

Chapter 14

The Orphan Liver Disease



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Key Learning Points

Porphyria

- Porphyrias are disorders of haem biosynthesis. They are classified as erythropoietic or hepatic based on the primary site of enzyme deficiency.
- Patients have neurovisceral or cutaneous symptoms or both, depending on which metabolites accumulate. Aminolevulinic acid (ALA) is neurotoxic, whilst porphyrins are associated with cutaneous symptoms. In patients with neurovisceral symptoms, check urine ALA and porphobilinogen (PBG) levels. In patients with cutaneous symptoms, check the plasma and urine porphyrin profile.
- Treatment depends on the type of porphyria. Patients should be advised to avoid triggers. Specific treatments include the use of haem and glucose in acute intermittent

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porphyria and the use of venesection and low-dose chloroquine in porphyria cutanea tarda. Givosiran, an ALA synthase I directed small interfering RNA, has now been approved in the USA for treatment of acute intermittent porphyria.

Alpha-1-Antitrypsin (A1AT) Deficiency

- A1AT is a serine protease inhibitor. A1AT deficiency is an inherited metabolic disorder in which A1AT cannot be exported from the liver. In the lungs, this causes emphysema, whilst accumulation of the abnormal protein in the liver causes hepatocyte apoptosis, inflammation and cirrhosis.
- Consider A1AT deficiency in patients who develop emphysema at a young age, or without a smoking history. It should be screened for in patients: (a) with unexplained deranged liver function tests, (b) with bronchiectasis of unclear aetiology, (c) with a family history of liver disease, bronchiectasis or emphysema.
- Serum A1AT can be quantified but the gold standard for diagnosis of A1AT deficiency is phenotyping using isoelectric focusing.
- Although pooled human plasma A1AT is used to treat associated pulmonary disease, there is currently no licensed specific treatment available for A1AT disease affecting the liver. Patients with advanced liver disease should be considered for liver transplant.
- Treatments under investigation include the use of siRNA to downregulate production of the mutant protein and use of carbamazepine to promote degradation of abnormal A1AT.

Cystic Fibrosis Liver Disease (CFLD)

- Around one-third of patients with cystic fibrosis develop liver disease, which is most commonly hepatic steatosis.
- Patients with CF secrete bile which is more viscous and less alkaline than normal. This can predispose to obstruction of the biliary tree and injury to the cholangiocytes and

hepatocytes. This can ultimately trigger fibrosis and then cirrhosis with portal hypertension.

- Assessment of patients with CFLD should involve annual review, including examination for hepatosplenomegaly, blood tests to assess liver function and abdominal ultrasound.
- Ursodeoxycholic acid can be used to treat patients with CFLD. Liver transplant can be considered in advanced liver disease but survival outcomes are worse than those undergoing liver transplant for other reasons.
- The disease modifying drug, Kaftrio, has recently been licensed in the UK for certain subgroups of patients with CF. Whilst it is associated with improvements in lung function (FEV1), it can have hepatobiliary side effects. Patients on Kaftrio should have regular monitoring of liver function tests, and use of Kaftrio should be avoided in patients with severe hepatic impairment (Child-Pugh C).

Case

A 46-year-old Caucasian male was referred to the gastroenterology clinic with abdominal distension and jaundice. His medical history included chronic obstructive pulmonary disease. He had a five pack-year smoking history and was a teetotaler. He had three brothers who died of liver failure aged in their 50s.

On cardiorespiratory examination, he had a prolonged expiratory phase and widespread wheeze. FEV1 on spirometry was 40%. Further examination revealed scleral icterus, asterixis and palmar erythema. His abdomen was soft and non-tender, with splenomegaly of 2 cm below the left costal margin. Below are the results of blood tests:

Hb 9.3 g/dL	Urea 5.5 mmol/L	Platelets 110 × 10 ⁹ /L
Bilirubin 56 µmol/L	Albumin 31 mmol/L	ALT 150 IU/L
Creatinine 69 µmol/L	INR 1.7	AST 110 IU/L

US abdomen showed a cirrhotic liver with 13 cm splenomegaly. A liver screen was performed. Ferritin, caeruloplasmin and AFP were normal. Viral screen (including hepatitis A, B and C, CMV and EBV) was unremarkable, and autoantibody screen was negative. Serum A1AT was reduced at 5 $\mu\text{mol/L}$.

Questions

1. What is the likely diagnosis?
2. How would you confirm the diagnosis?
3. What is 'augmentation therapy'?

'Orphan' diseases are rare conditions in which there is often reluctance by general physicians to manage the diseases because the diagnosis and management are relatively poorly understood. This chapter focuses on three orphan diseases of the liver: porphyria, alpha-1-antitrypsin deficiency and cystic fibrosis.

Porphyria

Overview

The porphyrias are eight inborn disorders of metabolism characterised by defective haem biosynthesis (Fig. 14.1). Haem is an important component of vital proteins including haemoglobin, myoglobin, cytochrome p450 enzymes and respiratory cytochromes. Approximately 80% of haem is synthesised in erythroid precursor cells in the bone marrow. Most of the rest is synthesised by hepatocytes in the liver. Haem synthesis is a multistep process that involves eight enzymes. The first reaction in this pathway, mediated by ALA synthase, is the rate-limiting step. ALA synthase has two isoforms: ALAS1 in non-erythroid cells and ALAS2 in erythroid cells. ALAS1 activity is inhibited by haem and high glucose levels, whereas activity is increased by cytochrome p450 inducers.

