoidal congestion and necrosis of hepatocytes with a mild inflammatory infiltrate in the centilobular zone. Fibrosis and cirrhosis may develop (Fig. 9.5).

Management is with intravenous defibrotide and/or antithrombin III to reduce the venous obstruction and is successful if started early.

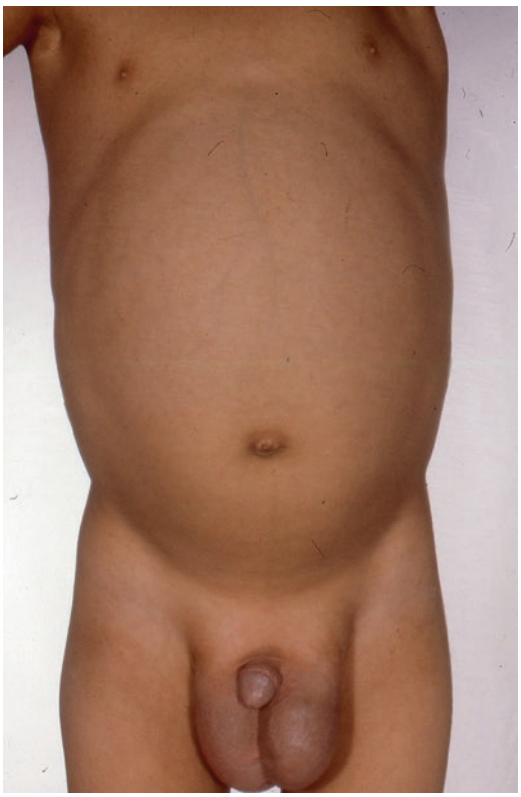


Fig. 9.3 This boy had a bone marrow transplant for acute leukemia and devloped ascites with veno-occlusive disease

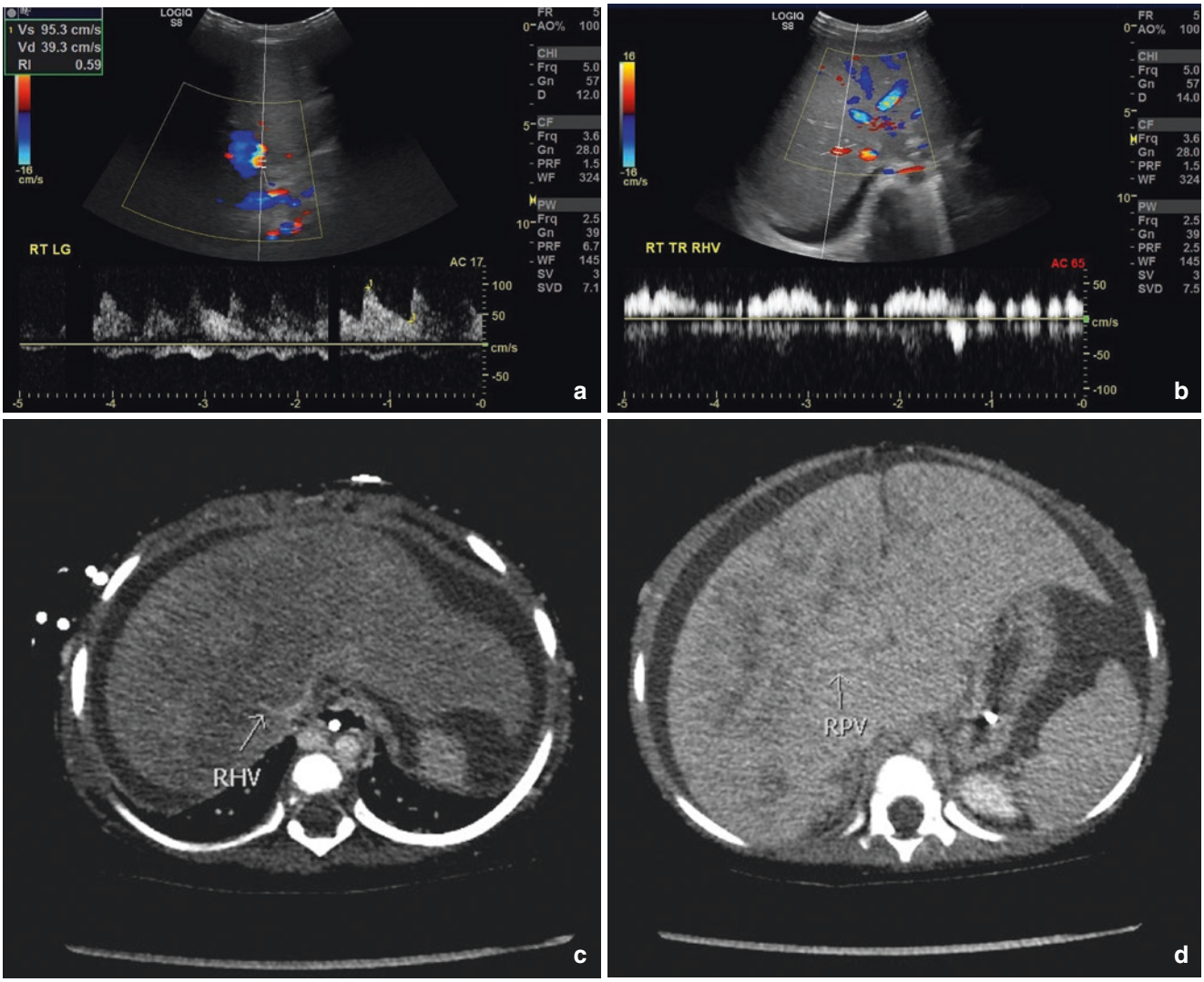
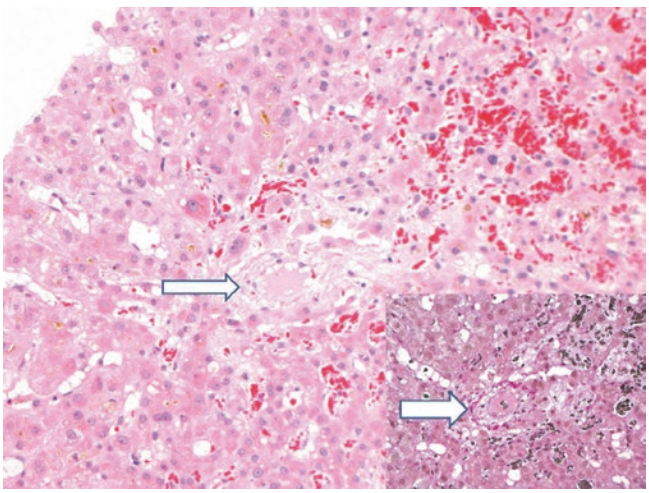


Fig. 9.4 (**a**, **b**) Ultrasound of a child with a stem cell transplant who presented with acute abdominal distention. Axial Doppler images of the liver reveal reversal of flow in the right branch of the portal vein and loss of triphasic hepatic venous flow. (**c**, **d**) Post intravenous contrast axial sections of the liver in the portal venous phase reveal severe narrowing of right branch of portal vein, all the three hepatic veins and large perfusion defect of the right lobe of liver

Fig. 9.5 (H&E original magnification ×200, insert Hematoxylin Van Gieson ×400). Veno occlusive disease is rarely biopsied. In this example loose fibrous tissue partially fills the central vein/hepatic vein branch forming a crescent marked by the arrow; the outline of the vein is highlighted on the Van Geison stain. Note the bright red blood cells in the top right hand corner where there is sinusoidal congestion. Canalicular cholestasis is also present



9.2 Post-bone Marrow Transplantation

Bone marrow or stem cell transplantation is indicated for many disorders, ranging from acute leukaemia to immunodeficiency. Liver dysfunction develops in approximately 30% of patients due to pre-existing liver disease, therapy with hepatotoxic drugs especially 6-thioguanine, infection, graft-vs.-host-disease (GVHD), veno-occlusive disease (VOD) Graft-vs.-host-disease.

GVHD is a systemic disorder involving skin, gut, lung, eye, pancreas and liver, typically occurring 7–50 days after BMT. The acute form presents with a desquamating skin rash, diarrhoea and the liver is involved in 40% of cases; manifested by mild jaundice, transaminitis and hepatomegaly. The diagnosis of GVHD is made by biopsy of symptomatic tissue (e.g. intestinal mucosa, skin if rash present). This child had a severe skin rash which improved on increased immunosuppression (Fig. 9.6a, b). Liver Histology demonstrates damaged bile ducts. There may also be endothelitis, and mild portal tract inflammation bile duct loss and cholestasis; the parenchyma is relatively (Fig. 9.7).

Management is with increased immunosuppression with high-dose corticosteroids, cyclosporin (trough levels 200–400 ng/ml monovalent assay) and tacrolimus (trough levels 8–15 ng/l). Rituximab, anti-CD20 chimaeric monoclonal antibody or extracorporeal plasma photophoresis may be effective for chronic GVHD. Liver transplantation is indicated if disease outside the liver is minimal and the bone marrow graft has been successful.

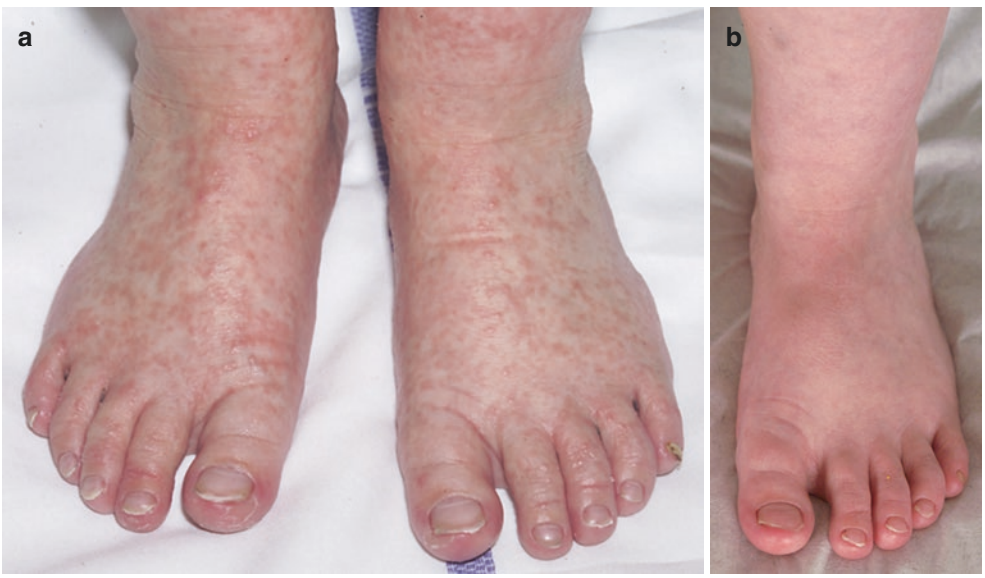


Fig. 9.6 Severe GVHD (**a**) which improved when his immunsosuppression was increased (**b**)

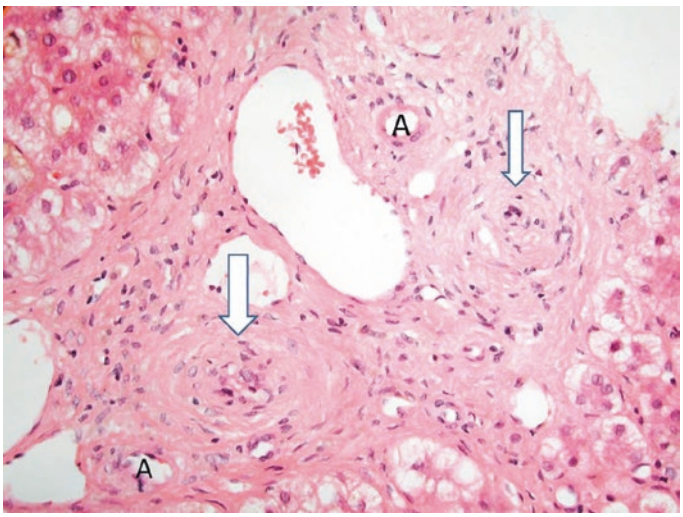


Fig. 9.7 (H&E original magnification ×400). Graft-versus-host disease. Note the damaged bile ducts, identifiable by their location adjacent to hepatic artery branches 'A'. Without treatment, the ducts disappear indicating irreversible damage. Unlike in biliary tract diseases, ductules are not seen at the portal tract periphery. Inflammation is typically minimal

9.3 Impaired Immune System

Children treated for malignancy are immunocompromised, which increases the incidence of bacterial, viral and fungal infections, resulting in liver dysfunction, especially cholestasis.

This young lady developed fungal hepatic and splenic abscesses producing cholestasis and gross hepatosplenomegaly. Radiology demonstrates the fungal lesions (Fig. 9.8a–c). The positive identification of fungi is very difficult except in overwhelming infections, so treatment with amphotericin (1–3 mg/kg/day) and/or flucytosine (100–200 mg/kg/day) is often empirical, based on risk factors and clinical suspicion.

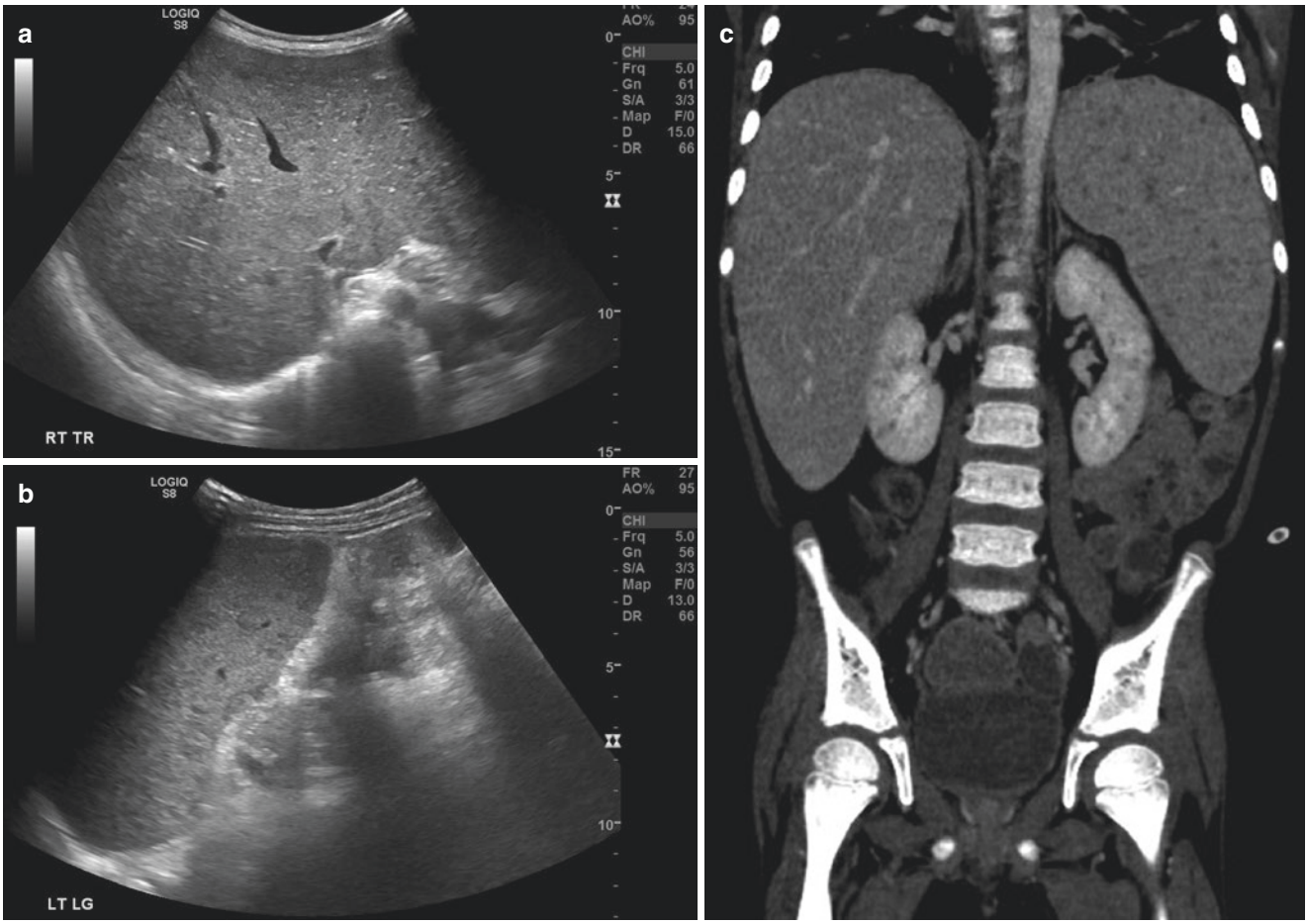


Fig. 9.8 Axial ultrasound sections of liver and spleen (**a**, **b**) and post Intravenous contrast enhanced coronal section of the abdomen (**c**) reveal diffuse fungal infiltration of liver, spleen and both kidneys

Further Reading

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Liver Trauma

10

Khalid Sharif

Liver trauma accounts for nearly 30% of abdominal organ injuries in children. Common causes of abdominal trauma include road traffic accidents, handle bar injuries in bicycle riders and other severe blows to the abdomen e.g. sports injuries, child abuse, penetrating abdominal injuries. Crushing of the abdominal organs against the vertebral column, sudden acceleration/deceleration resulting in shearing of the attachments or vascular supply is the underlying phenomenon.

Initial management of the trauma child is as advised by the Advance Paediatric Life support (APLS) guidelines i.e. evaluation of airways (A), Breathing (B) and Circulation (c). Further management of the child depends on haemodynamic stability and the extent of injuries. If the child is stable, CT (computerized Tomography) scan of the abdomen is performed to evaluate the severity of liver trauma and identify injuries to other abdominal organs (Fig. 10.1). Liver injuries are either graded at laparotomy (American Association for the surgery of Trauma) or by CT scan (Table 10.1; Figs. 10.2a, b, 10.3 and 10.4).

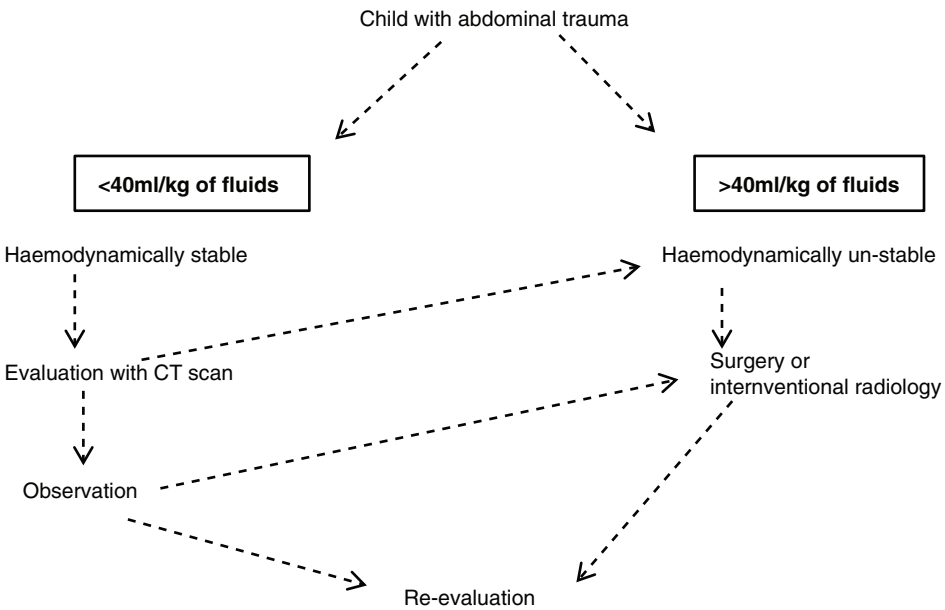

Fig. 10.1 Algorithm for the management of pediatric liver trauma

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D. Kelly et al. (eds.), *Atlas of Pediatric Hepatology*, https://doi.org/10.1007/978-3-319-69529-7_10

Table 10.1 Grading of liver injuries by CT scan

Moore et al. J Trauma. 1995;38(3):323–24		Sharif et al. J Pediatr Surg. 2002;37(9):1287–92	
Grade	CT description	Grade (No of CT slices)	CT description
I	Sub-capsular haematoma		Sub-capsular haematoma
II	Contusion or laceration 1–3 cm deep	Minor (1–2)	Mild parenchymal laceration
III	Laceration >3 cm, intra-parenchymal haematoma	Mild (3–5)	Parenchymal laceration without vascular injury/ intra-hepatic vascular injury
IV	Hepatic Transection, extensive lacerations, stellate dome Posterior Right lobe injury	Major >5	Parenchymal laceration extending to hilum or injury to PV,HA, HV, IVC, BD

PV portal vein, *HA* hepatic artery, *HV* hepatic vein, *IVC* inferior vena cava, *BD* bile duct

Conservative management is the mainstay of therapy for haemodynamically stable children with liver trauma. The child's clinical condition is evaluated after intravenous administration of 10–20 ml/kg of saline.

(a) Non-operative management:
If the child is haemodynamically stable or stabilises after administration of 1–2 bolus of 20 ml/kg of fluid, a CT scan of the abdomen is performed.
(b) Operative management:
If after 40 ml/kg of fluid administration, child is tachycardiac, hypotensive, has altered consciousness, the child should have angiographic embolization or surgical exploration following administration of blood and blood products (Fig. 10.5).

Complications are more likely following higher grades of Liver Trauma. They include an intra-parenchymal collection, best diagnosed on surveillance US/CT scan (Fig. 10.6a, b)

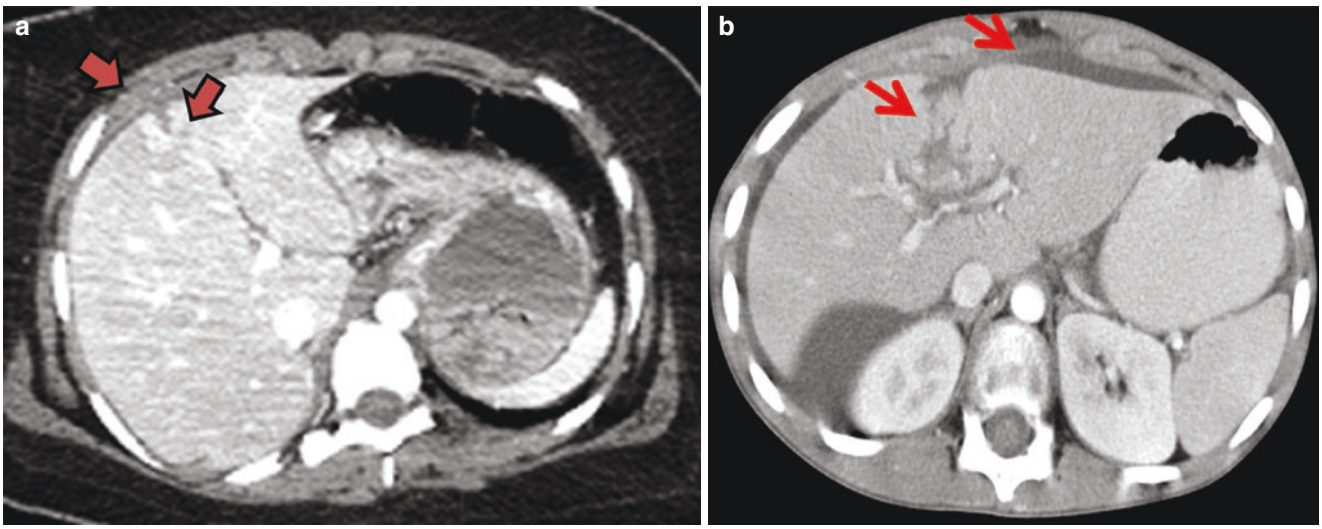

Fig. 10.2 Intravenous contrast enhanced axial scan of the liver in portal venous phase shows (**a**) laceration of the surface of liver with a small extension into the parenchyma, less than 1 cm (grade 1). (**b**) Laceration of the liver with extension to the porta and superior surface as well as a sub capsular hematoma (grade 2)

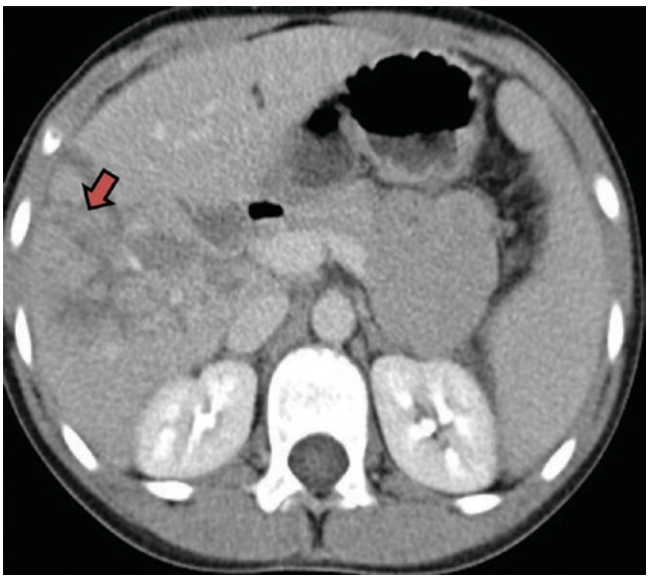

Fig. 10.3 Intravenous contrast enhanced axial scan of the liver in portal venous phase shows laceration of the liver surface extending to the IVC

which is aspirated if symptomatic; thrombosis of the portal vein (PV) or Inferior vena cava (IVC) (Fig. 10.7a–c) which do not require treatment.

Grade IV/Major Liver trauma may injure the bile duct which becomes obvious after few days. Diagnosis is by TiBIDA (radionuclide scan) on day 5–7 post trauma. Bile leaks may be localised within the liver, (intra-hepatic biloma), which may develop into a pseudo-aneurysm (Fig. 10.8) or leak into the peritoneal cavity (Fig. 10.9). Management includes percutaneous drainage, ERCP and biliary stenting or trans-cystic duct tube insertion to de-function the Ampulla of Vater (Fig. 10.10a, b). Chole-cystostomy is no longer practiced widely.

If surgery is required (Fig. 10.11), the child requires a laparotomy with haemostasis using stitches, cauterisation or insertion of trans-cystic duct drain across the ampulla and abdominal drain.

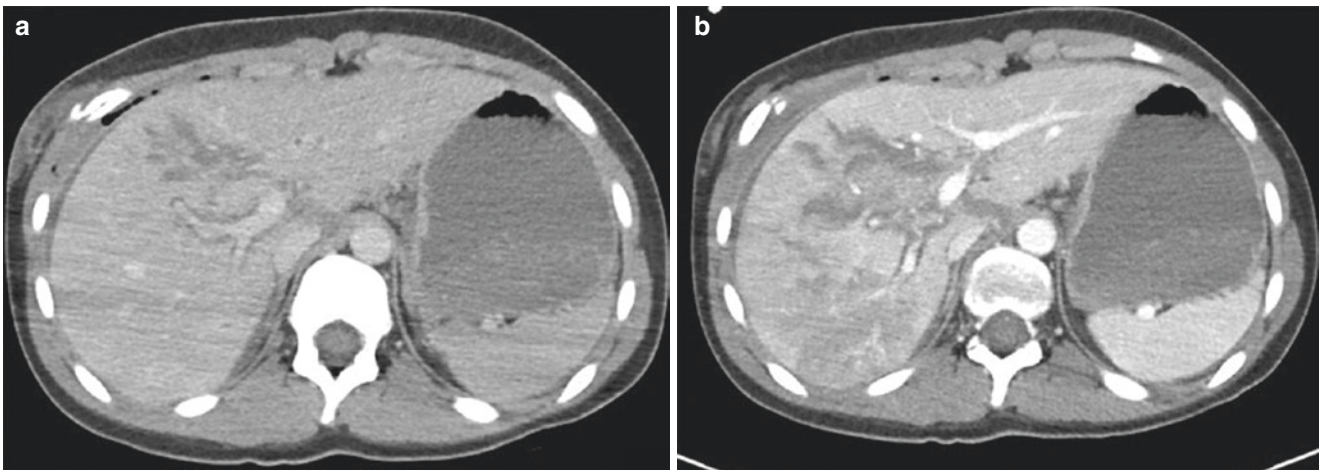

Fig. 10.4 (**a** and **b**) Intravenous contrast enhanced axial scan of the liver in portal venous phase shows laceration of the liver involving segments 5, 6, 7, 8 (**a**) and porta (**b**)

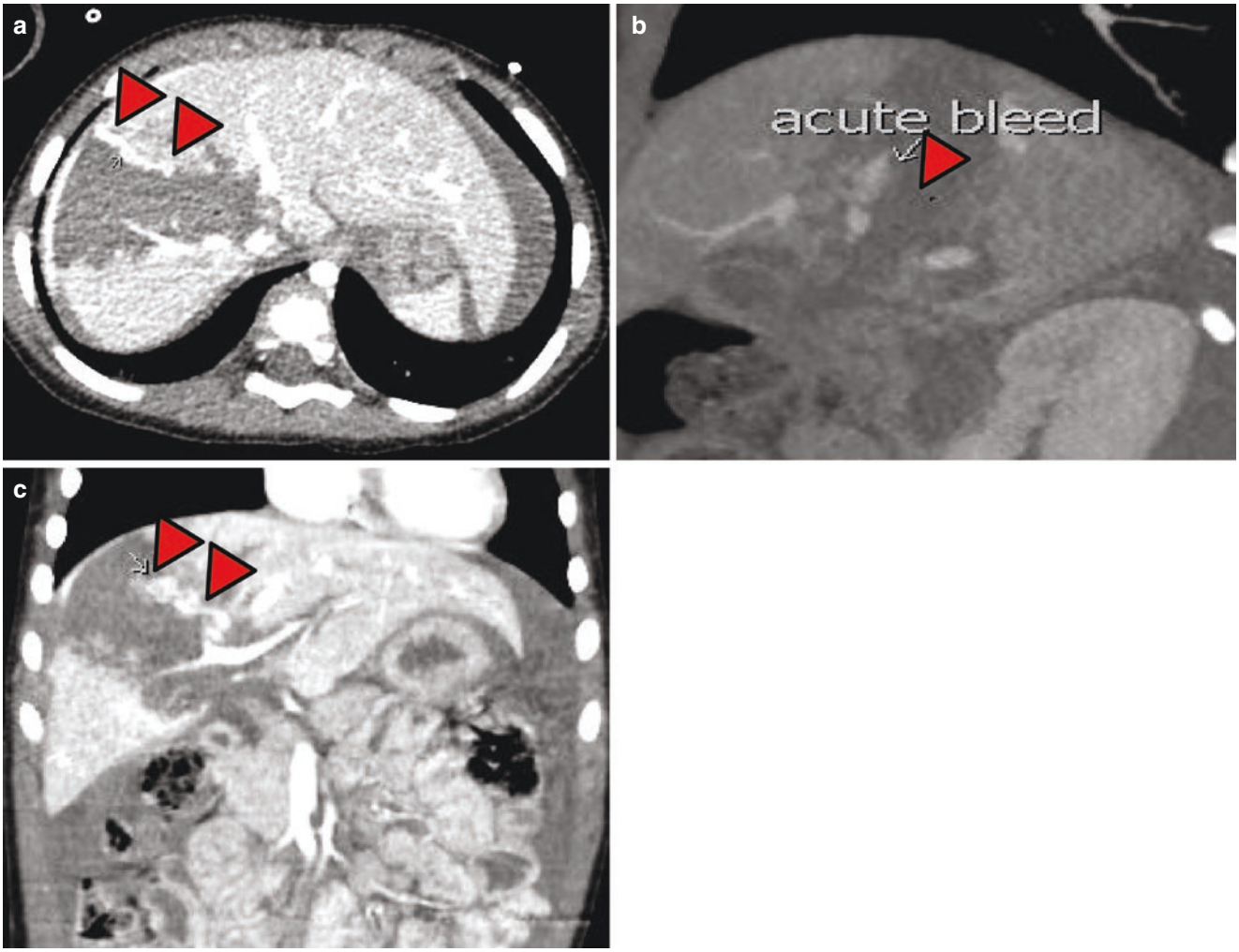

Fig. 10.5 (**a**–**c**) Intravenous contrast enhanced axial and coronal scan of the liver with Camp bastion wheel protocol reveals active contrast extravasation into the liver laceration from portal venous branches involved in the laceration

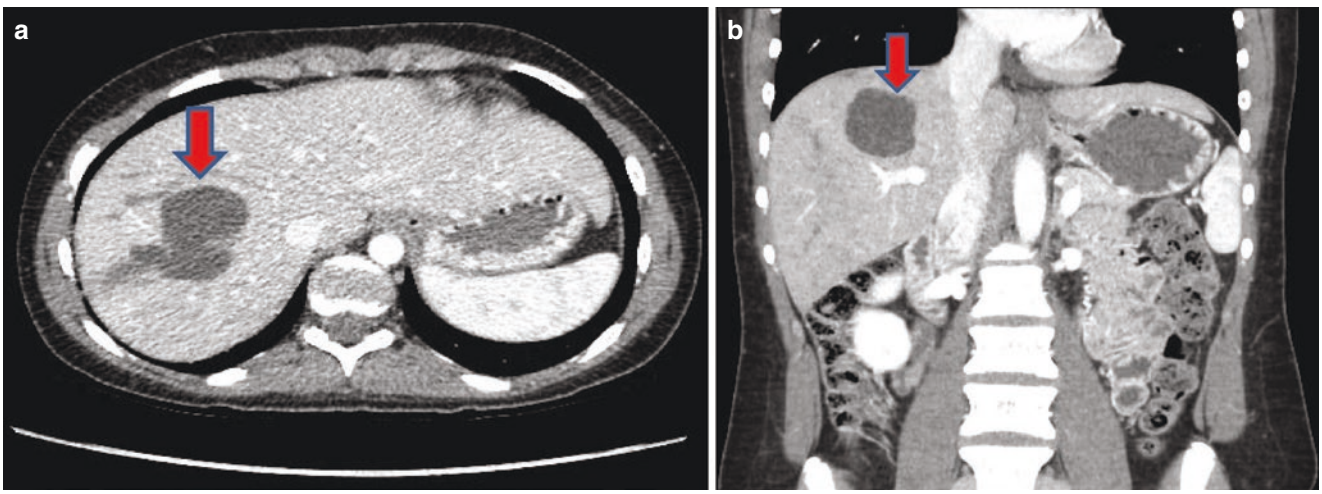

Fig. 10.6 (**a** and **b**) Intravenous contrast enhanced axial and coronal sections of the liver in portal venous phase reveals intrahepatic fluid collection in segment 7 & 8 following resolving liver laceration

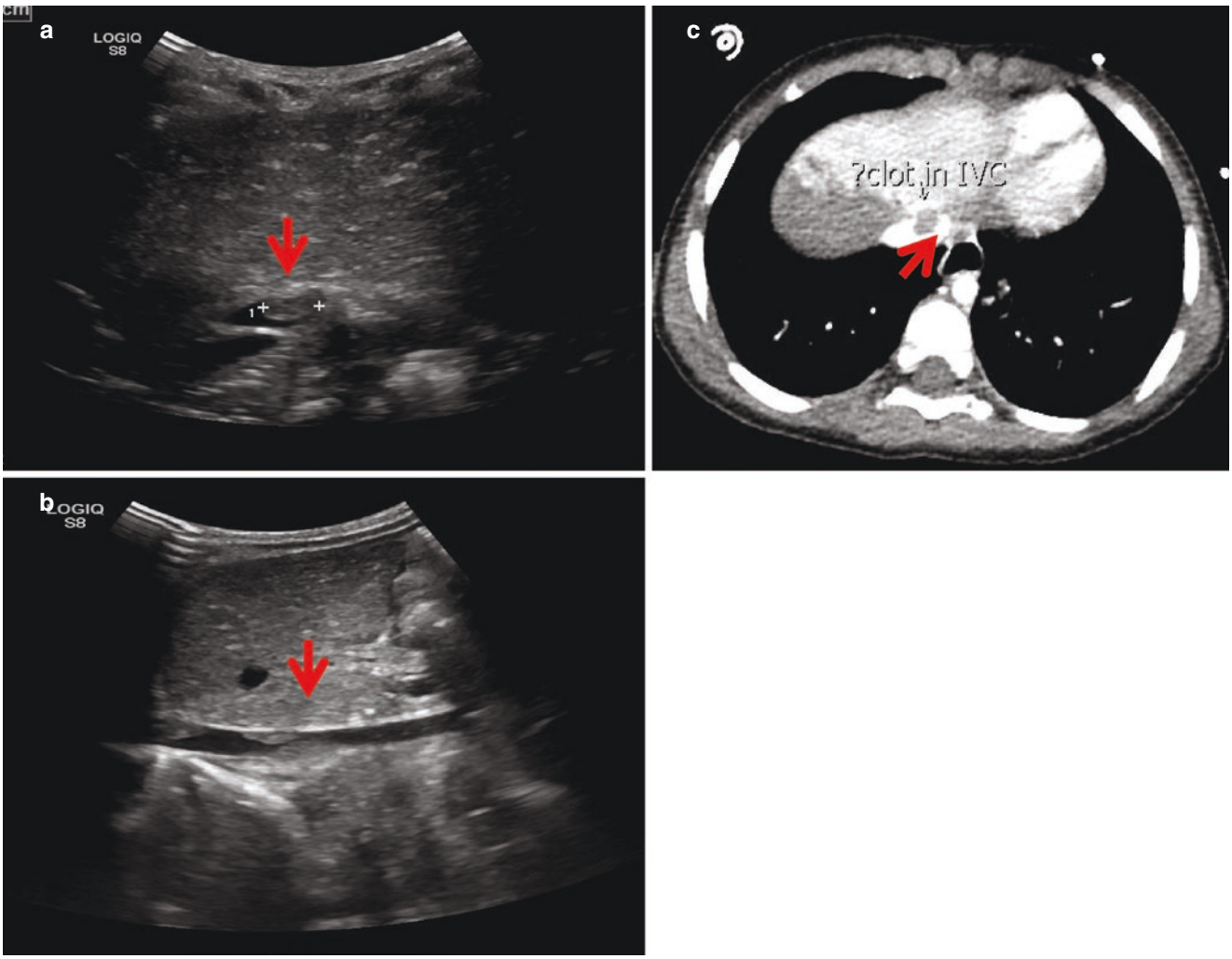

Fig. 10.7 Axial Doppler Scan (US) of the liver (**a** and **b**) and Intravenous contrast enhanced axial scan of the liver with Camp bastion wheel protocol (**c**), reveals laceration of the liver with non-occlusive thrombus within the IVC

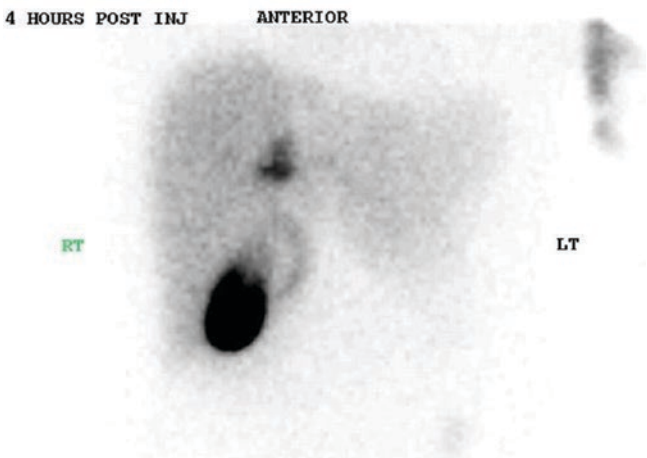

Fig. 10.8 TIBIDA scan 4 h after intravenous injection reveals intrahepatic extravasation of isotope suggestive of intrahepatic bilioma

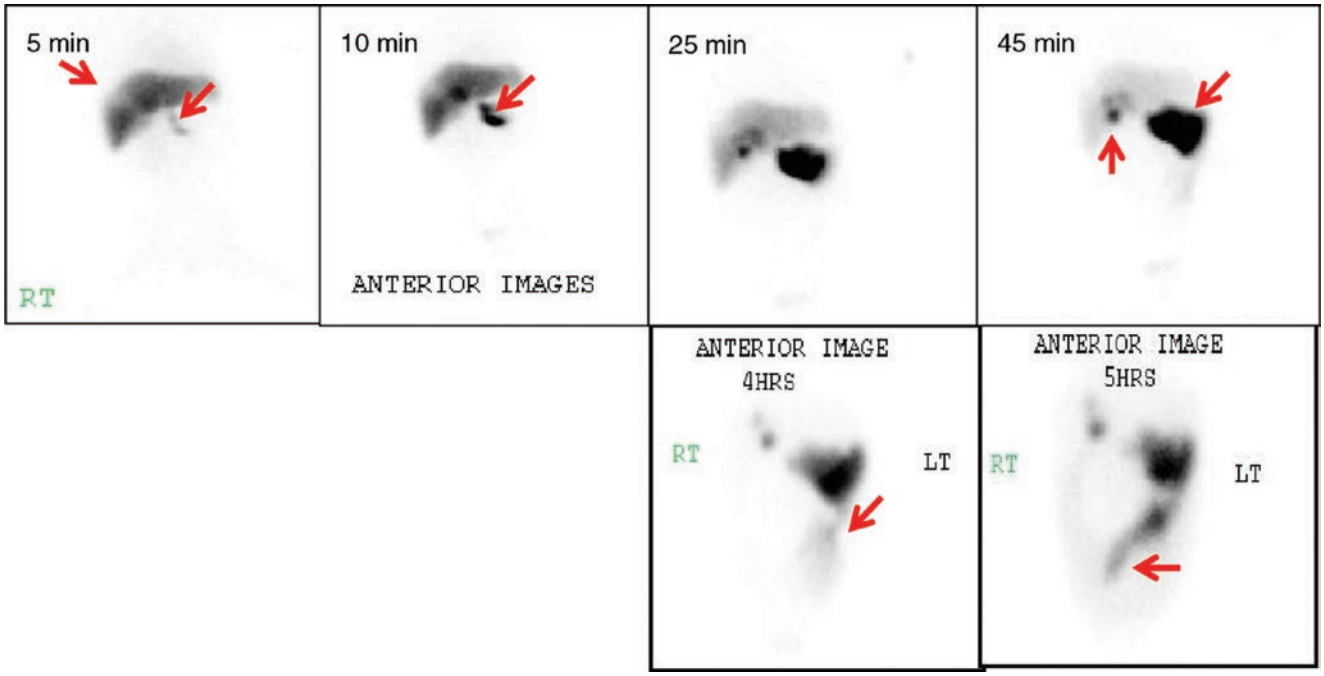

Fig. 10.9 Day 5—TIBIDA post Grade IV liver trauma. **First 5** min: good uptake with triangular, relatively photo-penic area, in the right lobe, activity can be seen near the porta, to the left of the midline, inferior to the liver consistent with a bile leak. This increases throughout the study and by 45 min large accumulation in the left side of the abdomen and gallbladder in normal position. Delayed images at 4 h and 5 h, show further activity in the left iliac fossa and extending down into the pelvis

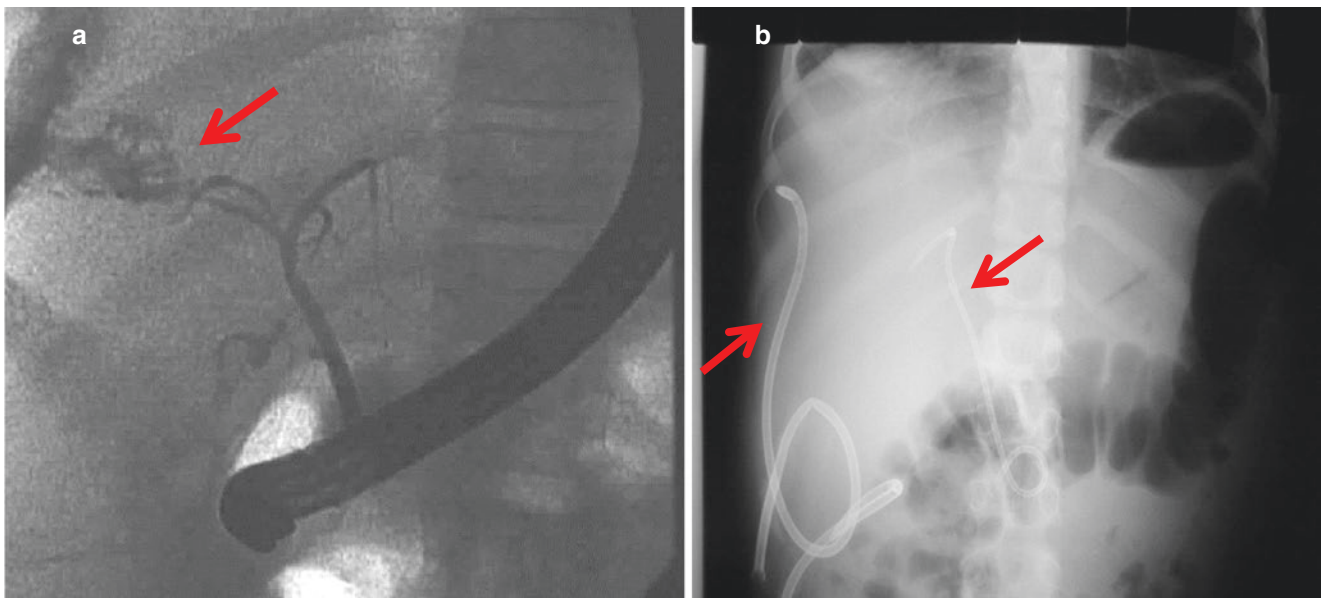

Fig. 10.10 (**a**) ERCP contrast injection of the biliary tree reveals leakage of contrast form the laceration site in keeping with biliary leak. (**b**) Abdominal X-ray shows biliary drain in situ to decompress the biliary tree and intra-abdominal drain to drain intraperitoneal bile leak

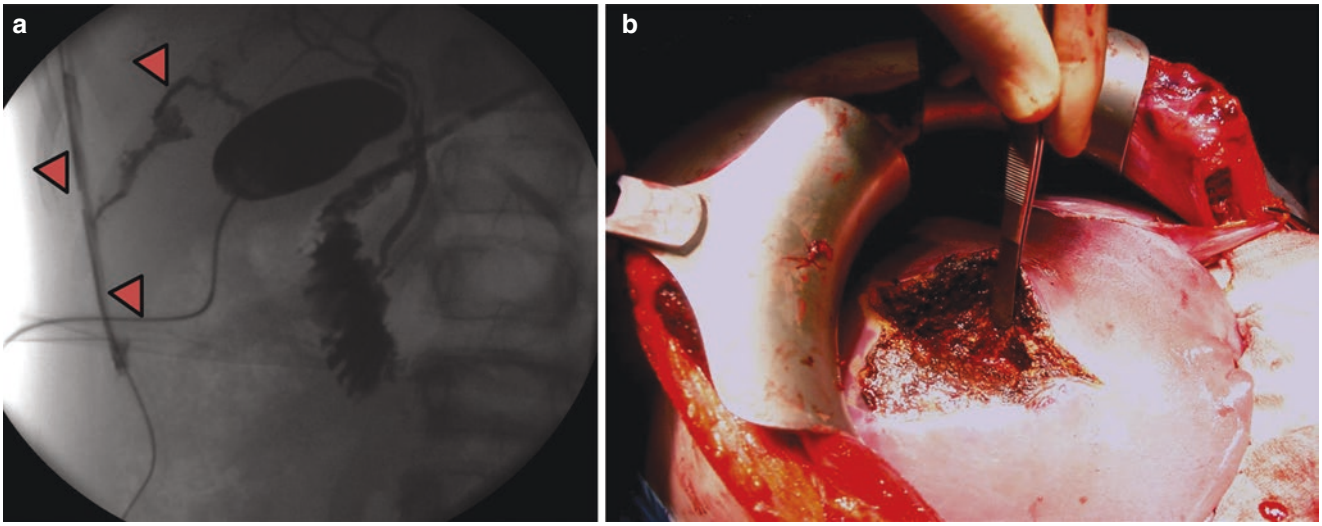

Fig. 10.11 (**a**) X-ray of the abdomen following a direct cholecystogram showing bile leak 2 weeks post injury, with intra-abdominal drain still draining bile. (**b**) Laparotomy photograph demonstrating surgical haemostasis

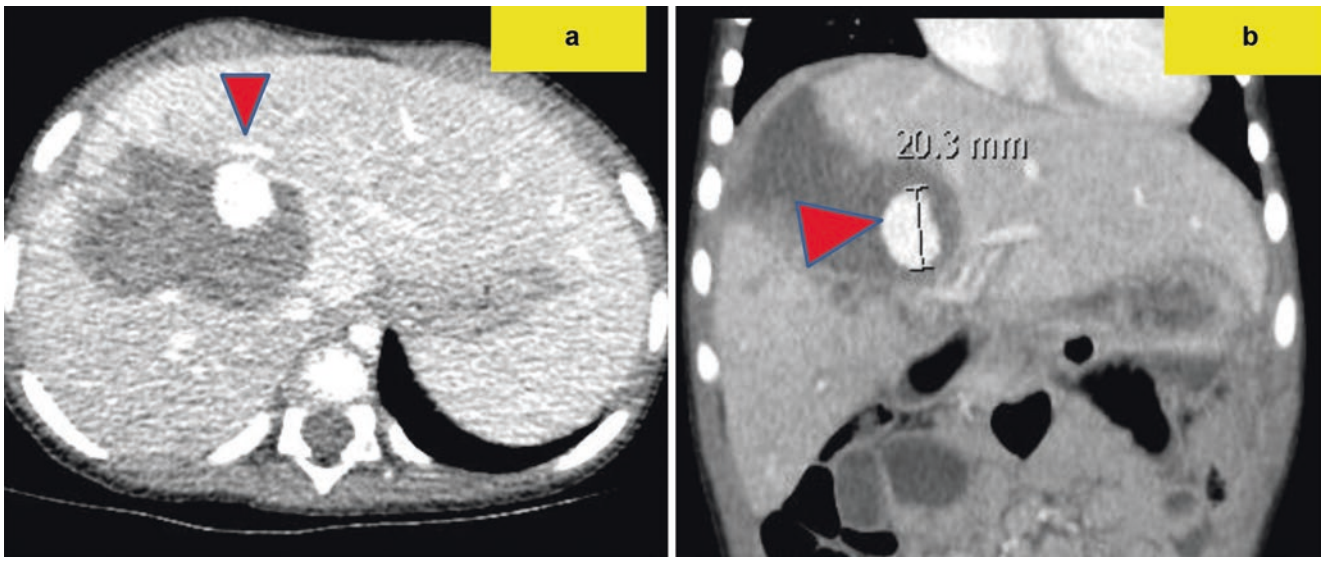

Fig. 10.12 (**a** and **b**) Intravenous contrast enhanced axial and coronal sections of the liver with Camp bastion wheel protocol reveals pseudo aneurysm of the hepatic artery coursing through the liver laceration

Repeat CT scans in first and third week should detect post-trauma pseudo-aneurysms (Fig. 10.12) which require embolization if larger than 1 cm (Fig. 10.13).

Children with grade I (minor) or II (Mild) liver trauma are followed up with Ultrasound scan. Morbidity and mortality rate is less than 10% whereas children with grade III–IV (major) trauma and managed conservatively require follow-up CT scan in the third week following liver trauma to rule out pseudo-aneurysms. Morbidity and mortality rates are up to 50% (Fig. 10.14).

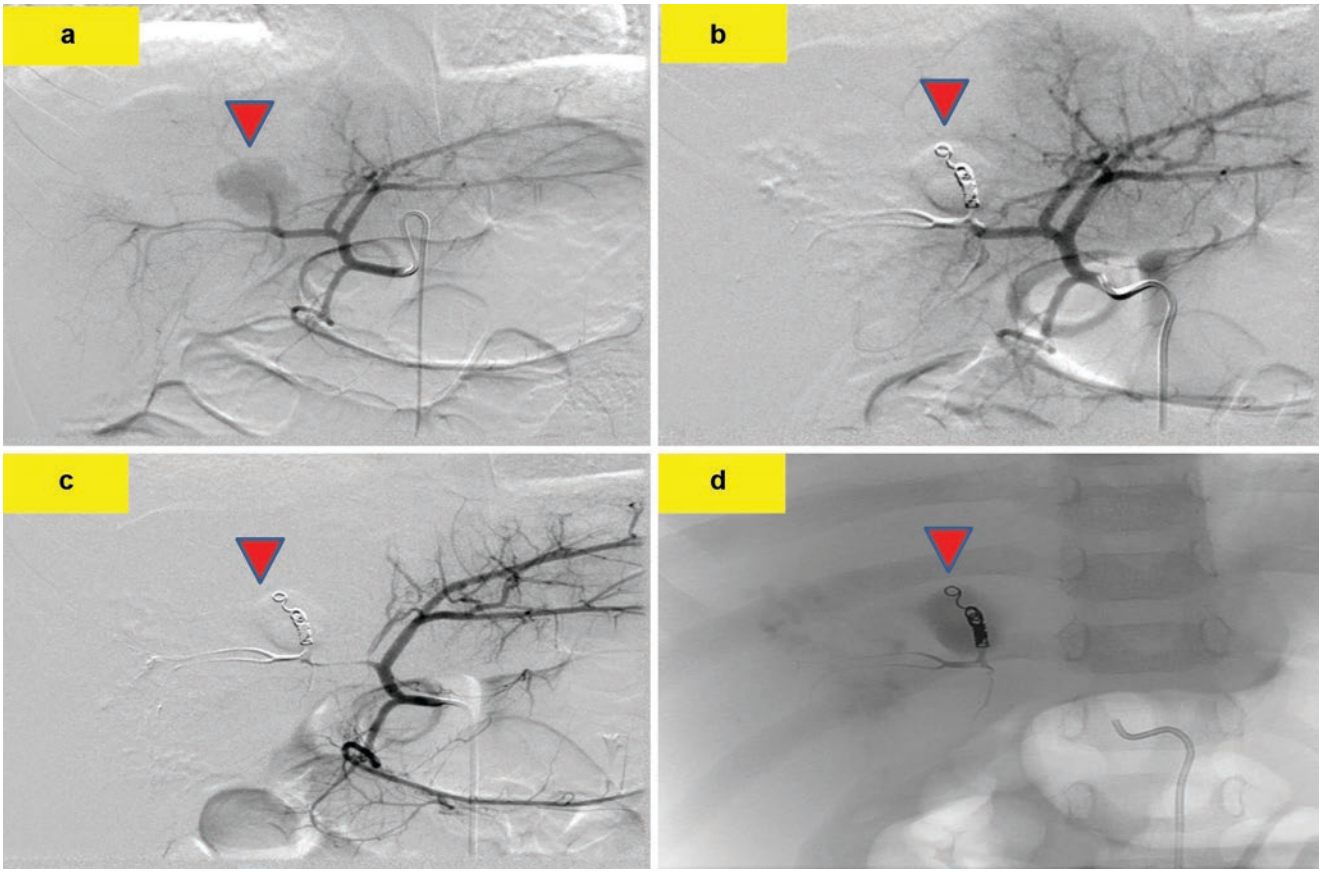

Fig. 10.13 Hepatic artery catheter angiogram reveals pseudo aneurysm of the hepatic artery within the liver laceration. (**a**) Aneurysm filled with contract, (**b**) embolization, (**c**) post-embolization no contract entering the aneurysm, (**d**) coils in place

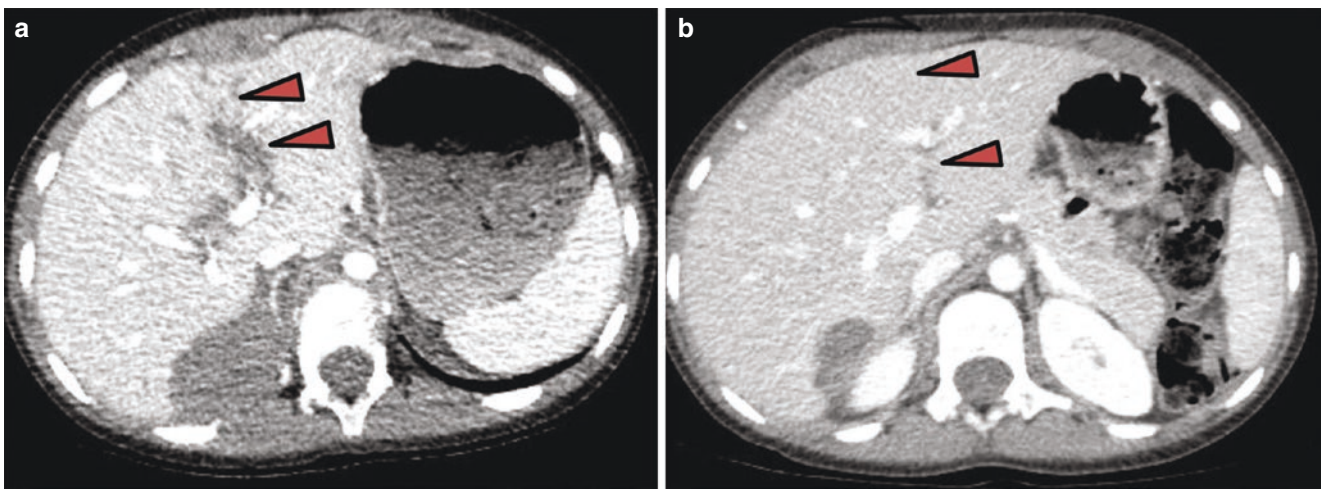

Fig. 10.14 CT scan showing healing fracture. (**a**) Intravenous contrast enhanced axial scan of the liver in portal venous phase reveals laceration of the segment 4 of liver with right supra renal haemorrhage. (**b**) Intravenous contrast enhanced axial scan of the liver in portal venous phase reveals almost complete healing of the liver laceration and right supra renal haemorrhage, 3 weeks after the initial injury

Further Reading

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The Child Who Needs a Liver Transplant

11

Khalid Sharif

Liver transplantation (LT) is standard care for children with end-stage, irreversible liver disease. Multidisciplinary medical management and improvements in surgical techniques have led to improved survival. The common indications for pediatric liver transplantation are cholestatic diseases, especially biliary atresia (43%), metabolic diseases (13%), acute liver failure (11%) and hepatic tumours (Table 11.1).

Table 11.1 Indications for liver transplantation

I. **Chronic Liver Failure**
Cholestatic liver disease
Biliary atresia
Idiopathic neonatal hepatitis
Alagille syndrome
Progressive familial intrahepatic cholestasis (PFIC 1-4)
Metabolic liver disease
Alpha-1-antitrypsin deficiency
Tyrosinaemia type I
Wilson's disease
Cystic fibrosis
Glycogen storage type IV
Chronic hepatitis
Auto-immune liver disease
Post viral (hepatitis B, C, other)
Fibropolycystic liver disease ± Caroli syndrome
Primary immunodeficiency
II. **Acute Liver Failure**
Neonatal Liver failure
Neonatal haemochromatosis (Gestational Allo-immune Liver Disease)
Tyrosinaemia type I
Infection
Fulminant hepatitis
Auto-immune hepatitis
Paracetamol poisoning
Viral hepatitis (A, B, C or sero-negative)
Metabolic liver disease
Wilson's disease
III. **Inborn Errors of Metabolism**
Crigler-Najjar type I
Familial hypercholesterolaemia
Organic acidaemias
Urea cycle defects
Primary oxalosis
IV. **Hepatic Tumours**
Unresectable malignant tumours

11.1 Children with Chronic Liver Failure

Many children with chronic liver disease develop cirrhosis and portal hypertension despite well-compensated liver function. However, gradual deterioration in hepatic function, failure of nutrition, growth and difficulty in maintaining normal life are acceptable parameters to consider liver transplantation. Clinical features include malnutrition, jaundice, ascites and hepatosplenomegaly (Fig. 11.1) (see also Chapters 1 and 7). The timing of transplantation may be difficult, but is based on: a persistent rise in total bilirubin >150 mmol/l, prolongation of prothrombin ratio (INR >1.4) and a fall in serum albumin <35 g/l. These parameters are included in the international Pediatric End-Stage Liver Disease Score (PELD) used to prioritise the waiting list.

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D. Kelly et al. (eds.), *Atlas of Pediatric Hepatology*, https://doi.org/10.1007/978-3-319-69529-7_11

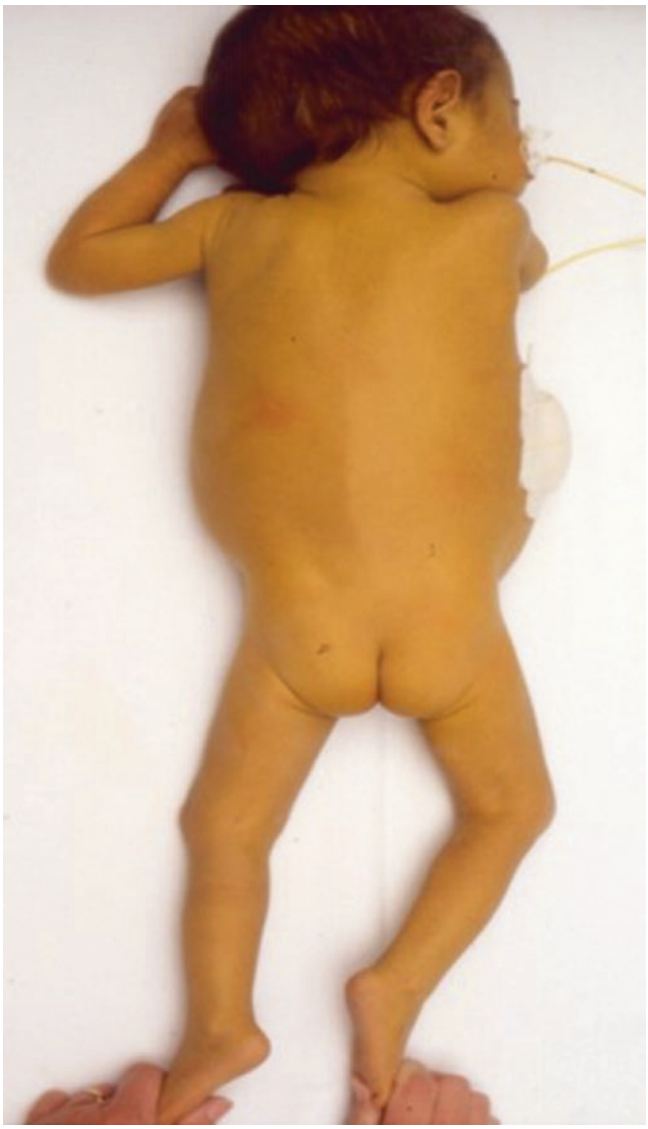


Fig. 11.1 This child with biliary atresia shows deep jaundice and malnutrition as evidenced by the muscle wasting and lack of fat stores. She received a successful transplant

11.2 Children with Acute Liver Failure

The most common causes of acute liver failure in neonates are; Herpes Simplex, HHV6; and inborn errors of metabolism or neonatal hemochromatosis (GALD) (see Chapter 2), (Fig. 11.2). In older children: Auto-immune hepatitis, drug induced liver disease, Paracetamol overdose or metabolic diseases such as Wilson's disease (see Chapters 6 and 7). The indications for transplantation in acute liver failure are agreed internationally. The UK Liver Advisory Group recommends that children who have a persistent coagulopathy (prothrombin time > 40; INR >4), encephalopathy without evidence of irreversible brain damage are candidates for transplantation, provided there is no irreversible multi system involvement.

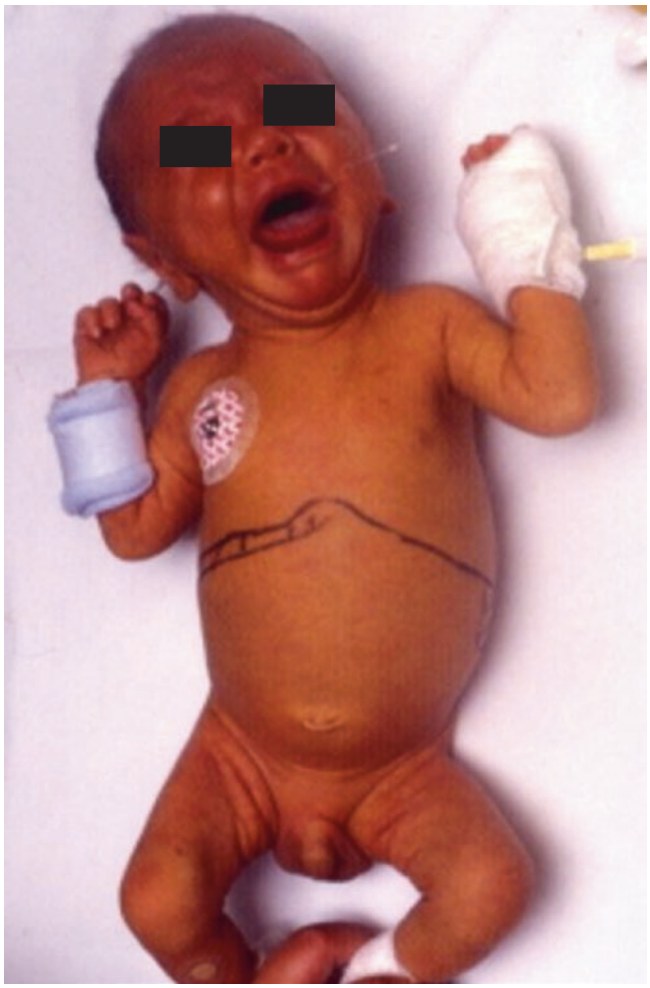


Fig. 11.2 This infant had acute liver failure from an echo virus infection. Note the small liver and his obvious distress

11.2.1 Un-resectable Liver Tumours

Liver tumours which cannot be completely resected are considered for transplantation, (see Chapter 4) as long as there are no extra-hepatic metastases (Fig. 11.3).

Transplantation Process

The operative procedure of liver transplantation is well standardised. The essential components include a thorough evaluation of the child and family to identify severity of disease, absence of contraindications, provide education and counselling prior to listing for transplant, surgical procedure and post procedure complications. The paucity of size matched donors mean that most children receive cut-down or split liver grafts from adult livers or relatives (Fig. 11.4a–c).

Post-transplant Management

The first 24–48 h following transplant are focused on establishing good respiratory and hemodynamic support, main-

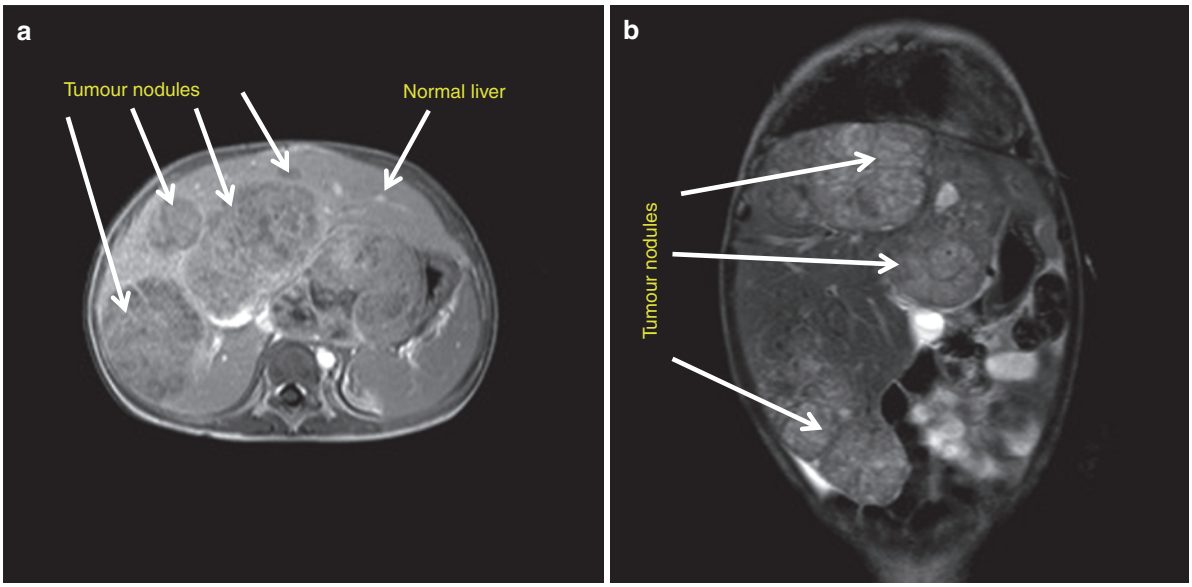


Fig. 11.3 Axial intravenous contrast enhanced fat suppressed T1 weighted image of the liver and coronal STIR sequence of the liver reveal multifocal lesions of tumour involving more than 3 sectors of liver. This mean the tumour is unresectable and therefore an indication for transplantation

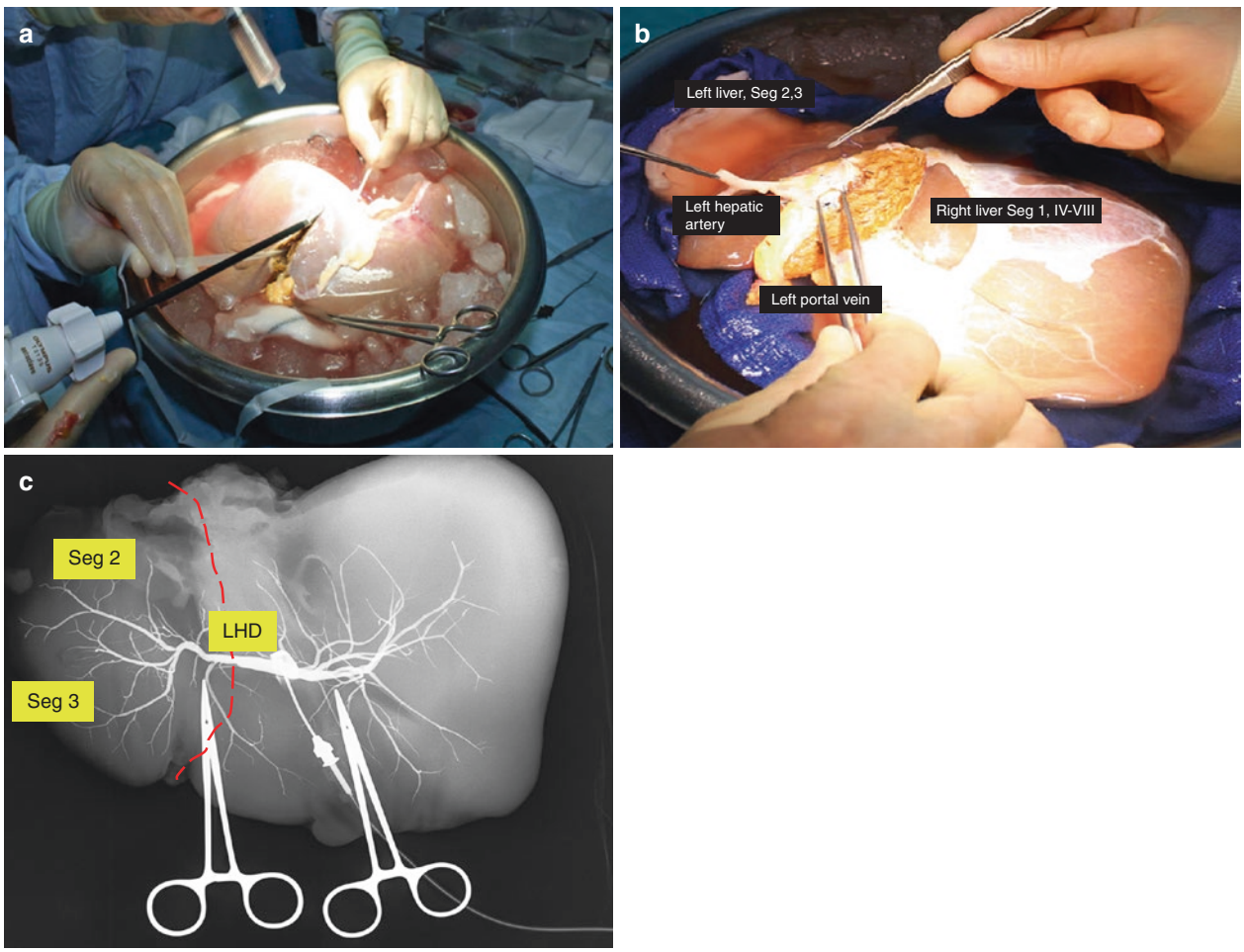


Fig. 11.4 In preparing a liver for splitting, the liver parenchymal is divided by harmonic device after carefully dividing the hepatic artery, portal vein, bile duct and hepatic vein (**a**). (**b**) At completion two liver grafts are produced with full set of hepatic vein, hepatic artery, portal vein and bile duct. (**c**) A back table cholangiogram is useful for guidance when dividing the parenchyma, segment 2 and 3 duct joining to form a single left hepatic duct (LHD), Red dotted line indicates the liver parenchymal dividing plane

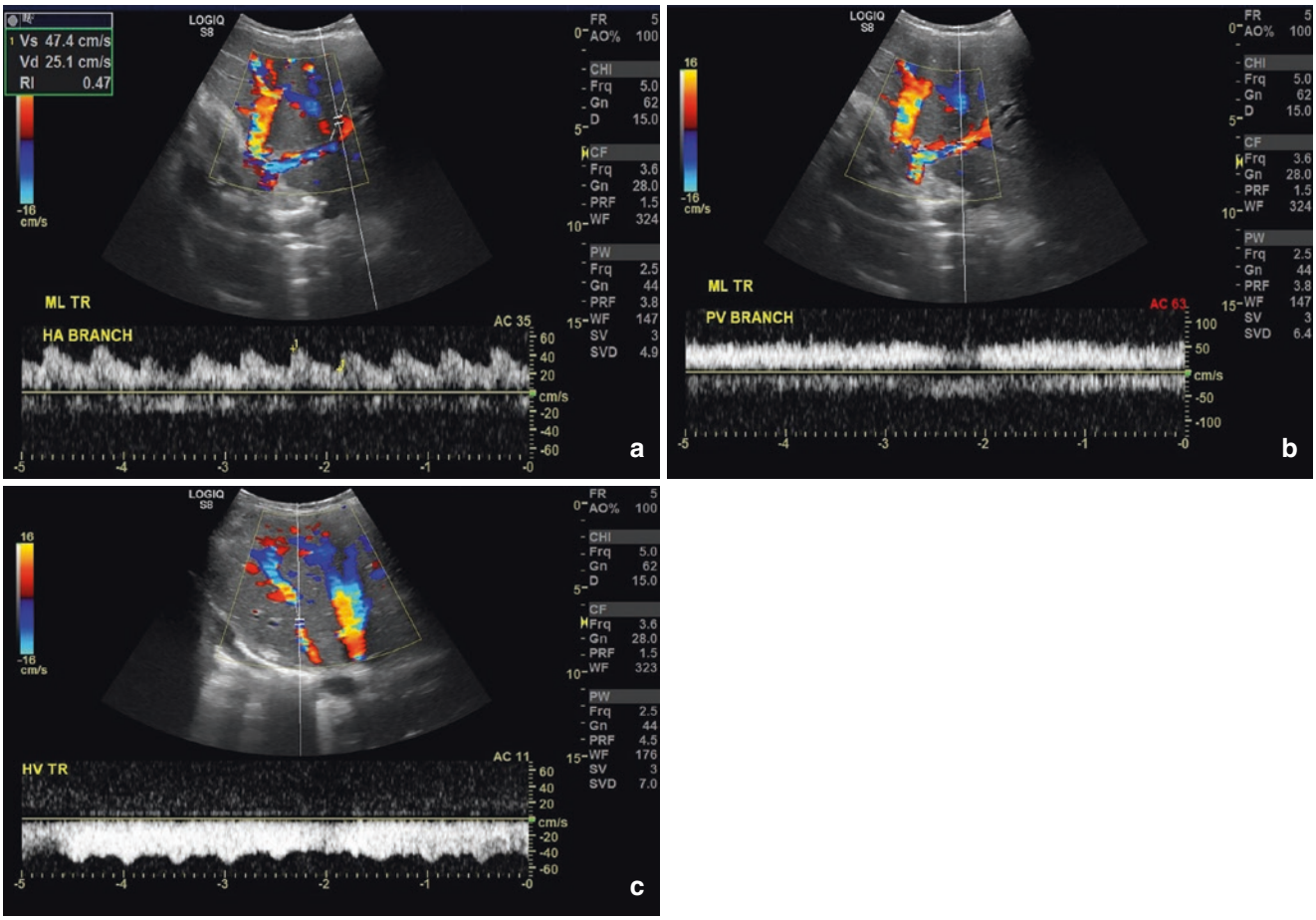


Fig. 11.5 Ultrasound Doppler of the transplant liver reveals normal Doppler traces of (**a**) hepatic artery, (**b**) portal vein and (**c**) hepatic vein with normal liver echogenicity

taining fluid balance, renal output and ensuring good pain relief. Graft function is assessed with regular liver function and coagulation tests. Liver ultrasound with colour flow Doppler is performed for the first 5–7 days and later as clinically indicated to confirm vascular patency and the absence of biliary dilatation (Fig. 11.5).

Most complications in the early post-transplant period (first 2 weeks) are related to technical factors such as hepatic artery thrombosis (HAT). (Fig. 11.6) or portal vein thrombosis or stenosis (PVT) Portal vein stenosis is managed by angiography and balloon dilatation (Fig. 11.7d–f). Hepatic outflow obstruction (HVO) is managed with angiography and balloon dilatation (Fig. 11.8a–c). Inferior vena cava thrombosis/stenosis may require venography and dilation (Fig. 11.9).

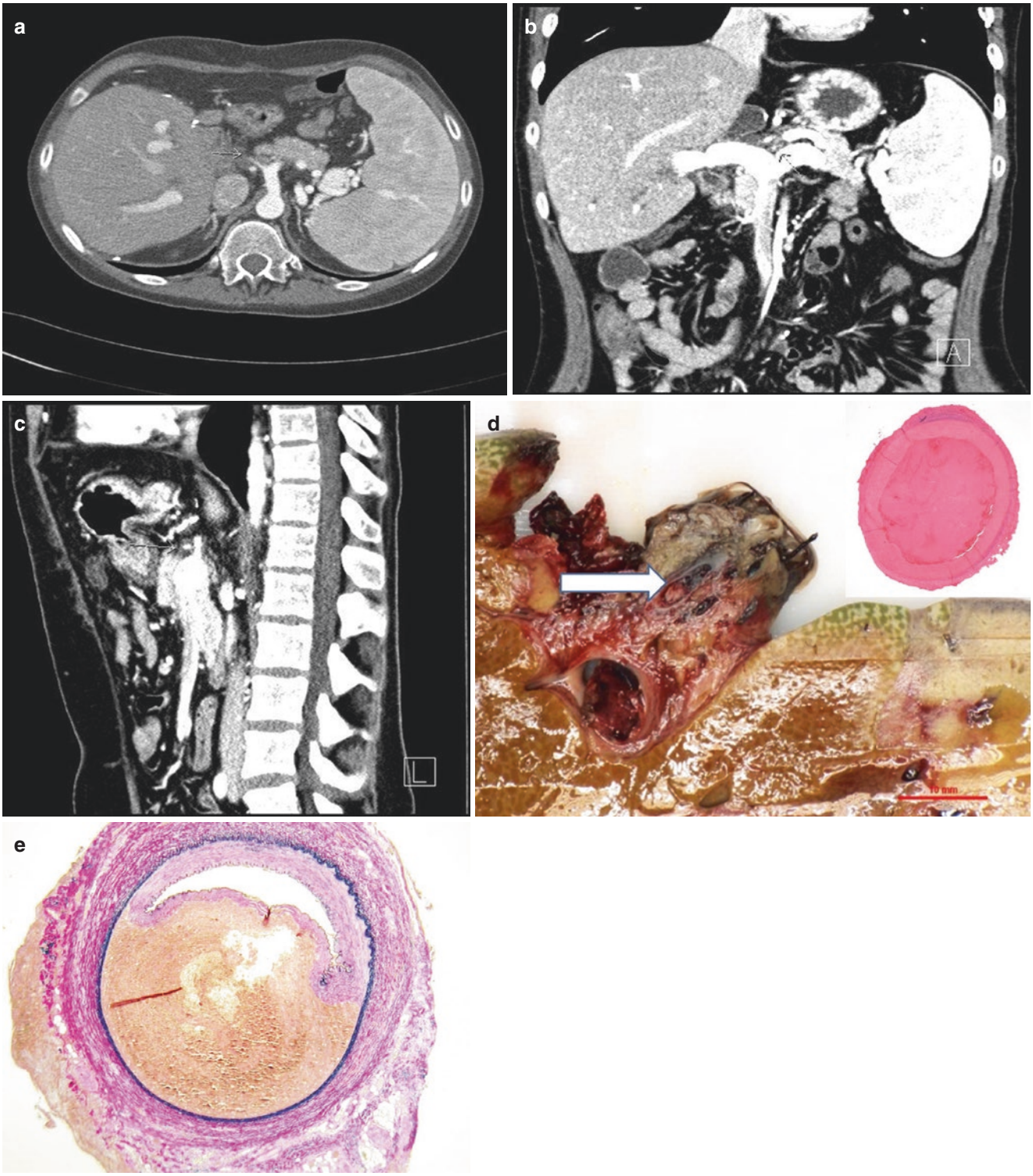


Fig. 11.6 (**a**–**c**) Intravenous contrast enhanced CT scan of the abdomen reveals narrowing of the hepatic artery at its origin from coeliac axis with complete occlusion distally. (**d**)This gross image from an allograft liver removed at the time of retransplantation shows hepatic artery thrombosis marked with an arrow. (**e**) transverse section through the hepatic artery showing occlusion of the lumen by thrombus

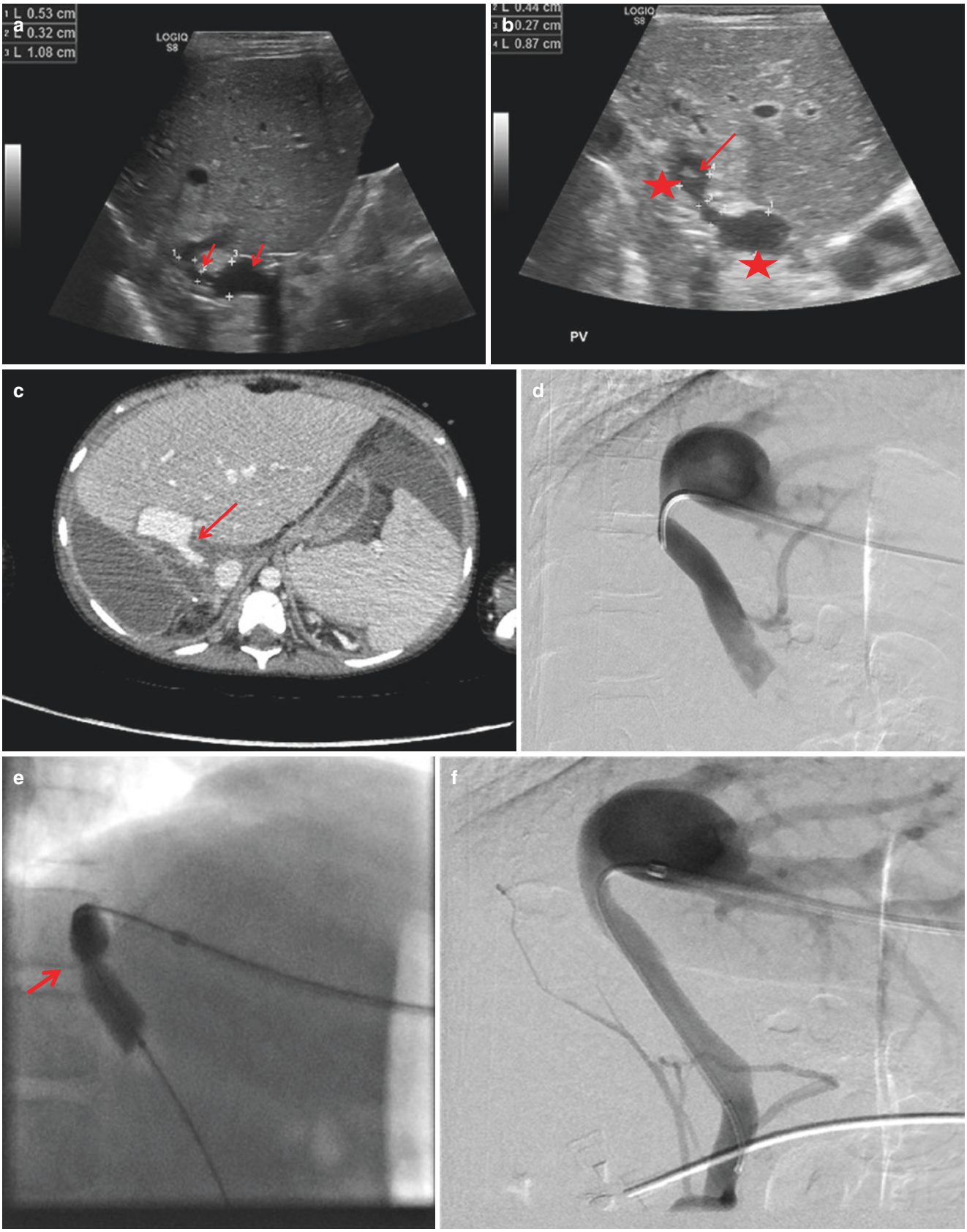


Fig. 11.7 (**a**) Ultrasound scan showing narrowing with pre-stenotic dilatation (**b**) Ultrasound scan with pre and post stenotic dilatation (marked with star) amd echogenic material in the post-stenotic dilatation (? Thrombus) marked with arrow. (**c**) Intravenous contrast axial CT scan of the abdomen reveals caliber change at the site of anastomosis (arrow) of the portal vein in keeping with portal vein stenosis. (**d**) Angiography showing narrowing at the anastomosis (**e**) dilatation balloon waist confirming narrowing (**f**) post dilatation, no narrowing, post stenotic dilatation still present

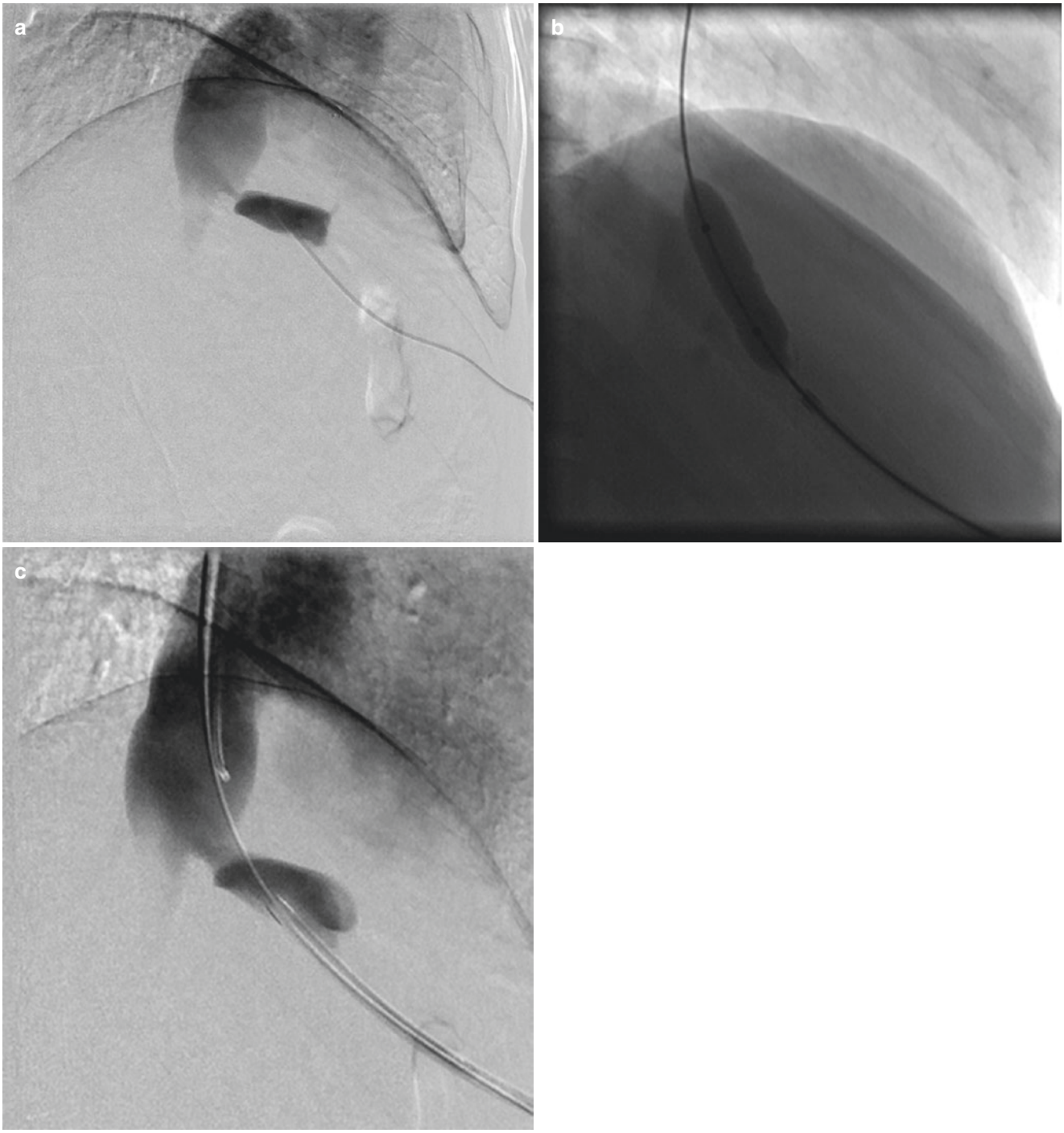


Fig. 11.8 (**a**) Venogram of hepatic vein reveals stenosis of the hepatic venous junction with IVC (**b**) balloon dilatation (**c**) post dilatation

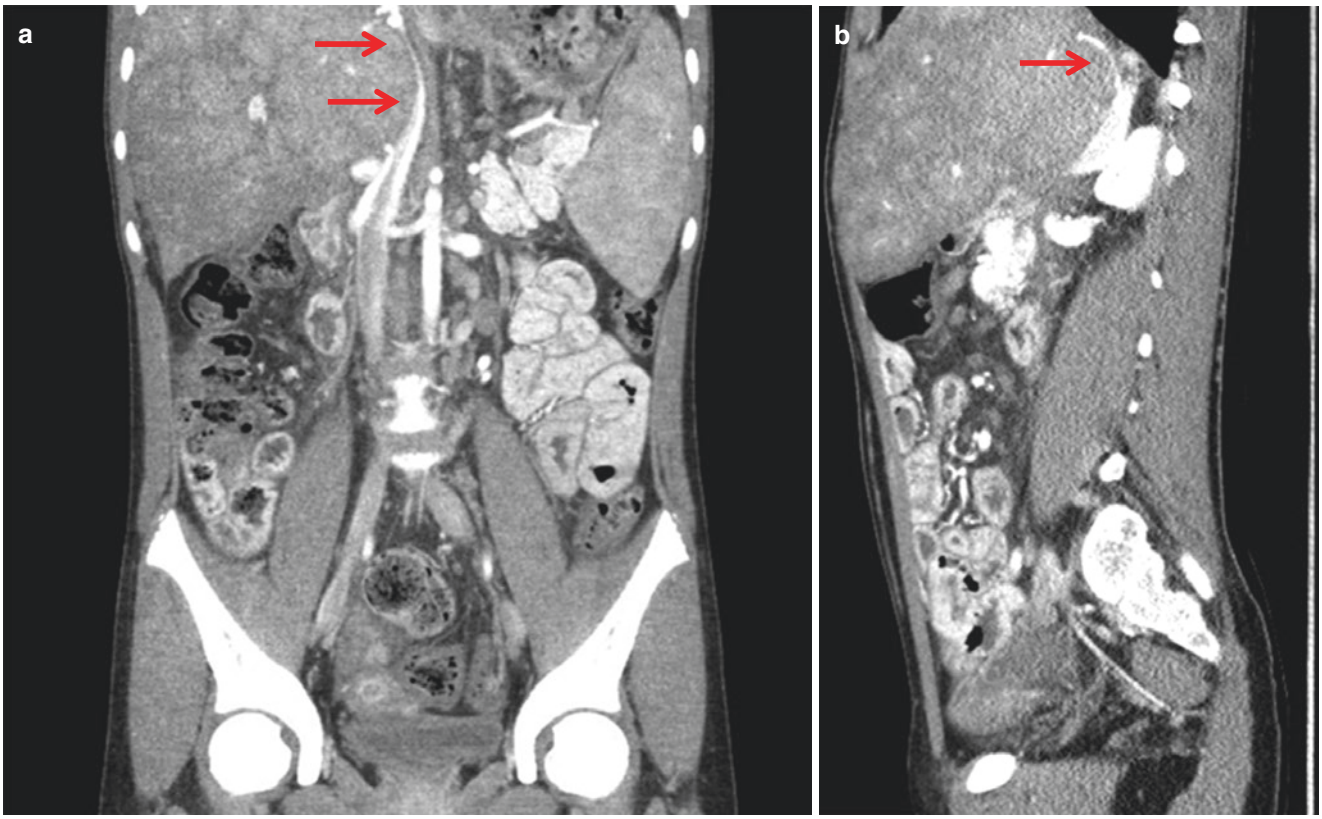


Fig. 11.9 IVC narrowing. CT scan abdomen showing compression of IVC (arrows) coronal and lateral view

11.2.2 Biliary Complications

Bile leak, anastomotic strictures, and non-anastomostic strictures of the donor bile duct have a reported incidence of 10–20% depending on the graft type. Ultrasound and MRI are the principal imaging modalities used for detection of these complications (Fig. 11.10).

Early biliary complications are best treated by immediate surgery and re-anastomosis if required. Late stricture formation may be satisfactorily dealt with by endoscopic or percutaneous balloon dilatation or stenting. Histology will demonstrate large bile duct obstruction (Fig. 11.11).

Diaphragmatic paresis and herniae: are rare complications of liver transplantation. Cross clamping of the IVC at the level of the diaphragmatic hiatus, trauma at operation (dissection and diathermy) are some of the contributory factors (Fig. 11.12).

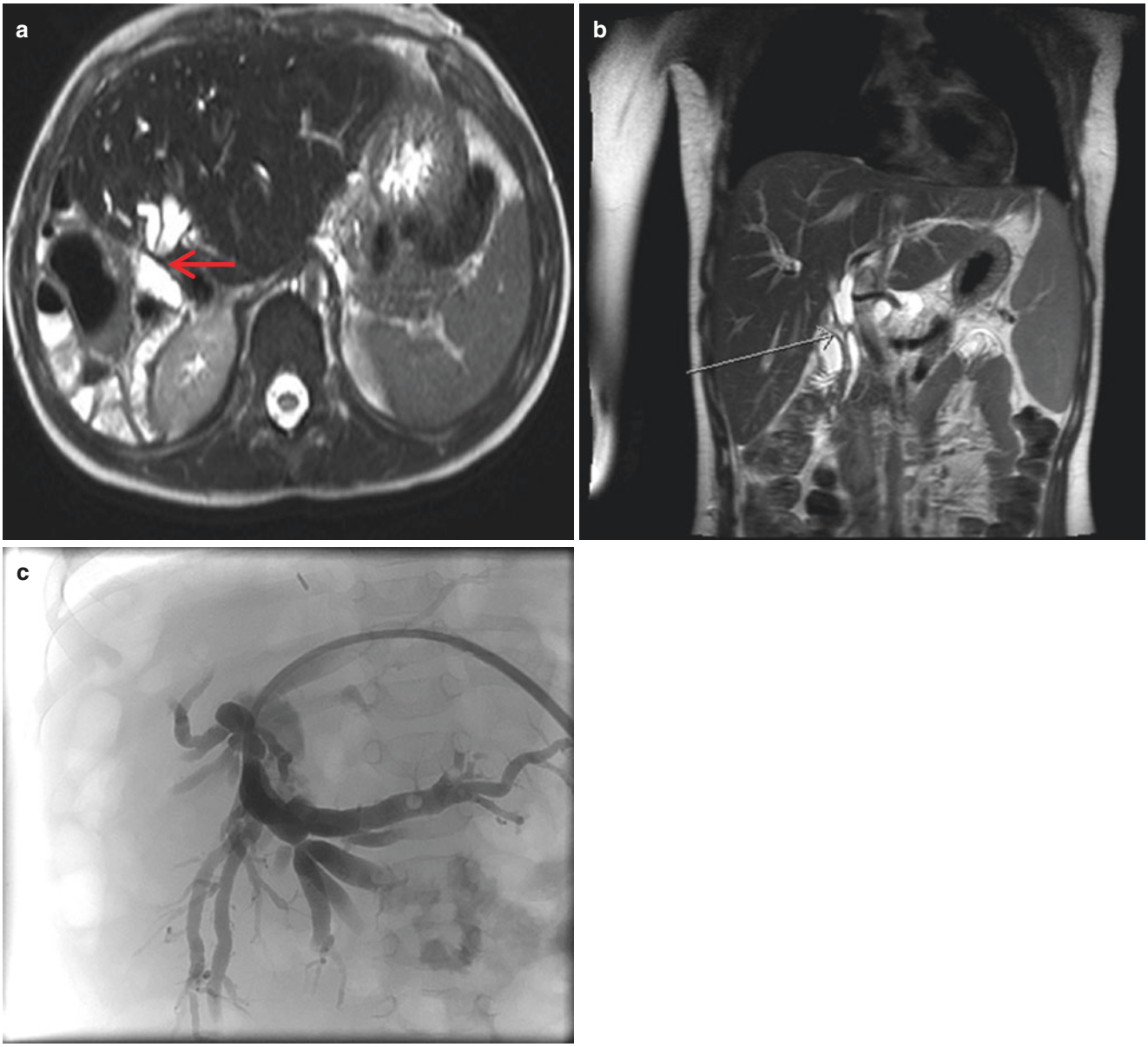


Fig. 11.10 (**a**) Axial T2 sequence of liver reveals severe narrowing of all the biliary ducts of the transplant liver at their junction with the Roux-en-y in keeping with multiple biliary strictures (**b**) Coronal T2 sequence showing stricture at duct to duct anastomosis in a full size graft (**c**) Percutaneous Transhepatic Cholangiogram of biliary system reveals severe narrowing at the junction of hepatic bile ducts with the roux-en-y with proximal dilatation in keeping with multiple biliary strictures

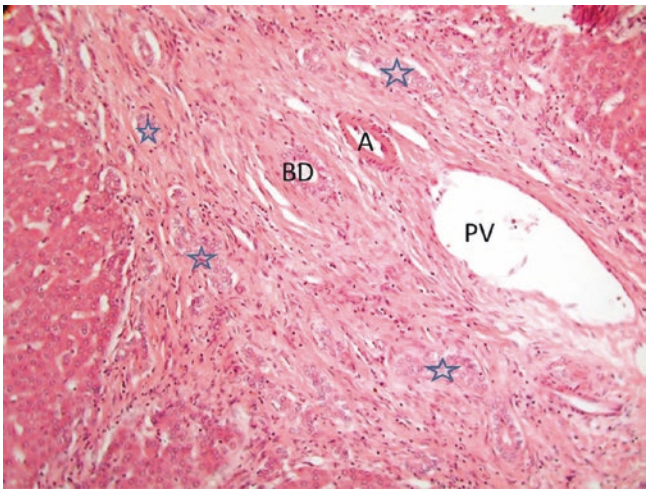


Fig. 11.11 This portal tract demonstrates biliary features (H&E ×100). The bile duct itself 'BD' is normal, it is close to, and a similar size to, the hepatic artery 'A'. There is a normal portal vein 'PV'. The stars mark biliary ductules at the margins of the portal tract, copper associated protein is often visible on an orcein stain corroborating biliary changes. In the allograft this should prompt consideration of large bile duct obstruction, hepatic artery thrombosis can also cause this picture referred to as ischaemic cholangiopathy

11.3 Medical Complications

Common medical complications post-transplant include acute or chronic rejection, bacterial, viral, fungal and opportunistic infections, renal dysfunction, hypertension. Of particular concern is post-transplant lympho-proliferative syndrome (PTLD) associated with a primary Epstein Barr Virus (EBV).

Rejection: *Acute rejection* is suspected if a child presents with fever, malaise, a tender graft and loose stools. Biocmical liver function tests demonstrate abnormal hepatic transaminases, gamma glutamyl transpedtidase and raised alkaline phosphatase. Diagnosis is confirmed by histology. The grade of rejection is assessed according to established histological criteria on a scale of 0–4 (Fig. 11.13).

Acute rejection is treated with three doses of intravenous methyl prednisolone (10 mg/kg) on 3 successive days with adjusted baseline immunosuppression. If corticosteroid resistant acute rejection develops, other therapies include addition of mycophenolate mofetil, sirolimus, antithymocyte globulins (ATG) or monoclonal anti-CD3 antibodies.

Chronic rejection: occurs at any time. It may respond to immunosuppression, but is usually irreversible which is

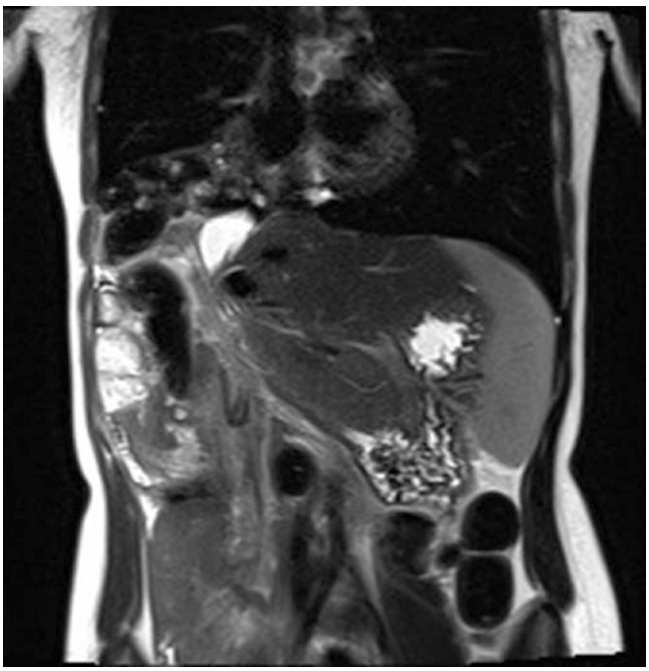


Fig. 11.12 T2 coronal sequence of the abdomen reveals abnormally raised right dome of diaphragm and transplant liver in keeping with right diaphragmatic paralysis

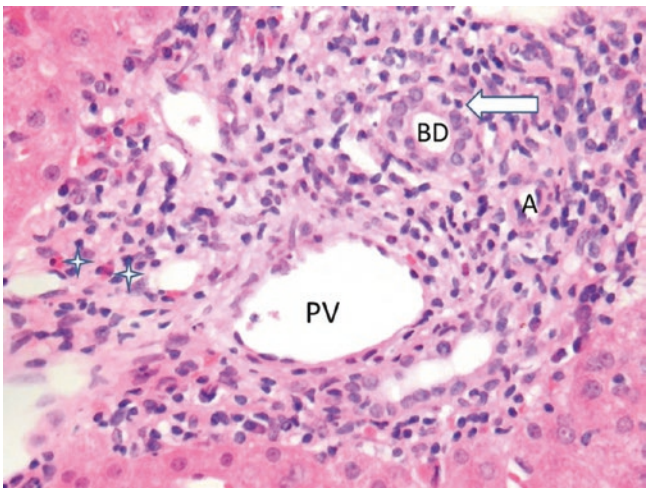


Fig. 11.13 Acute cellular rejection H&E ×400. The triad of features indicating acute, T cell mediated, rejection are; a portal inflammatory infiltrate often including eosinophils (marked by stars) damage to the bile duct 'BD' the arrow is pointing to infiltration of biliary epithelium by inflammatory cells and endothelitis. This latter lesion is seen in the portal vein 'PV' note that instead of a smooth endothelial lining inflammatory cells infiltrate beneath the endothelium and cells appear to 'drop-off' into the lumen. 'A' denotes the hepatic artery

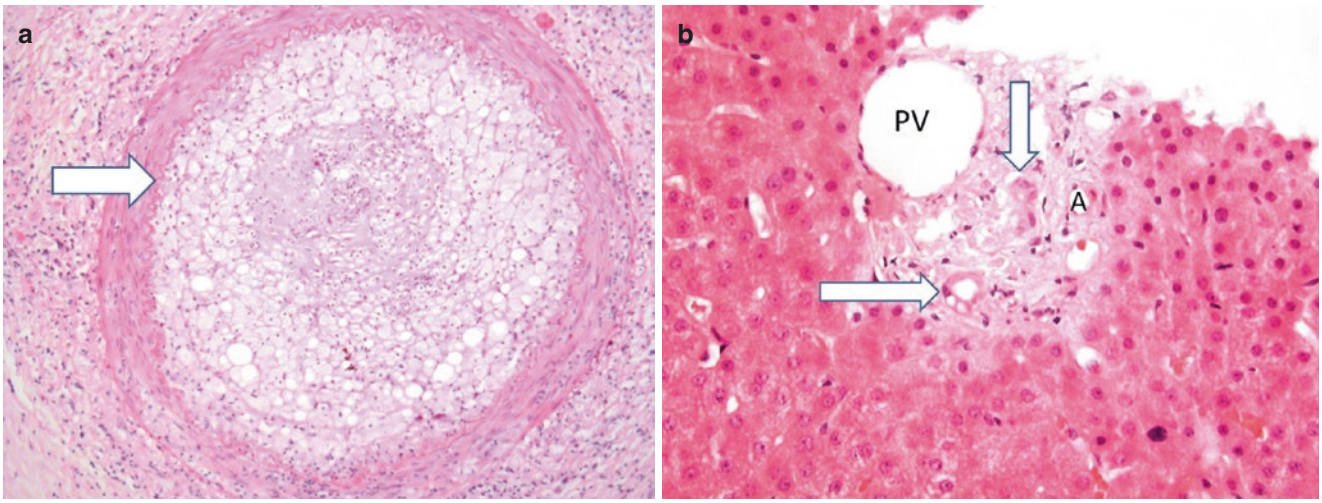


Fig. 11.14 (**a**) Foam cell arteriopathy in chronic rejection. This is an image (H&E ×200) of a large hepatic artery branch at the hilum of an allograft liver removed at the time of retransplantation. The arrow is pointing to the internal elastic lamina. The lumen of the vessel is entirely replaced by foamy macrophages. (**b**). Chronic rejection, H&E ×400. In contrast to the acute situation, illustrated in Fig. 11.13, there are barely any inflammatory cells here. Two profiles of a bile duct are present in this portal tract, marked by arrows, the accompanying artery is labelled 'A'. These ducts have a 'dysplastic' appearance, many nuclei have been lost and with progression the duct disappears entirely. The portal vein 'PV' has a normal appearance

manifested by disruption of bile duct radicals with development of the vanishing bile duct syndrome (Fig. 11.14). Re-transplantation may be required.

Patients in the post-transplant period have reduced immunity and are prone to bacterial, viral, fungal and parasitic infections. Gram-positive bacteria predominate over gram-negative bacteria. The commonest viral infections are Cytomegalovirus (CMV) and Epstein Barr virus (EBV). Epstein-Barr virus (EBV) is the main cause of post-transplant lympho-proliferative disorder (PTLD) which usually occurs in EBV negative recipients who receive an EBV positive donor. Patients may present with non-specific symptoms, anaemia, diarhoea and/or lymphadenopathy. The diagnosis is made on detecting an elevated plasma EBV PCR, compatible radiology (Fig. 11.15) and confirmed by histology (Fig. 11.16).

Management strategies include reduction of immunosuppression, which may require complete withdrawal, Rituximab, an anti-CD 20 monoclonal antibody which reduces B cells and should be used with replacement immunoglobulin therapy. If no response, then standard anti-lymphoma chemotherapy is required. Mortality varies from 20 to 70%.

Occasionally, the graft develops nodular regenerative hyperplasia related to altered blood flow through the liver (Fig. 11.17).

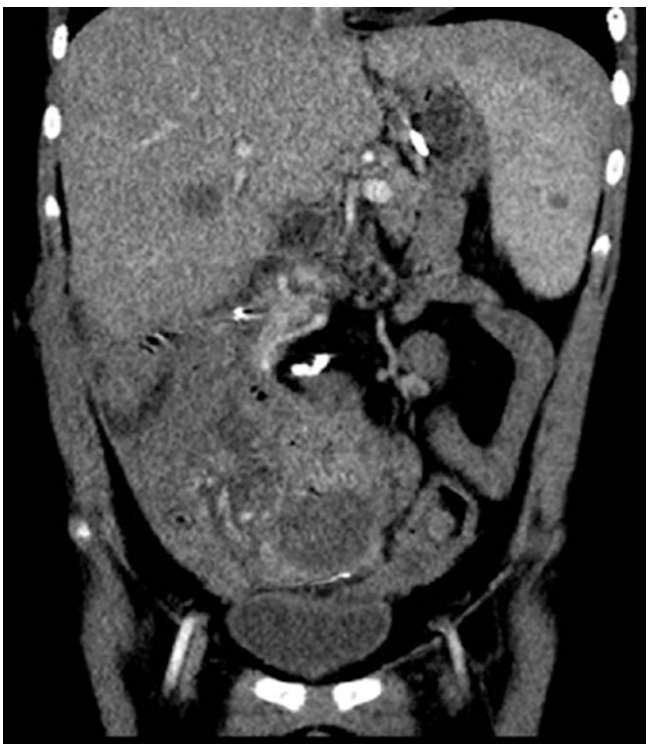


Fig. 11.15 Intravenous contrast enhanced coronal CT scan of the abdomen reveals hypo dense lesions within the liver, spleen and mesentery in keeping with PTLD

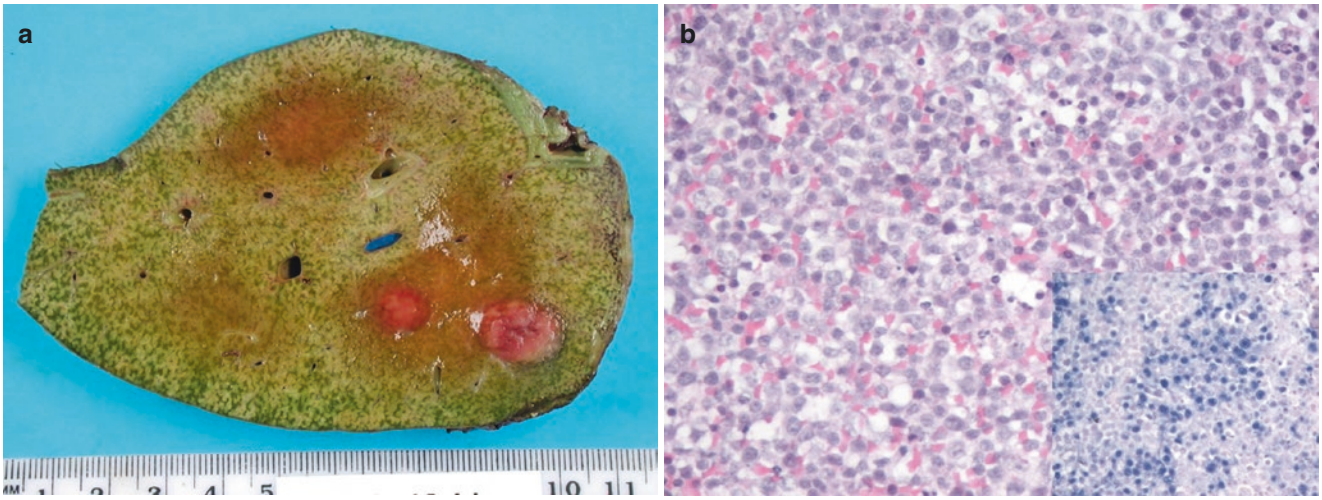


Fig. 11.16 (**a**) These grossly identifiable nodules of PTLD were seen in an allograft liver removed at the time of retransplantation. (**b**) Post transplant lymphoproliferative disorder (PTLD) encompasses a spectrum. This lesion indicates the malignant end of the spectrum. The image shows a monotonous population of blast-like lymphoid cells (H&E ×400) as seen in lymphomas. The inset shows nuclear positivity for Epstein-Barr virus encoded early RNAs (EBERs). The patient had suffered from rejection and had therefore received augmented immunosuppression

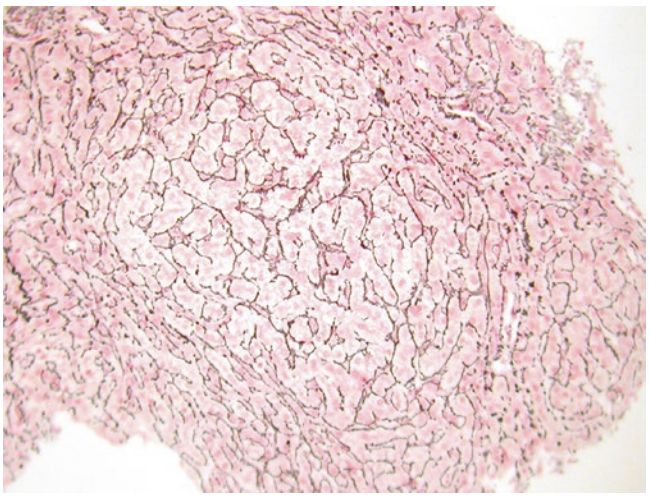
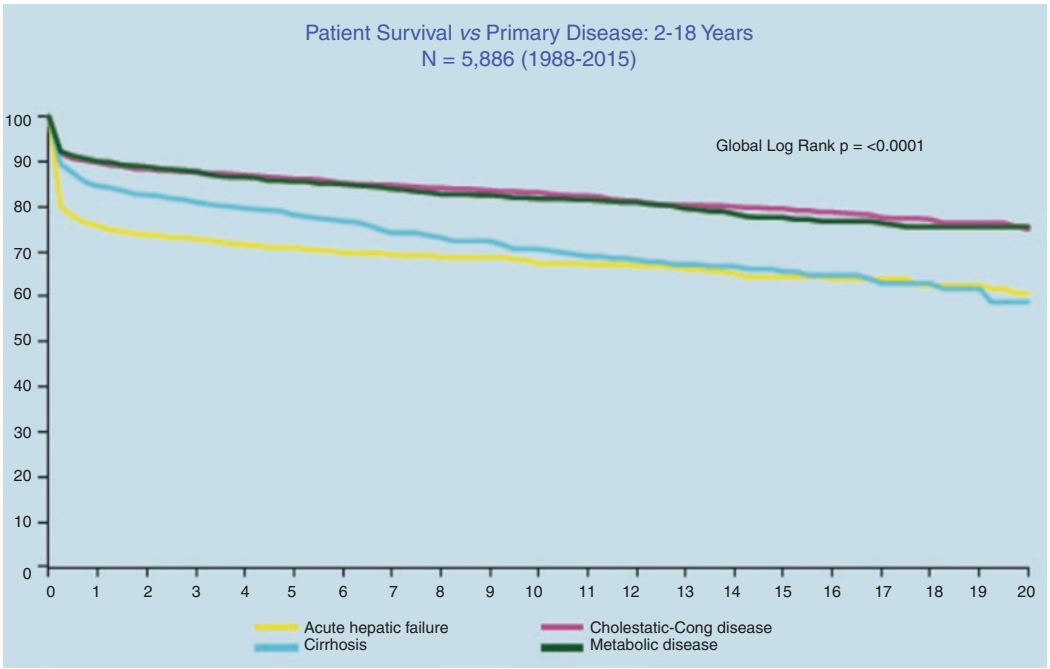


Fig. 11.17 Nodular regenerative hyperplasia (reticulin stain ×200). Long-term allografts can develop lesions related to altered blood flow through the liver. In this image the reticulin is outlining a nodule, this nodule is not surrounded by fibrous tissue, as seen in cirrhosis, but rather by atrophic liver cell plates. This is one of the lesions in the spectrum of non-cirrhotic portal hypertension. Its natural history in the allograft is at present unclear

11.3.1 Survival

The advances in immunosuppression, organ preservation, refinements of the operative technique and effective antimicrobial prophylaxis have resulted in, pediatric LT being a routine operation with excellent patient outcomes. Survival is 70–90% at 1 year and >80% at 20 years (European Liver transplant registry) (Fig. 11.18). Children regain normal growth and development, enter puberty, complete secondary education, become parents and contribute to society (Fig. 11.19).



Details : Logrank P

		prob3
Acute	Chol_	<0.0001
Acute	Cirrh	0.004
Acute	Metab	<0.0001
Chol_	Cirrh	<0.0001
Chol_	Metab	0.75
Cirrh	Metab	<0.0001

Survival%

Main_disease	1 yr	3 yrs	5 yrs	8 yrs	10 yrs	12 yrs	14 yrs	16 yrs	18 yrs	20 yrs
Acute hepatic failure	76%	73%	71%	69%	67%	67%	65%	64%	63%	61%
Cholestatio- Cong disease	90%	88%	86%	84%	83%	81%	80%	79%	77%	75%
Cirrhosis	85%	81%	78%	73%	71%	68%	67%	65%	63%	59%
Metabolic disease	90%	88%	86%	83%	82%	81%	78%	77%	76%	76%

Number of exposed patients

	Total	1 yr	3 yrs	5 yrs	8 yrs	10 yrs	12 yrs	14 yrs	16 yrs	18 yrs	20 yrs
Acute hepatic failure	1091	695	549	464	345	274	235	179	130	93	61
Cholestatio- Cong disease	2329	1803	1473	1224	929	778	623	484	364	242	149
Cirrhosis	863	598	451	355	241	192	152	116	86	53	34
Metabolic disease	1603	1234	969	800	558	464	377	276	210	162	111

Fig. 11.18 Long term survival from the European Liver transplant registry demonstrating more than 90% survival 1 year and 20 years 70–80%

Fig. 11.19 Long term survivors post liver transplant competing in the Transplant Games

Further Reading

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Intestinal Transplantation

12

Khalid Sharif

The incidence of Intestinal Failure (IF) in children is estimated to be 1–2 per million population. In children, the causes of IF are: short bowel syndrome, disorders of bowel motility and primary mucosal disease (Table 12.1). The indications for Intestinal transplantation (ITX) in children are irreversible intestinal failure (IF) associated with complications such as: loss of central venous access or life threatening line sepsis. A combined liver/intestine transplant is indicated if the child has developed intestinal failure associated liver disease (IFALD). Children should be considered for intestinal transplant assessment before they develop irreversible multi-organ failure.

Most children considered for intestinal transplantation have a combination of aetiological factors, e.g. children with Gastroschisis and intestinal atresia have both short gut and dysmotility. Children with symptoms and signs of intestinal obstruction, but without an identifiable mechanical cause are considered to have chronic intestinal pseudo-obstruction (CIP) and may have involvement of other hollow viscera such as the bladder. Megacystis Microcolon Intestinal Hypoperistalsis Syndrome (MMIHS) is a rare autosomal recessive disorder characterized by hypoperistalsis of the entire gastrointestinal tract, non-obstructive urinary bladder distension and intestinal malrotation which requires intestinal transplantation.

Currently, children with severe neurologic disabilities or irreversible or life threatening systemic diseases are not considered as candidates.

Table 12.1 Aetiology of Intestinal failure in children

Short bowel syndrome	1. Gastroschisis 2. Malrotation with volvulus 3. Bowel atresia 4. Necrotizing enterocolitis 5. Crohn's disease 6. Tumors 7. Trauma
Motility disorders	1. Hirschprung's disease 2. Hollow visceral myopathy 3. Megacystis-Microcolon-Hypoperistalsis syndrome 4. Neuronal intestinal dysplasia
Mucosal disorders	1. Microvillous inclusion disease 2. Tufting enteropathy (primary epithelial dysplasia) 3. Autoimmune enteropathy (primary &secondary)

12.1 Technical Aspects

A. *Types of intestinal graft*

The choice of intestinal grafts depends on:

1. Severity of the liver disease. e.g. Isolated intestinal grafts (Fig. 12.1) are indicated for children with mild liver disease and no evidence of portal hypertension. In those with advanced irreversible IFALD (Figs. 12.2 and 12.3) or portal hypertension, a combined liver/intestine transplant is required (Fig. 12.4).
2. Effective stomach emptying. Children with motility disorders have delayed/ineffective stomach emptying (Fig. 12.5a–c) and so require a multi-visceral or modified multi-visceral graft including the stomach (Fig. 12.5d) Inclusion of the right colon in the intestinal graft is variable.

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D. Kelly et al. (eds.), *Atlas of Pediatric Hepatology*, https://doi.org/10.1007/978-3-319-69529-7_12

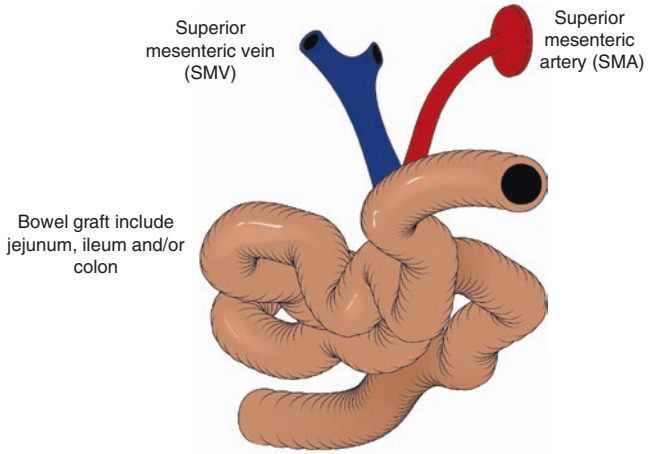

Fig. 12.1 An isolated bowel graft is indicated for those without liver disease

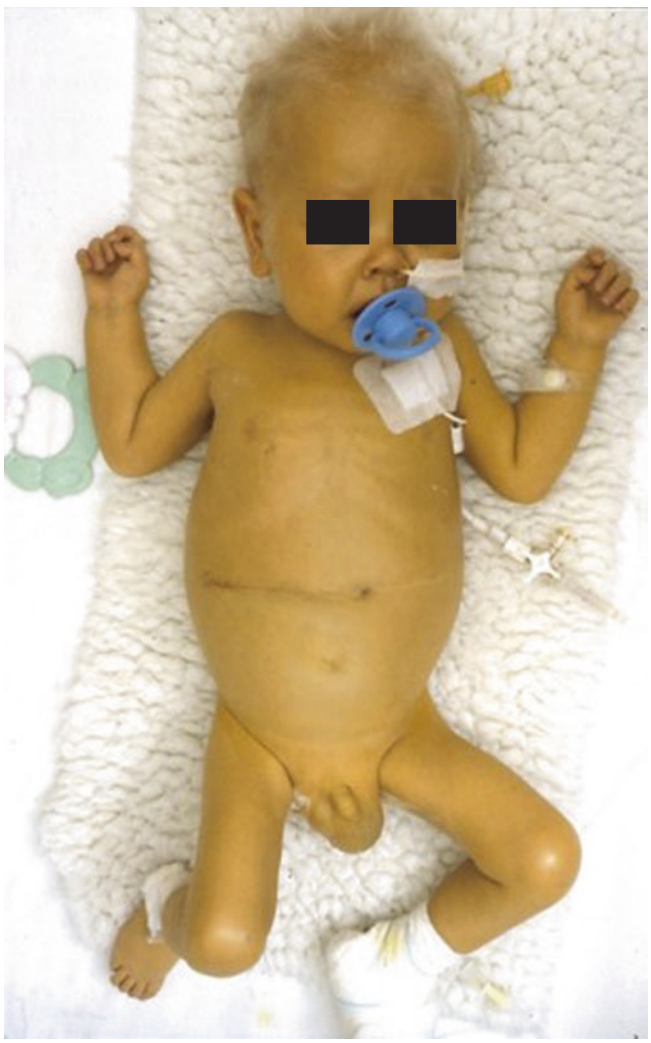

Fig. 12.2 This infant had short bowel syndrome from intestinal atresia. He was maintained on parenteral nutrition but developed sever IFALD with jaundice and malnutrition. Note the laparotomy scar and the extensive malnutrition. He died waiting for a combined liver and bowel graft

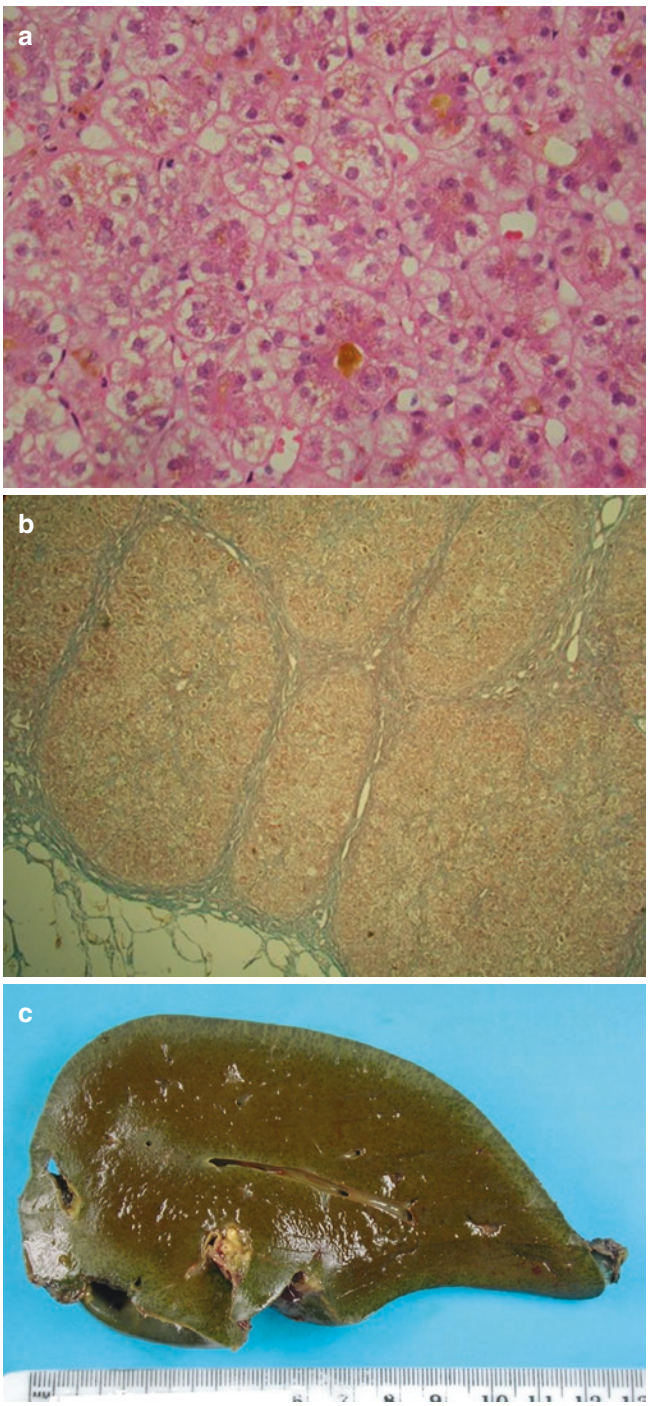

Fig. 12.3 The histological signs of IFALD include cholestasis (note the bile plugs) (**a**) and subsequent fibrosis and cirrhosis (**b**). This slice through a liver removed at the time of multi-visceral transplantation is intensely green demonstrating extensive cholestasis (**c**)

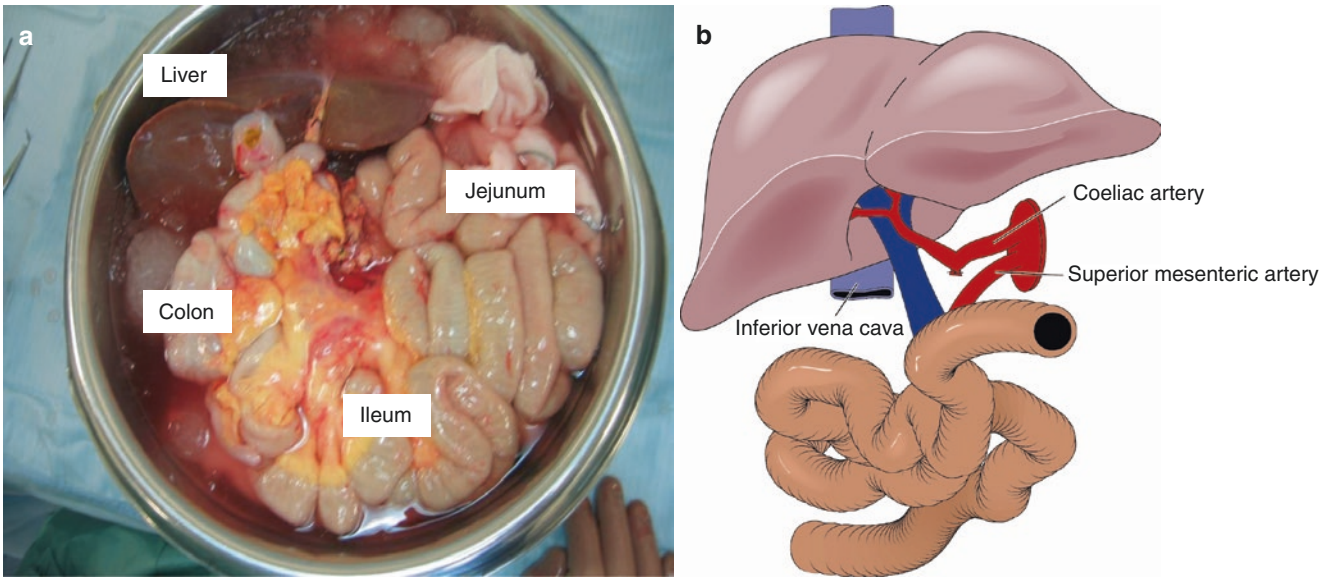

Fig. 12.4 A combined liver and bowel graft is a more extensive operation with significant complications (**a**) a picture of a liver/bowel graft in bowl following retrieval (**b**) cartone showing "classical" liver bowel graft

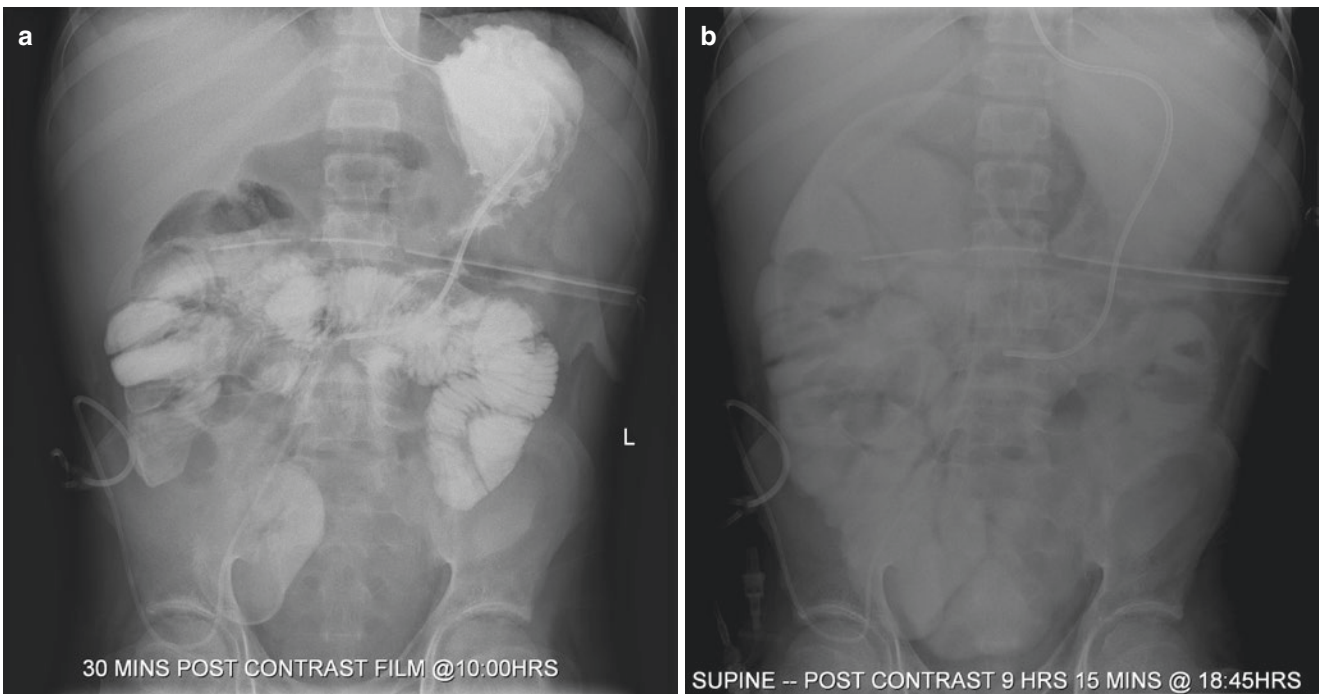

Fig. 12.5 In children with motility disorders, X-ray of the abdomen demonstrates delays of 30 min (**a**), 9 h (**b**) and 24 h (**c**) as a result of ineffective gastric and small bowel emptying. (**d**) Cartoon-A multi visceral graft including stomach, liver and bowel

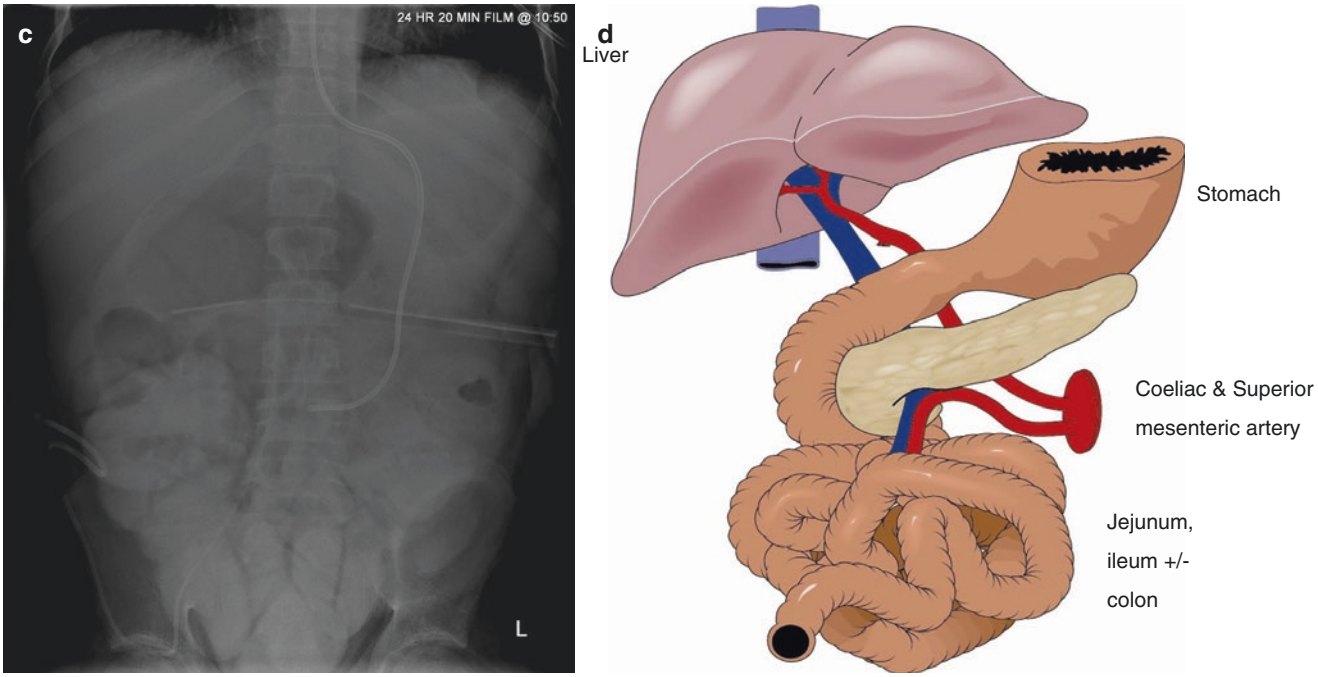

Fig. 12.5 (continued)

B. *Types of transplant*

The technique of combined liver intestinal graft harvesting has been refined over the years. The classical liver/intestinal graft with a separate bile duct anastomosis was modified to en-bloc liver/intestinal graft with duodenum and pancreas to reduce the high incidence of biliary and vascular complications (Fig. 12.6).

C. *Other technical modifications*

There are many different technical modifications but the most important is the development of reduced en-bloc liver and intestinal graft by removal of the right lobe of the liver from adult donors in order to transplant small children (Fig. 12.7a). Other techniques to manage size mismatch include use of tissue expansion pre-transplant (Fig. 12.7b), staged abdominal closure (Fig. 12.7c).

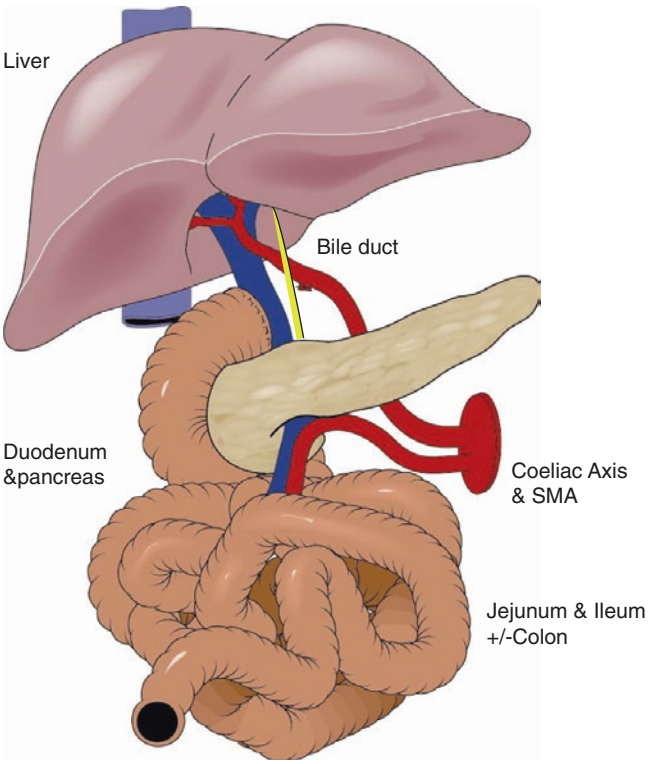

Fig. 12.6 An en-bloc liver bowel graft-contains duodenum and pancreas and intact biliary system to avoid biliary anastomosis and reduce complications

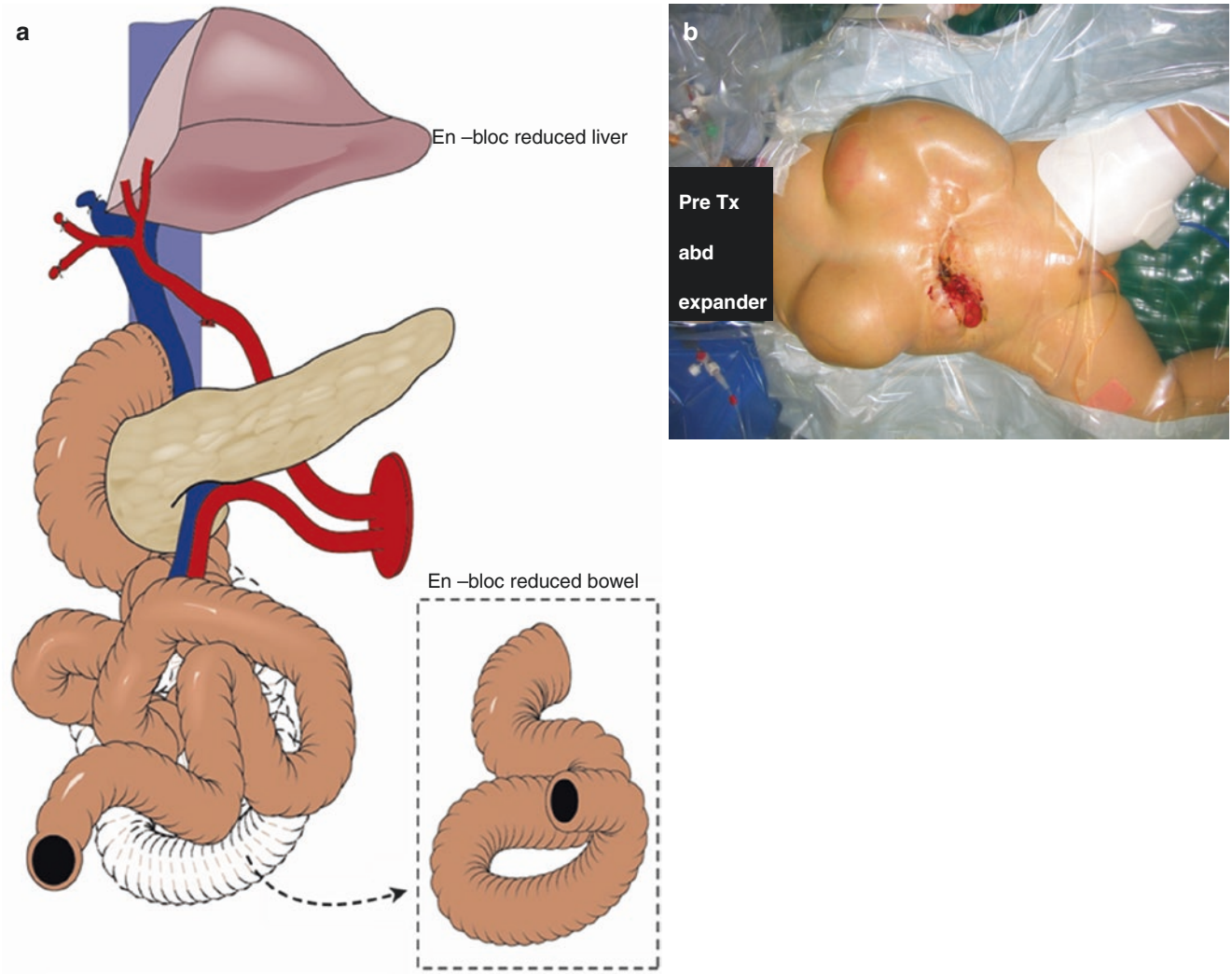

Fig. 12.7 En-bloc reduced liver and bowel graft (**a**) enables the surgeon to use an adult donor and reduce to fit a child. (**b**) Pre-transplant tissue expansion helps to develop skin expansion to allow the use of a larger graft and to close the abdomen. Occasionally, skin closure is delayed and gradually the wound is closed with use of bio-synthetic material (**c**)

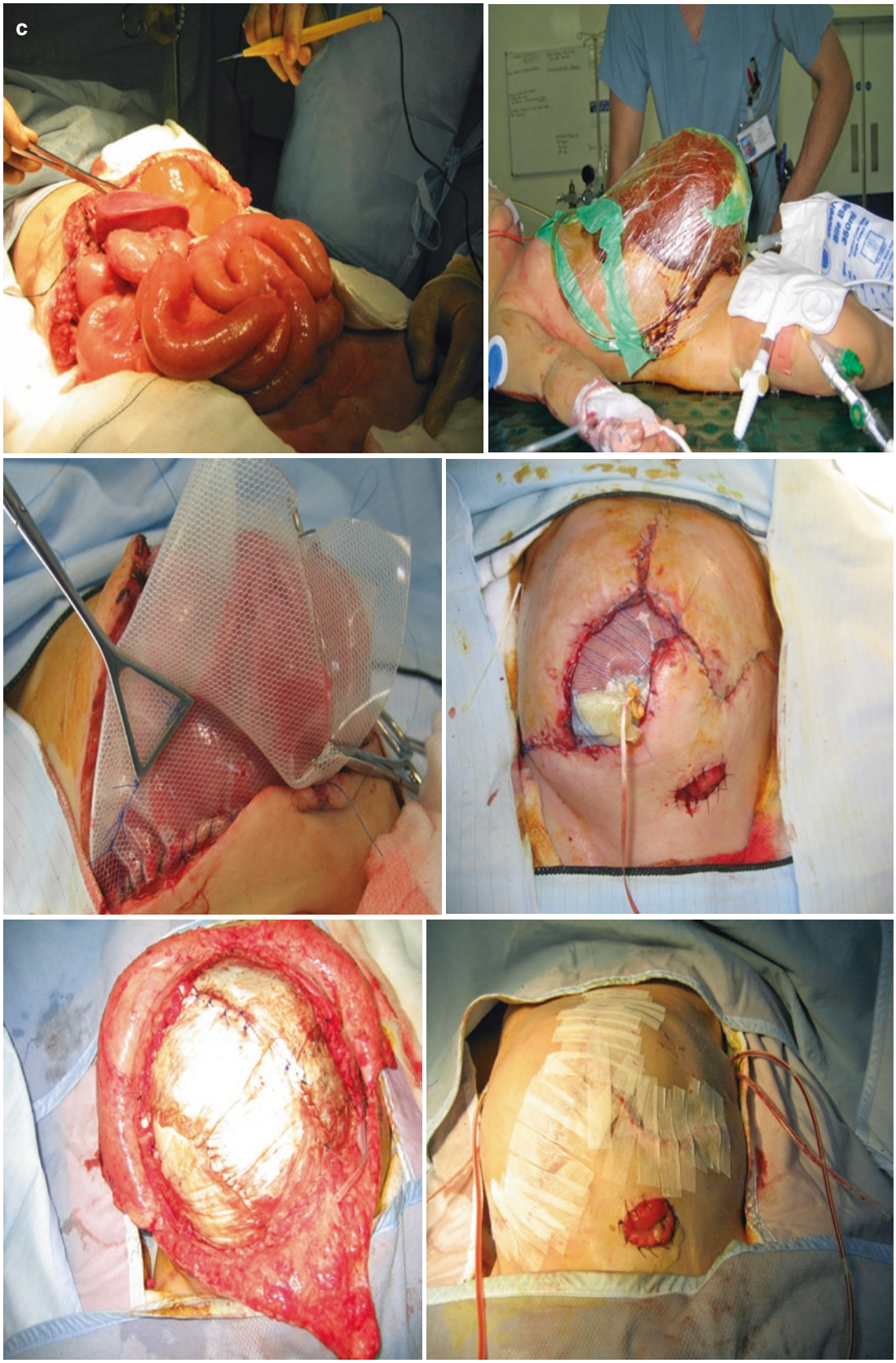

Fig. 12.7 (continued)

12.2 Immunosuppressant Protocols

All major intestinal transplant programme immunosuppression protocols include an anti-CD 25 monoclonal antibody (IL2 receptor antagonist) or anti-lymphocyte globulin with Tacrolimus and steroids. Maintenance immune suppression consists of the combination of Tacrolimus and another agent e.g. Mycoplenolate Mofetil or Sirolimus.

12.2.1 Post-transplant Monitoring

Intestinal grafts are highly immunogenic due to large amount of lymphoid tissue transplanted with the graft; hence require vigilant monitoring.

Complications

(a) *Rejection*: The incidence of rejection is high in the first few weeks post-transplant although it can occur at any time. Clinical features include fever, malaise, abdominal pain, increased stoma output/graft dysfunction. Diagnosis is made by histology (Fig. 12.8). Intestinal rejection is graded as mild (Fig. 12.8a), moderate (Fig. 12.8b) or severe (Fig. 12.8c). Mild or moderate rejection is treated by optimising the immunosuppression with pulse doses of intravenous methylprednisolone (10–20 mg/kg to a maximum of 400 mg). Severe rejection is difficult to treat and is associated with a poor prognosis. Protocols include use of anti-thymocyte globulin, IL2 blockers, campath (anti CD52).

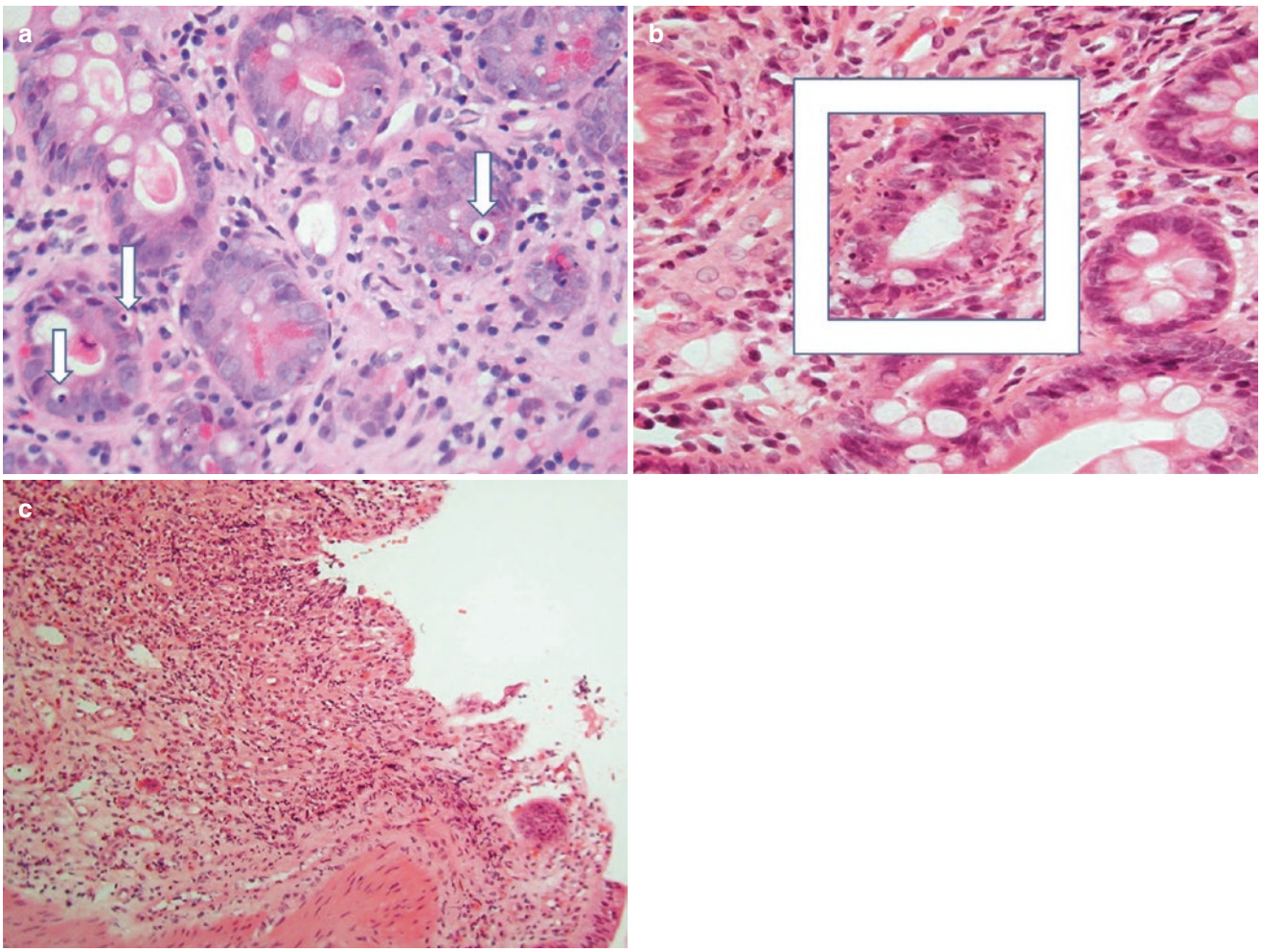

Fig. 12.8 Histology of intestinal rejection. (**a**) Acute cellular rejection of the small bowel allograft. (H&E ×400). The hallmark of rejection is the presence of increased apoptotic bodies within crypt epithelium (arrows). It is helpful to count the number of apoptotic bodies seen in ten consecutive crypts, and six or above is considered rejection. Viral infections and drugs may also cause increased apoptosis in small bowel epithelium and so clinical correlation is required. It is also helpful to compare the appearances in the graft to those in residual native bowel. (**b**) Moderate acute cellular rejection is a point at which crypts are beginning to disappear. The highlighted crypt in this image shows multiple apoptotic bodies becoming 'confluent'. As rejection progresses this crypt will 'dropout'. (**c**) In acute cellular rejection once the crypts have been lost all that remains in place of the mucosa is ulcerated granulation tissue. In isolation this is not specific, but may have evolved from more recognisable rejection. Biopsies from several different sites may resolve the issue

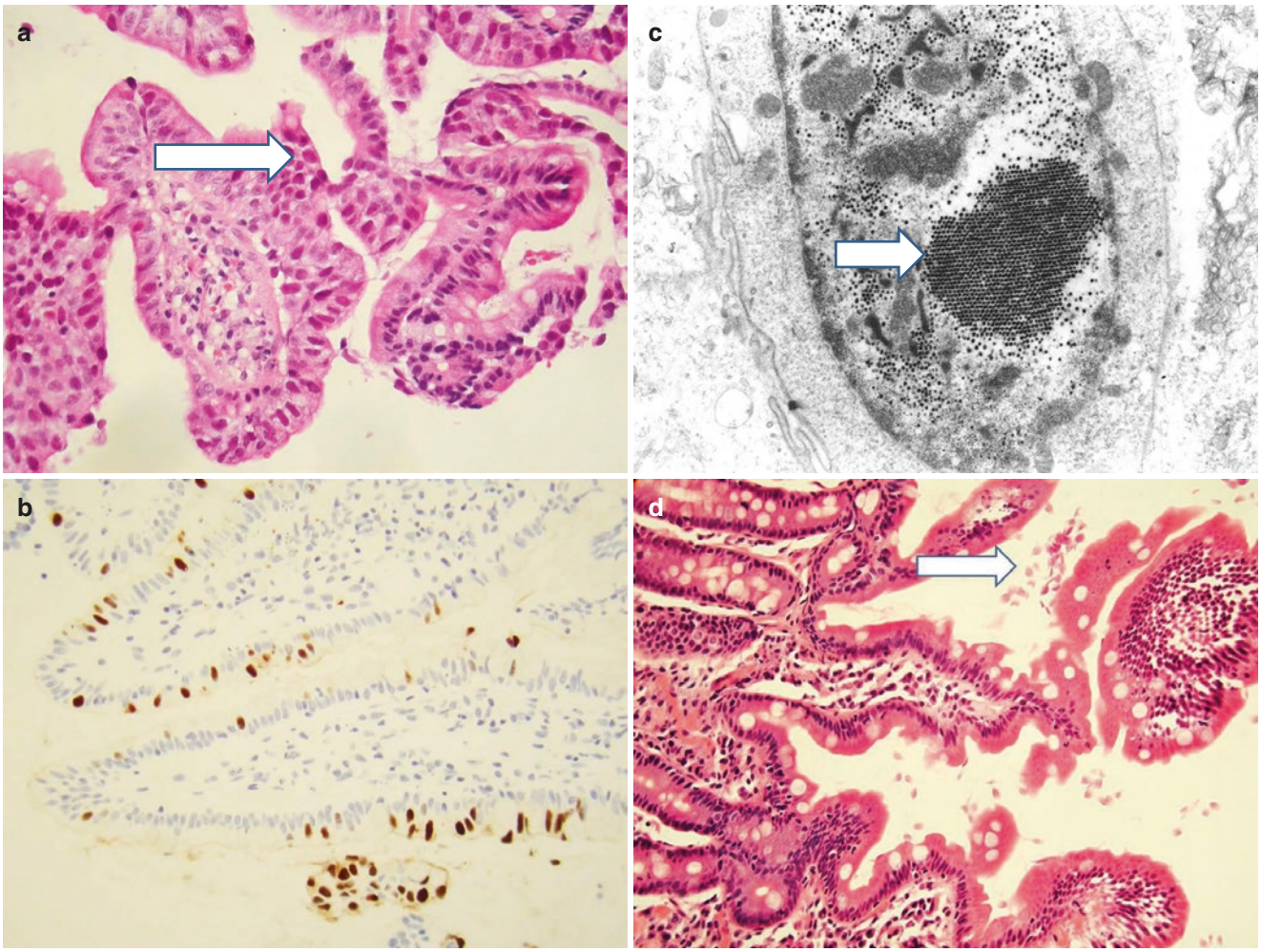

Fig. 12.9 *Infectious complications* in the small bowel allograft are common. (**a–c**) Adenovirus is the most common. The small bowel epithelium assumes a regenerative multi-layered appearance, the nuclei contain inclusions in H&E sections (**a**). Confirmation is usually by immunohistochemistry (**b**) while an electron microscope picture demonstrates the appearance of adenovirus ultra-structurally (**c**). Figure (**d**) shows Giardia lamblia marked with an arrow

(b) *Infection*: Bacterial, vial and fungal infections are common following intestinal transplantation and are associated with high morbidity and mortality (60–70%). Cytomegalovirus (CMV) and Epstein Barr virus (EBV) related post-transplant lymphoproliferative disease (PTLD) lead to significant morbidity.

(c) *Post-transplant infectious enteritis*: Infectious enteritis is caused by several viruses. The most common are: (Fig. 12.9a–c) Adenovirus, Rotavirus and Norovirus or protozoa such as Giardia Lamblia and Cryptosporidia (Fig. 12.9d). The clinical presentation of infectious enteritis mimics rejection and is an important differential diagnosis. In addition, infection, particularly rotavirus and adenovirus enteritis may trigger episodes of acute rejection.

(d) *Post-transplant lymph-proliferative disorder* (*PTLD*): EBV infection may lead to PTLD in 30–40% of patients. Clinical features include pallor, lymphadenopathy, hypo-albuminemia, anaemia, thrombocytopenia and neutropenia. The diagnosis may be difficult as although imaging of the abdomen and the chest is useful in staging the disease (Fig. 12.10), histopathological examination of affected tissue (Fig. 12.11) is required to confirm the diagnosis of PTLD. Reduction of immunosuppression in association with Rituximab/Cyto-toxic lymphocytes/ chemotherapy are usually effective in the management of established PTLD.

(e) *Chronic rejection*: The incidence of chronic rejection is 10–20% and may occur at any time post-transplant. Clinical signs include diarrhoea or excess stoma output, hypoalbuminemia, inability to tolerate enteral feeding and reliance on parenteral nutrition. The diagnosis may be suggested by demonstrating thickened bowel walls with oedema (Fig. 12.12). A full thickness intestinal biopsy is required to establish the diagnosis of chronic rejection (Fig. 12.13a–c).

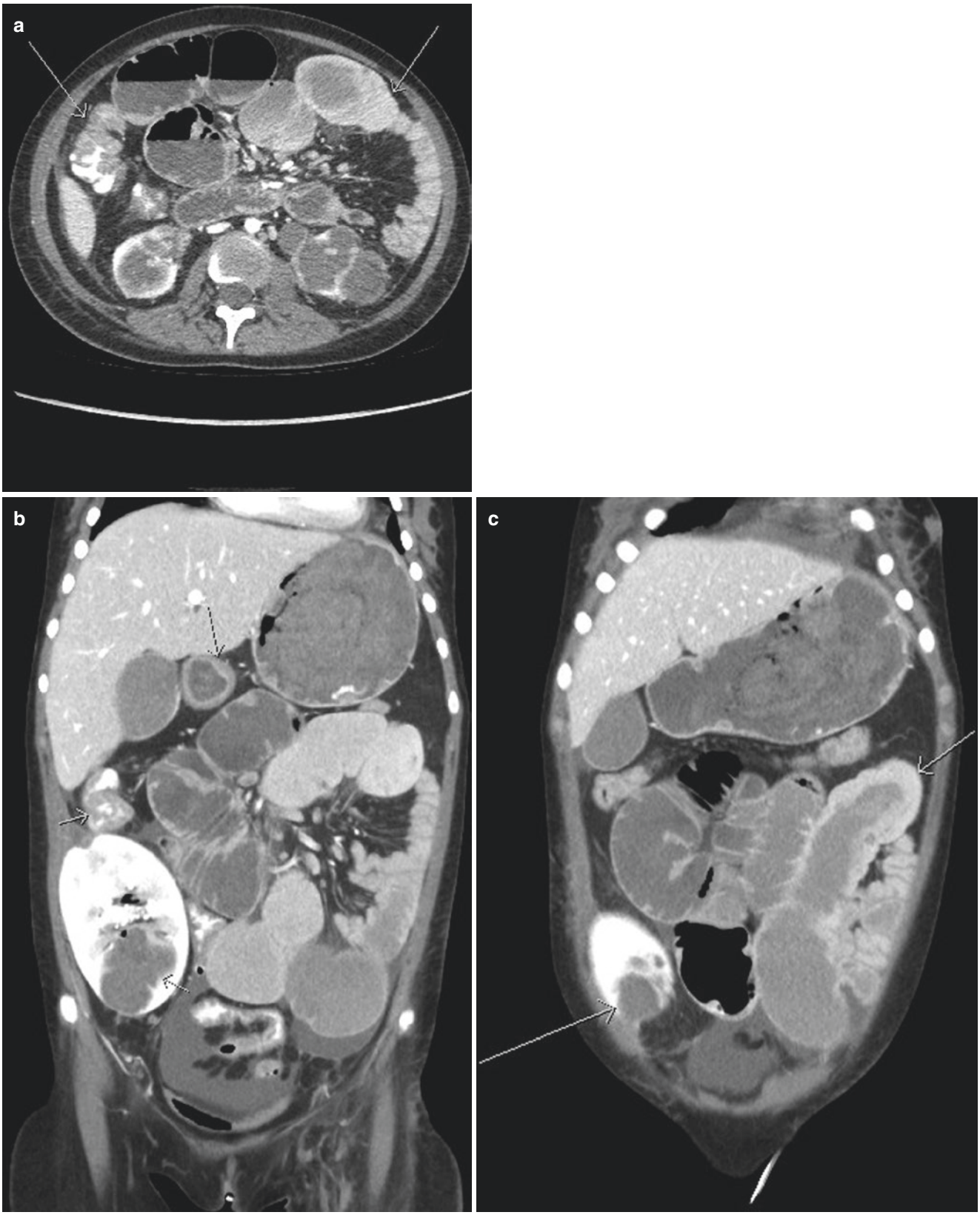

Fig. 12.10 Intravenous contrast enhanced axial (**a**) and coronal (**b**, **c**) sections of the abdomen and pelvis reveals abnormal thickening and enhancement of multiple bowel loops and large non-enhancing lesion in the lower pole of right transplant kidney, suggestive of PTLD

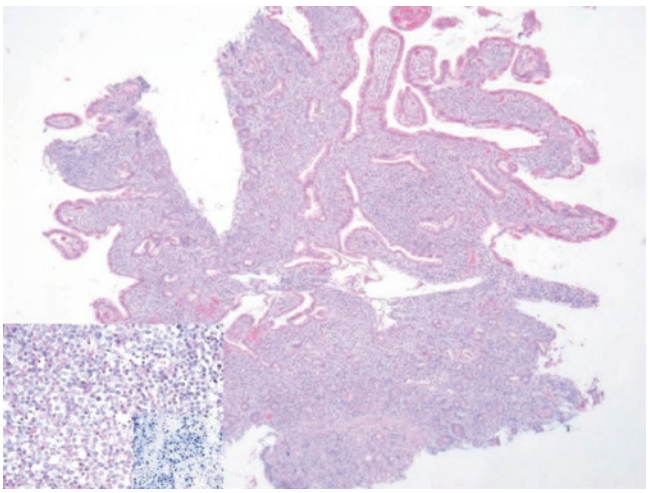

Fig. 12.11 Post-transplant lymphoproliferative disorder (PTLD) is a spectrum of conditions. Progression towards the malignant end of this spectrum usually gives rise to grossly visible lesions and is denoted by a lymphoid infiltrate which begins to destroy the normal architecture of the organ. In this image the cellularity in the lamina propria is increased and crypts have been destroyed. At higher magnification the infiltrate is monotonous and blast-like (inset). PTLD is usually composed of B cells and is related to EBV infection (small inset Epstein-Barr virus encoded early RNAs EBERs)

(f) *Graft versus host disease* (*GVHD*): The reported incidence of GVHD following bowel transplant is 5–10%. It may present with a fleeting skin rash, which becomes extensive and blisters (Fig. 12.14). Other organs may be involved such as the gut (with diarrhoea, abdominal pain and malabsorption). Management of the disease depends on the severity of GVHD. It is important to optimise immunosuppression and provide increased steroids as multiple pulses of methylprednisolone. Further management includes reduction of immunosuppression with use of ECP (extra-corporeal photopheresis) and mesenchymal stem cells.

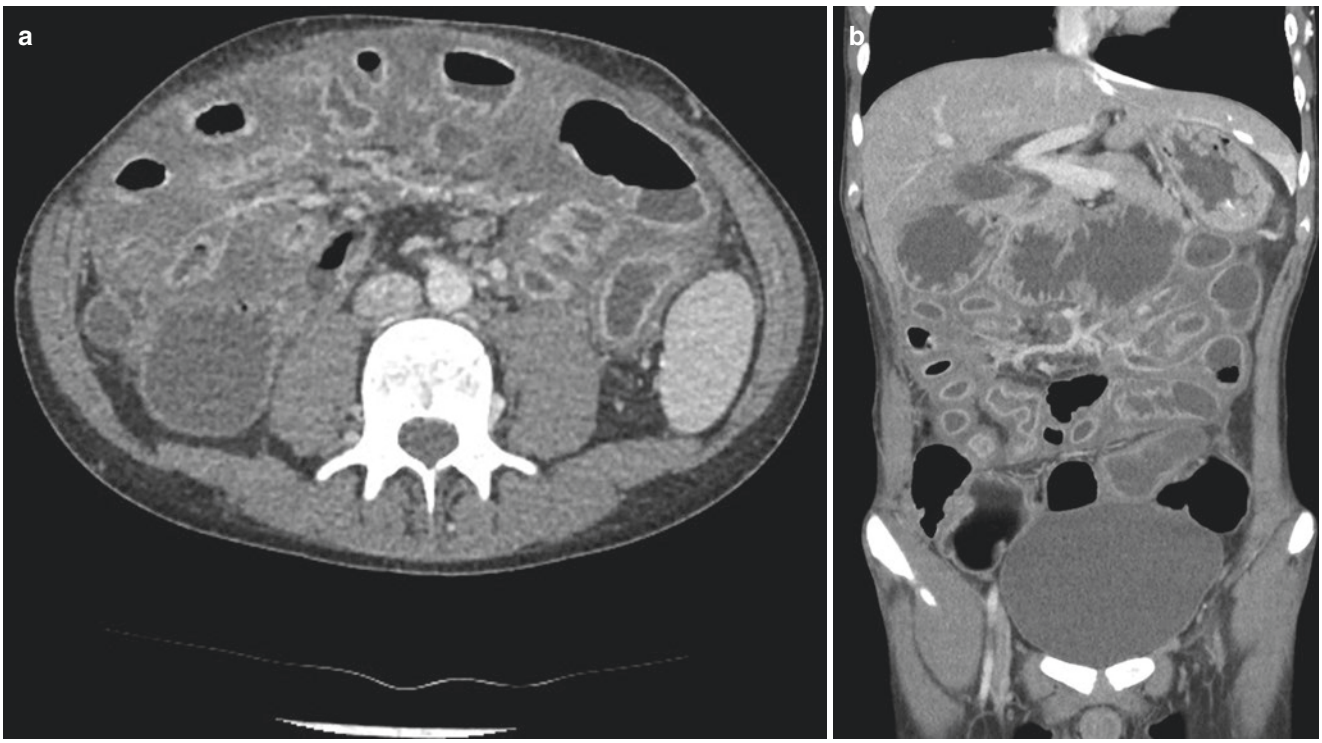

Fig. 12.12 Intravenous contrast enhanced axial (**a**) and coronal (**b**) sections of the abdomen reveals diffuse bowel wall thickening, abnormal enhancement with diffuse edema and enhancement of mesentery, suggestive of chronic rejection post intestinal transplantation

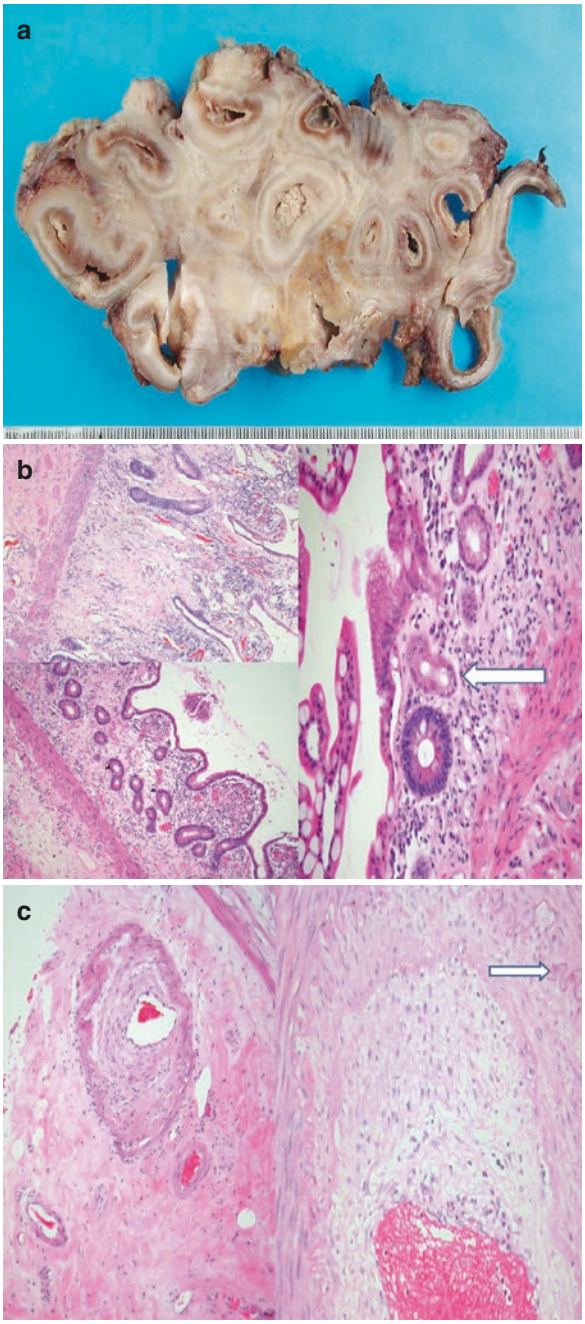

Fig. 12.13 Histological features of chronic rejection (**a**). This is a slice through a removed small bowel allograft. The bowel wall is grossly thickened and there is so much serosal fibrosis that separate loops cannot be dissected out. This is usually associated with chronic rejection but could be multifactorial. (**b**) Mucosal biopsies are not diagnostic in chronic rejection as the typical vascular lesions are usually not biopsied. The mucosa becomes atrophic. In these images, fibrous tissue has replaced crypts (top left), and the villi are blunted (bottom left). The image on the right includes a crypt lined by simplified pyloric type epithelium, which is also seen in inflammatory bowel disease. (**c**) Foam cells are not as conspicuous in the arteriopathy of chronic rejection in the small bowel allograft compared to other solid organ grafts but intimal thickening is seen in the internal elastic lamina of an artery (arrow). In the normal situation very little tissue is expected between this and the lumen of the vessel. The lumen, filled with red blood cells, is identifiable at the bottom of the picture

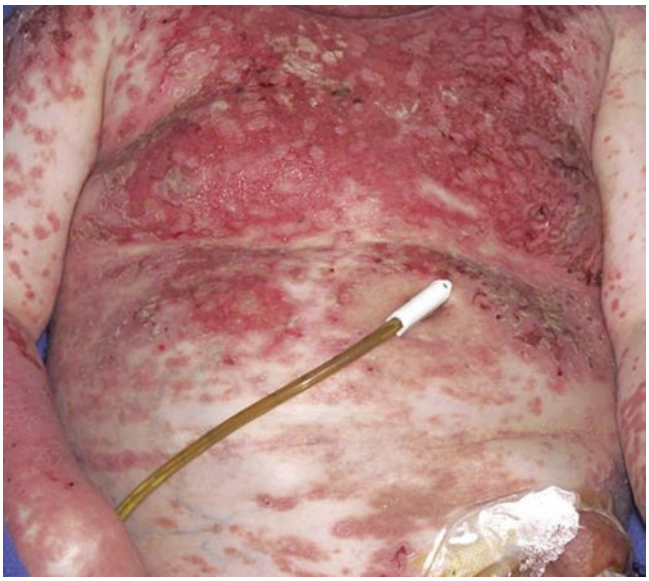

Fig. 12.14 This boy had an isolated small bowel transplant, but developed extensive Grade III GVHD involving his skin with blistering and exfoliation. He sadly died despite medical therapy

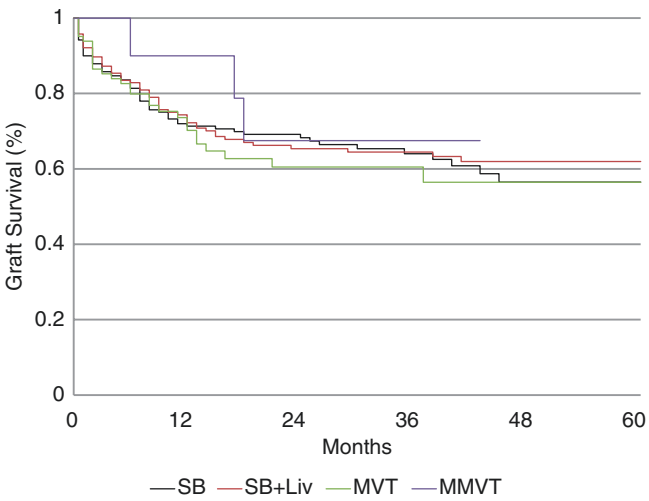

Fig. 12.15 Intestinal transplant registry (ITR) report-2013. 1 year survival following intestinal transplant is 80%–90% whereas 5 year survival is 50–60%

12.2.2 Outcome

The long term outcome of intestinal transplantation is still evolving. Current 1 year survival is >80%, 3 and 5 year survival is 60% and 40% respectively. Many children develop chronic rejection by 5 years post-transplant and require re-transplantation (Fig. 12.15).

Further Reading

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Diseases with Liver and Kidney Involvement

13

David Milford

Many congenital and acquired diseases involve both concomitant kidney and liver disease. In these conditions the rate of disease progression is independent in each organ and a co-ordinated approach between nephrologist and hepatologist is essential for management, particularly when considering a need for combined transplantation.

13.1 Primary Hyperoxaluria (PH)

Primary hyperoxaluria type 1 (PH1) is the commonest of the 3 types of PH, presenting in infancy or in mid-childhood, often with chronic kidney disease, nephrocalcinosis and calculi (Fig. 13.1). Failure of liver synthetic function is not a feature but the genetic defect in the peroxisomes of hepatocytes leads to overproduction and accumulation of oxalate with systemic deposition and significant renal damage (Fig. 13.2).

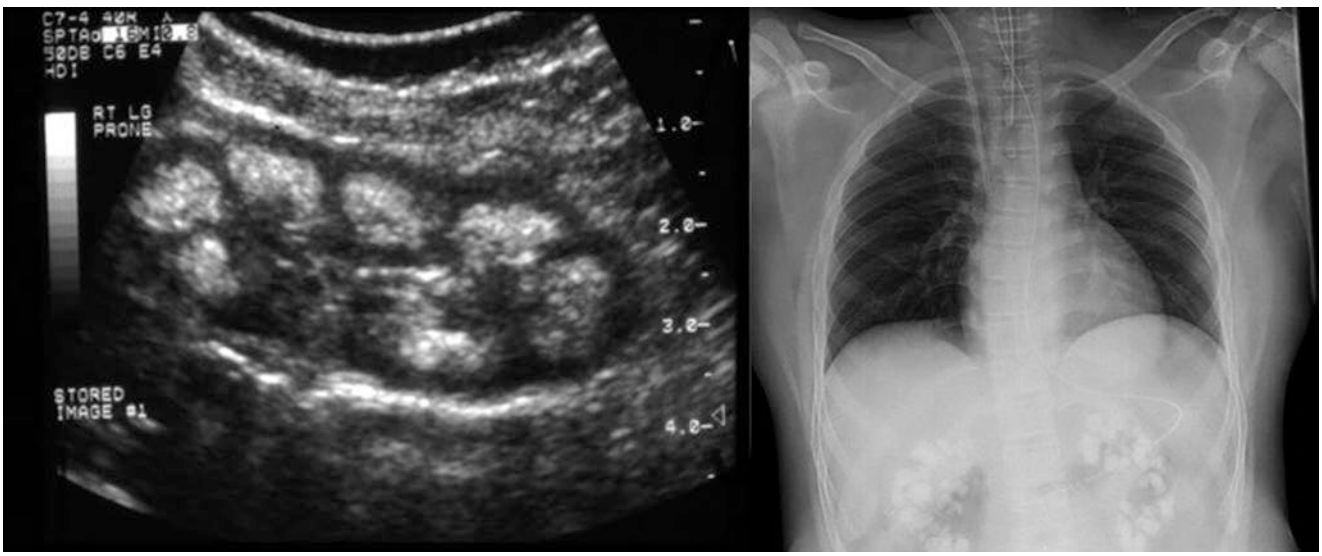

Fig. 13.1 Radiological findings in primary hyperoxaluria: ultrasound coronal section of right kidney shows echogenic medulla and X-ray including the upper abdomen reveals renal calcification of medulla in keeping with nephrocalcinosis

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D. Kelly et al. (eds.), *Atlas of Pediatric Hepatology*, https://doi.org/10.1007/978-3-319-69529-7_13

Oxalate binds calcium forming calcium oxalate crystals in many tissues including the kidneys, the retina, blood vessels and myocardium as well as in bones (Fig. 13.3a, b). The progressive loss of renal tissue leads to declining renal function with reduced oxalate excretion and consequently increasing oxalate accumulation. The rate at which this process takes place varies between patients and is determined by the nature of the genetic defect.

Treatment: Pyridoxine supplementation in those that are pyridoxine sensitive; isolated liver transplantation if renal function is declining but GFR greater than 40 ml/min/1.73 m; combined liver and kidney transplantation when the GFR is less than 40 ml/min/1.73 m.

Children with systemic oxalosis who have successfully undergone isolated liver or combined liver and kidney transplantation no longer produce excessive oxalate but accumulated oxalate is slow to be removed because it is insoluble. The architecture of bones may be disrupted

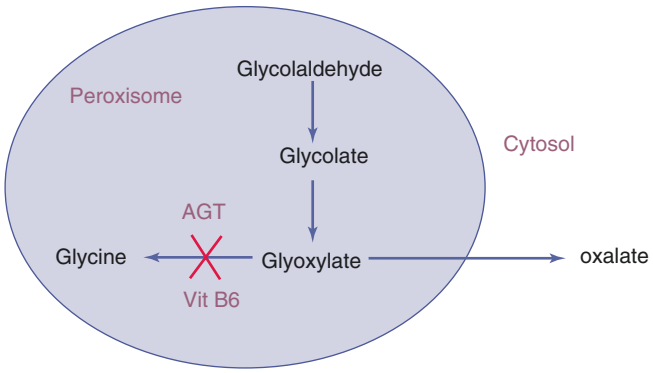

Fig. 13.2 Glyoxylate is normally metabolised via Alanine-glyoxylate aminotransferase (AGT) to glycine in the peroxisome. In PH1 AGT is inactive leading to the conversion of glyoxylate to oxalate by glycolate oxidase. Plasma oxalate is filtered at the glomerulus leading to renal deposition with progressive destruction of renal tissue. Oxalate is also deposited in other tissues

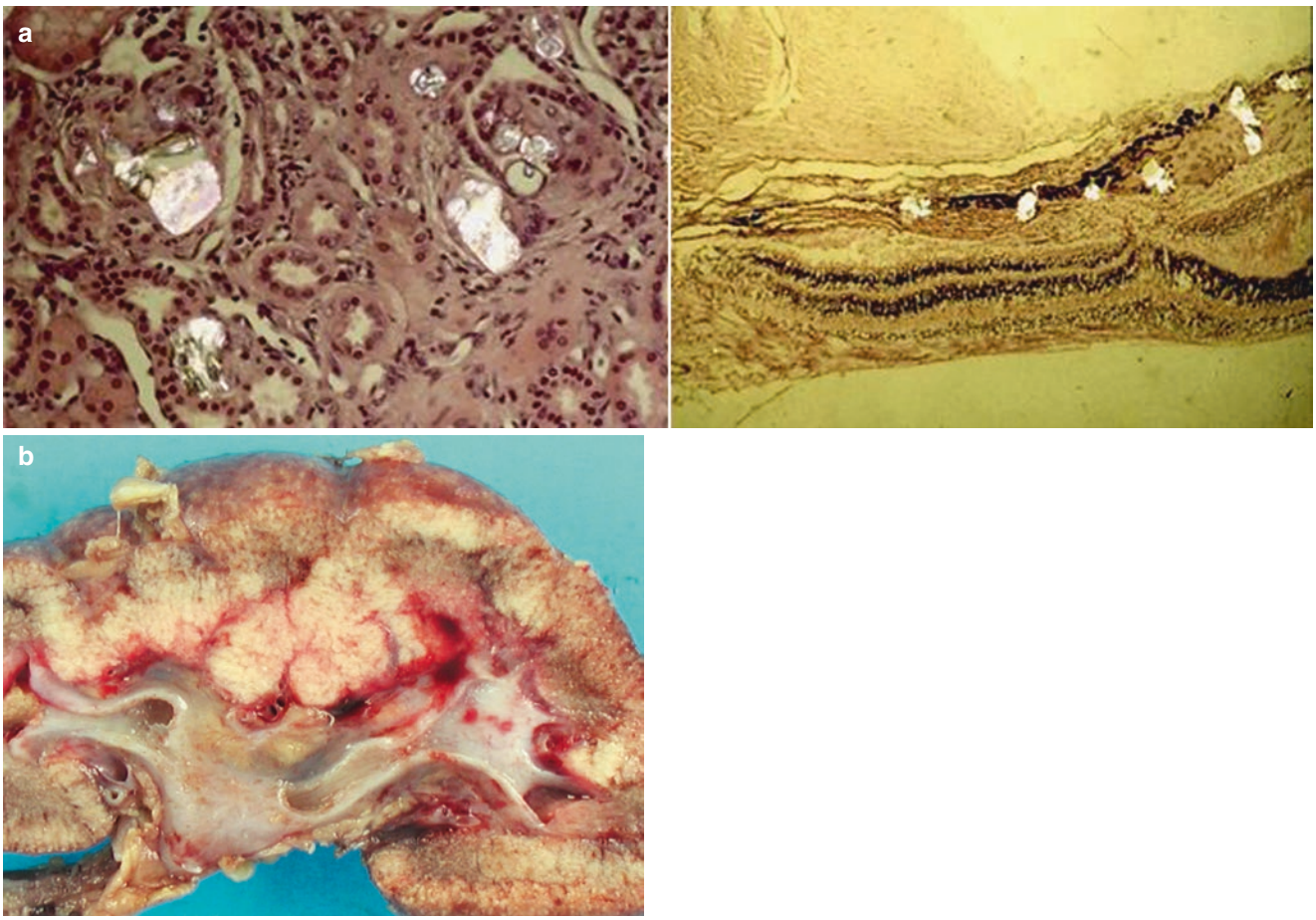

Fig. 13.3 (**a**) Left panel: Oxalate crystals in the kidney, seen here ×400 under polarised light. Right panel: Oxalate crystals in the retina. (**b**) Nephrectomy specimen showing widespread atrophy and tissue destruction secondary to oxalate deposition

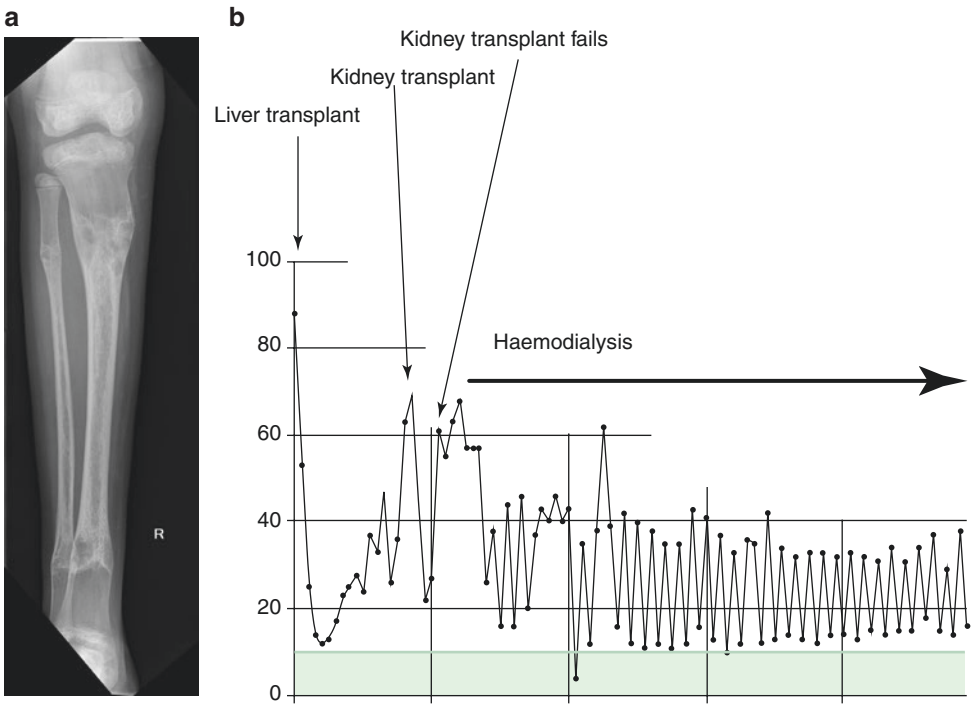

Fig. 13.4 (**a**) Frontal X-ray of the right tibia and fibula reveals severe demineralization manifested as areas of lucency and also variable remodelling at stress points in proximal and distal shafts due to recurrent fractures with healing resulting from oxalate deposition. (**b**) Plasma oxalate levels in a child with renal failure from primary hyperoxaluria who underwent sequential liver and kidney transplant. There is an initial fall in plasma oxalate after the liver transplant because of intensive haemofiltration and a subsequent increase when returned to maintenance haemodialysis. There is a transient fall in the oxalate level after kidney transplantation but a subsequent rise after renal transplant failure. The oxalate levels on haemodialysis were undertaken before and after haemodialysis sessions

leading to recurrent fractures and bone pain (Fig. 13.4a). In some children who have undergone combined liver and kidney transplantation the oxalate burden is so great that the transplanted kidney becomes damaged as the stored oxalate is mobilised and deposited in the transplanted kidney leading to loss of renal function and a requirement for on-going dialysis (Fig. 13.4b). Unfortunately both haemodialysis and peritoneal dialysis have poor oxalate clearance leading to a slow reduction in the burden of total body oxalate, consequently it may be necessary to treat a child with both dialysis modalities to optimise oxalate removal.

The other two forms of PH (type 2 and 3) are much less common and tend to have a less severe clinical course.

13.2 Ciliopathies

The ciliopathies are a newly recognised collection of genetic disorders arising from mutations of proteins affecting the structure and function of the primary cilium which is present on the surface of every nucleated cell. This complex structure has mechano- and chemo-sensory functions (Fig. 13.5). The ubiquitous distribution of this organelle leads to defects in multiple apparently unrelated systems and there is great phenotypic variation. It is estimated that more than 1000 proteins comprise the primary cilium, consequently there are increasing numbers of genetic conditions now classed as a ciliopathy.

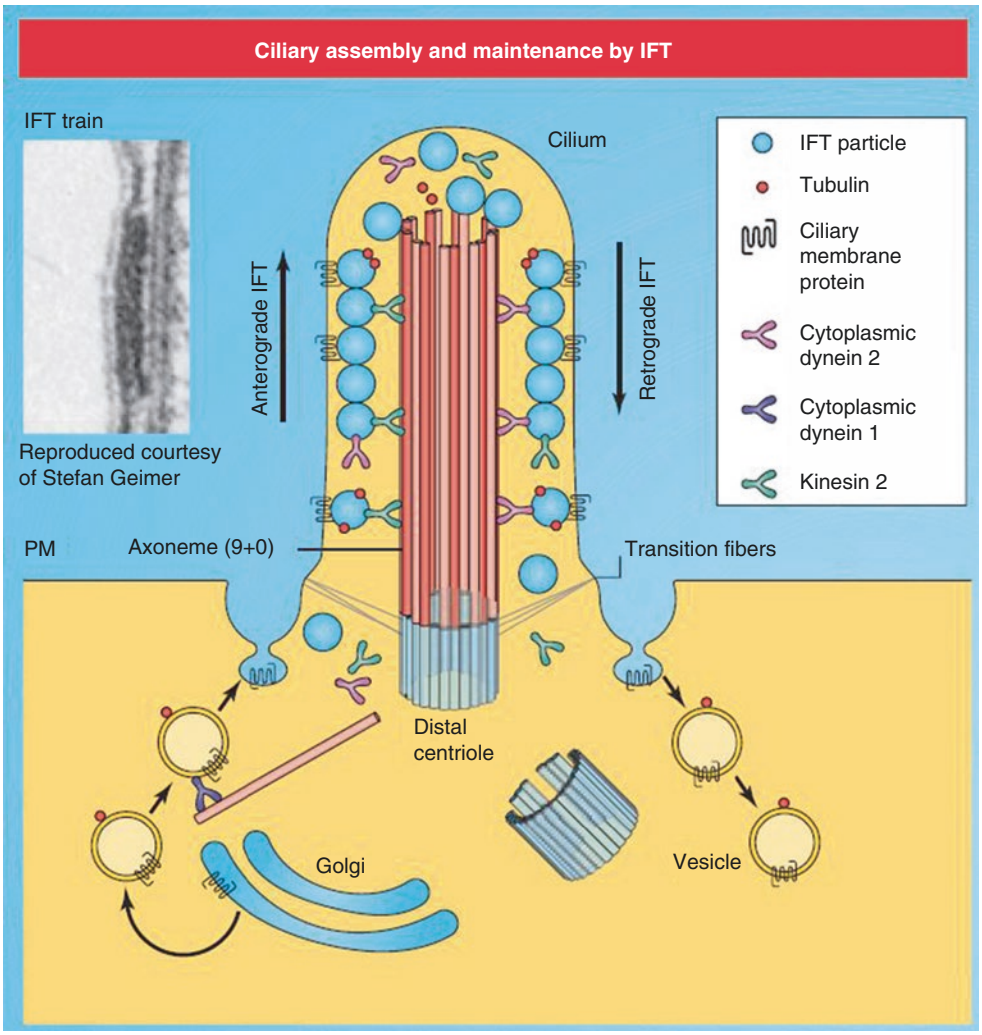

Fig. 13.5 Diagram showing the complex structure of the primary cilium and the intraflagellar transport (IFT) mechanism that is key to the sensory and excretory function of the organelle (from J Cell Sci. 2010; 123: 499–503)

13.2.1 Jeune Syndrome

Jeune syndrome, also known as asphyxiating thoracodystrophy, is now considered one of a group of disorders known as short-rib thoracic dysplasia (SRTD) with or without polydactyly. Presentation can be at birth (or antenatally) but also later in those with a milder phenotype. The first gene identified was mapped to 15.13, and subsequently a further 15 genes have been identified, all of which directly or indirectly influence the function of the primary cilium.

Children present with a restricted thoracic cage, which causes respiratory problems (Fig. 13.6), short ribs, shortened tubular bones, and a 'trident' appearance of the acetabular roof. While respiratory symptoms usually predominate, there may be progressive renal disease (juvenile nephronophthisis), a condition in which there is a progressive breakdown of the tubular basement membrane leading to interstitial fibrosis and cystic tubular dilatation. Hepatic fibrosis progressing to biliary cirrhosis with portal hypertension occurs in some children. Prolonged neonatal cholestasis may be an early presenting feature although older children are found to have hepatic lesions with fibrosis, cirrhosis and portal hypertension leading to liver failure. Isolated or combined organ transplantation may be required depending on the rate of decline in kidney and liver function.

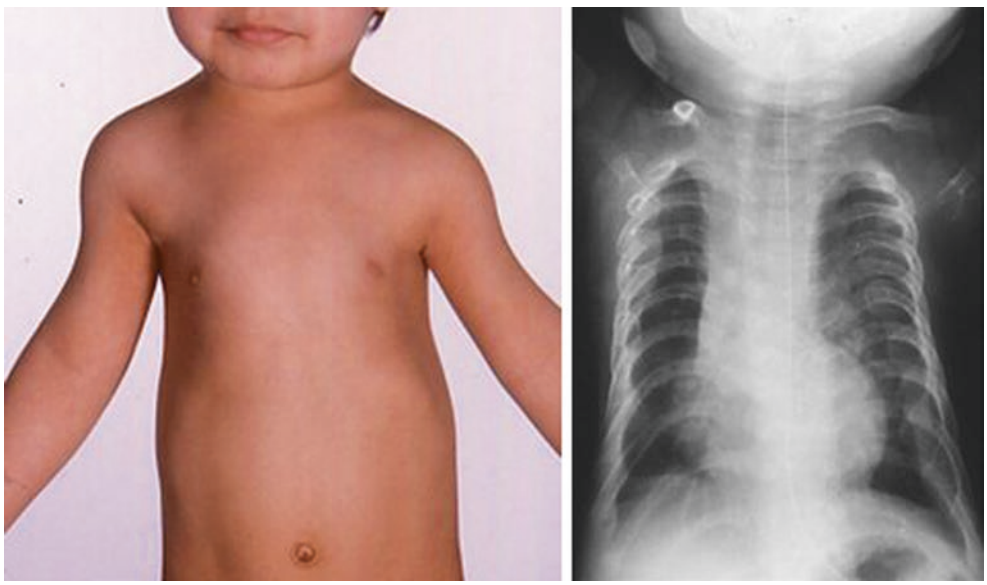

Fig. 13.6 Left panel: narrow chest as a result of restricted rib growth in a child with Jeune syndrome. Right panel: frontal chest X-ray of a child with Jeune syndrome reveals short narrow elongated chest, high riding clavicles and irregular costochondral junctions

13.2.2 Bardet Biedl Syndrome

This multi system disease presently has more than 20 identified genes, all impacting on the structure or function of the primary cilium with most having autosomal recessive expression. Affected individuals have hyperphagia-associated obesity (Fig. 13.7), post-axial polydactyly, progressive blindness from rod-cone dystrophy (Fig. 13.8) and varying degrees of developmental delay. Other clinical features include renal structural abnormalities of varying severity in up to 50%, chronic kidney disease in 30–40%, liver disease, bronchiectasis, significant constipation (Hirschprung disease has been identified in some children) and polyuria and polydipsia arising from resistance to AVP. Skeletal abnormalities including genu valgum and pes planus may be marked and progressive, exacerbated by the marked obesity. Type 2 diabetes develops in 15% of adults as a complication of the obesity and may progress to insulin dependency (see also Sect. 7.1.2, Chapter 7).

There is marked phenotypic variability, particularly with regard to the developmental abnormalities, with some affected individuals demonstrating marked autistic behaviour while others have normal educational attainment and develop successful careers.

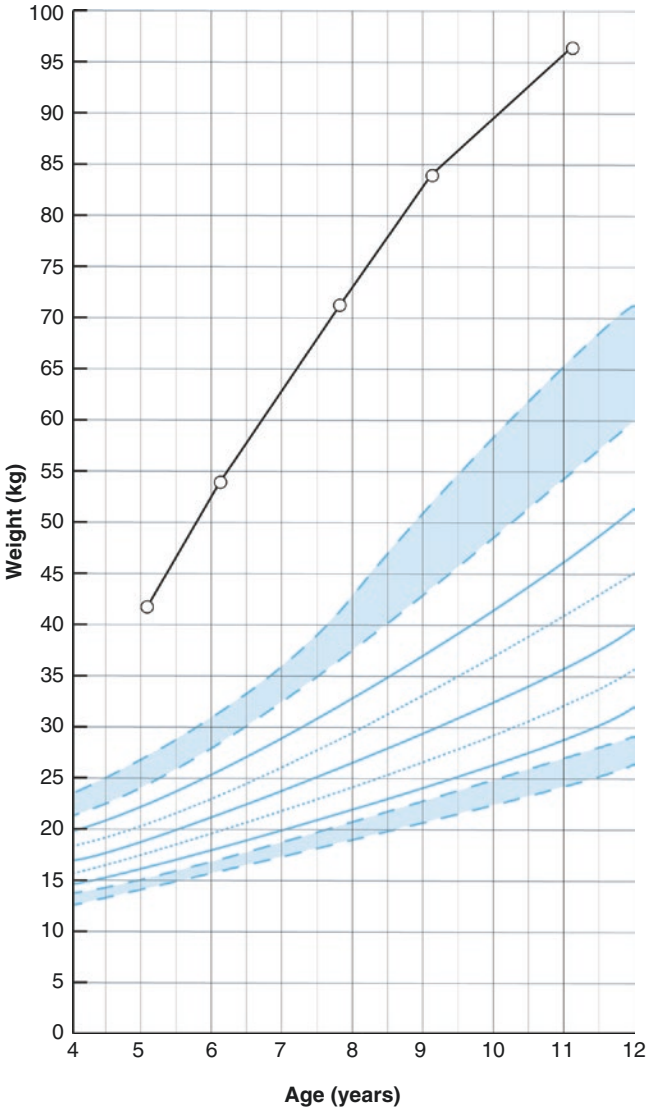

Fig. 13.7 Growth chart showing early and continuing excessive weight gain in a child with Bardet Biedl syndrome

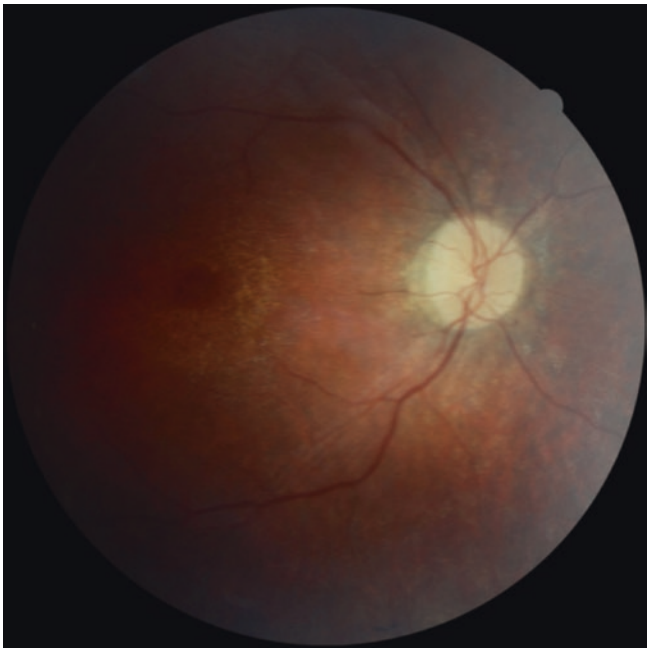

Fig. 13.8 Colour fundus photograph of right eye showing pale optic disc, attenuated retinal vessels, with depigmentation and granular appearance of the macula in a child with Bardet Biedl syndrome

13.3 Autosomal Recessive Polycystic Kidney Disease

The diagnosis of ARPKD is often made on antenatal scanning when the foetus is noted to have enlarged, echo bright kidneys with poor corticomedullary differentiation and oligohydramnios. ARPKD occurs in 1:20,000 to 1:40,000 live births and is caused by a mutation in the PKHD1 gene which codes for a fibrocystin/polyductin protein complex, a receptor-like protein expressed in the primary cilium of epithelial cells that has been identified in renal collecting ducts and the Loop of Henle, in pancreatic epithelial ducts and in hepatic biliary ducts.

Affected foetuses may have oligohydramnios as a consequence of poor urine output and, together with marked renal enlargement, causing lung compression with significant pulmonary hypoplasia leading to a mortality rate of approximately 30% in the neonatal period.

Affected children have a variable renal and liver phenotype. Histologically, there is non-obstructive, fusiform, cystic distension of renal collecting ducts with sometimes massive renomegaly (Fig. 13.9), impaired renal function and hypertension. In some children renal (and liver) enlargement is so great it impacts on feed tolerance as a result of gastric compression.

Although most neonates (70–80%) have renal impairment, renal failure requiring dialysis or transplantation rarely develops early in childhood and the actuarial renal survival rates are 86% at 5 years, 71% at 10 years, and 42% at 20 years. Hypertension is common (75% affected), especially in children with preserved renal function, and can be severe requiring multi drug therapy or even nephrectomy.

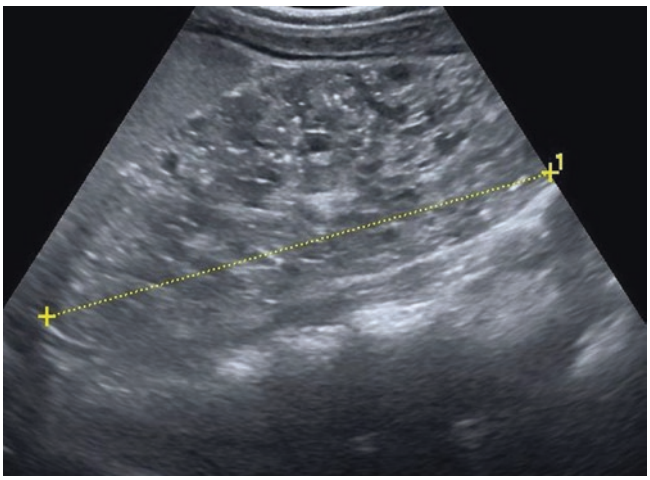

Fig. 13.9 Ultrasound coronal section of right kidney reveals enlargement with loss of normal architecture due to the presence of multiple tiny cysts in a child with autosomal recessive polycystic kidney disease

There are varying degrees of congenital hepatic fibrosis (CHF), as a result of a biliary ductal plate malformation. Progressive biliary disease leads to periportal fibrosis or CHF or Caroli's disease, a cystic widening of the intrahepatic bile ducts and the common bile duct. The main complication is portal hypertension manifested by hepatosplenomegaly, hypersplenism with low platelet count, variceal bleeding and an increased risk of ascending cholangitis. Survival has improved as a result of aggressive management of nutrition, hypertension and isolated organ or combined liver and kidney transplantation during childhood.

13.4 Liver and Kidney Transplant

Simultaneous combined liver and kidney transplantation (CLKT) is a major procedure but has an excellent outcome provided children are carefully selected and the procedure is undertaken in a centre with appropriate experience.

Children with liver disease and chronic kidney disease should be considered for pre-emptive transplantation (before dialysis) if they have an estimated GFR of less than 45 ml/min/1.73 m^2 because isolated liver transplantation may cause a decline into established renal failure requiring dialysis.

CLKT is advisable in children with liver disease who are on dialysis and who are at risk of progression of liver dysfunction because the risk of cholangitis is increased in those on immunosuppression after isolated renal transplantation or because of progression of portal hypertension.

CLKT is a proven therapeutic option for children with metabolic disease as a result of defective hepatic enzyme function leading to CKD, as in primary hyperoxaluria type 1.

There is some evidence that the liver provides an immune modulatory function that is beneficial to the transplanted kidney, leading to better long-term renal transplant function and outcome in comparison to isolated kidney transplants (Fig. 13.10).

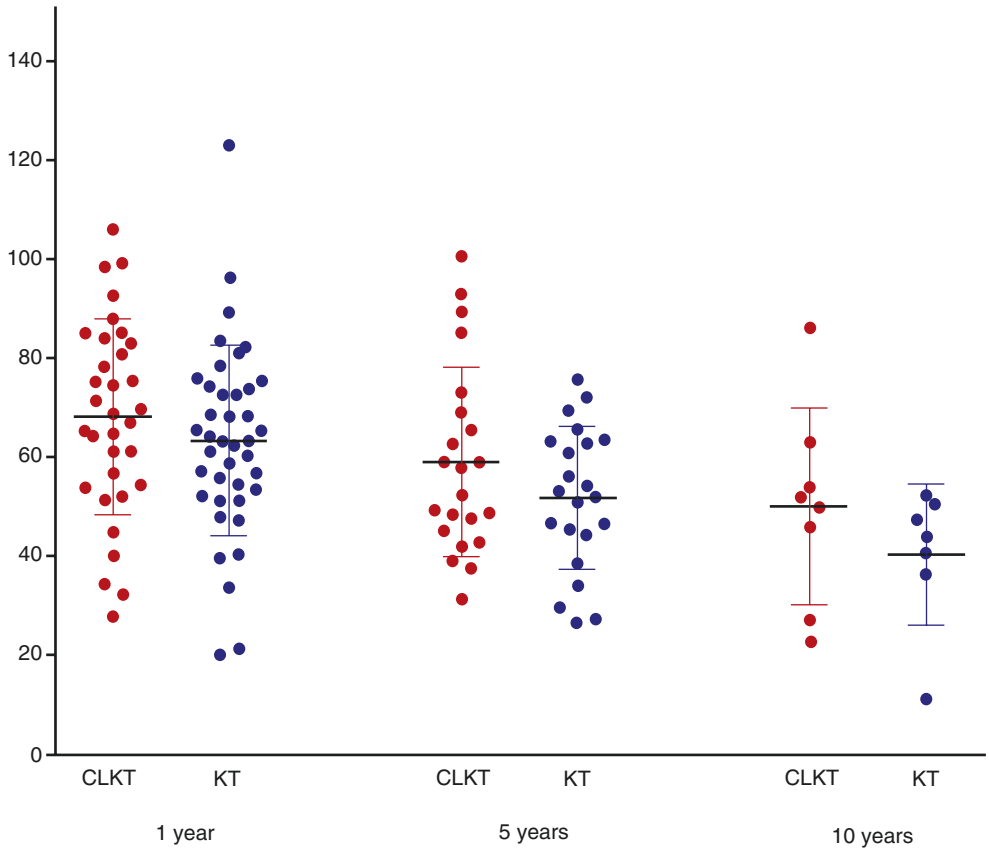

Fig. 13.10 Renal graft function in 40 combined liver and kidney transplant (CLKT) recipients compared with matched isolated kidney transplants (KT). (From Pediatr Nephrol. 2016; 31: 1539–43)

Further Reading

Bardet Biedl support group. Information leaflet. http://www.lmbbs.org.uk/LMBBS/file/Medical%20Booklet%202016(1).pdf.

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