Abnormalities in haem biosynthesis can result in accumulation of pathway intermediates, such as 5-aminolevulinic

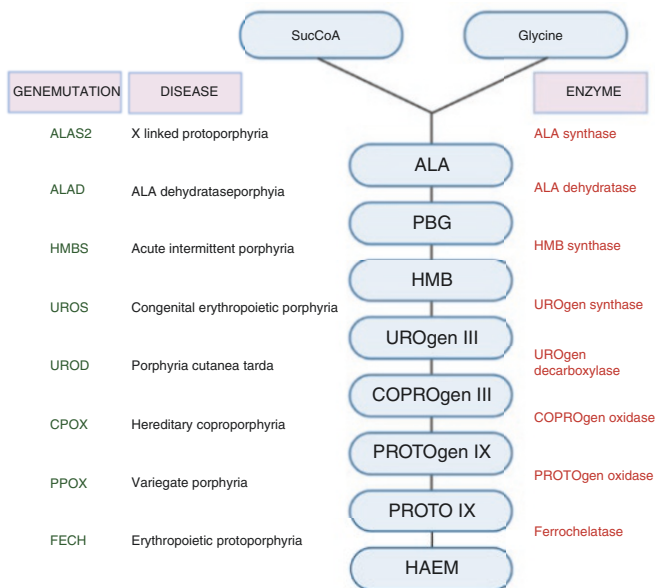


FIGURE 14.1 An overview of the haem biosynthesis pathway, and the enzyme and genetic defects associated with the eight porphyrias. *ALA* δ -aminolevulinic acid, *ALAD* ALA dehydratase, *CPOX* coproporphyrinogen oxidase, *FECH* ferrochelatase, *HMB* hydroxymethylbilane, *HMBS* hydroxymethylbilane synthase, *PBG* porphobilinogen, *SucCoA* Succinyl-CoA, *UROD* uroporphyrinogen decarboxylase, *UROgen* uroporphyrinogen, *COPROgen* coproporphyrinogen, *PPOX* protoporphyrinogen oxidase, *PROTOgen* protoporphyrinogen, *PROTO* protoporphyrin

acid (ALA), porphobilinogen (PBG) and porphyrins, which bring about the clinical manifestations of the porphyrias. ALA is neurotoxic, whereas porphyrinogens cause photosensitivity.

The enzymatic defects can be inherited, with a variety of modes of inheritance. However, haem biosynthesis depends on interplay between both genetic and environmental factors. Therefore, patients with inherited enzymatic defects may never have any clinical disease manifestations.

Classification of Porphyrrias

Porphyrias can be classified according to the primary site of enzyme deficiency (i.e. hepatic or erythropoietic) or clinical features (i.e. acute vs chronic, and whether symptoms are neurovisceral vs cutaneous, or a mixture). If porphyria is suspected, determine if the symptoms are neurovisceral or cutaneous. Then biochemical analysis can help to identify which step in haem biosynthesis is abnormal. Subsequently, analysis of gene mutations allows confirmation of the diagnosis (Fig. 14.2). Following diagnosis, screening relatives at risk enables counselling for asymptomatic patients on the importance of avoiding triggers.

There are **four acute hepatic porphyrias (AHP)**: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP) and ALA dehydratase defi-

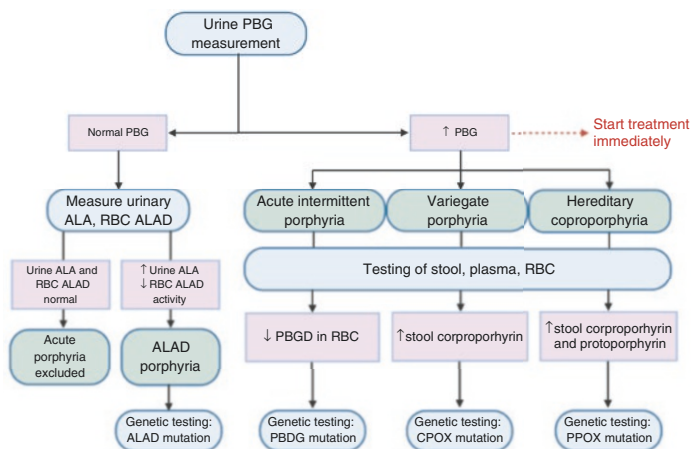


FIGURE 14.2 An algorithm for diagnosing acute porphyrias in patients with neurovisceral symptoms. Using a combination of urine, stool and blood testing for characteristic biochemical abnormalities, it is possible to determine the likely underlying porphyria. ALA δ -aminolevulinic acid, ALAD ALA dehydratase, CPOX coproporphyrinogen oxidase, PBDG porphobilinogen deaminase, PBG porphobilinogen, PPOX protoporphyrinogen oxidase, RBC red blood cell

ciency porphyria (ADP). AIP is the most common and severe of these. Symptoms include neurologic attacks, cramping abdominal pain, constipation, abdominal or bladder distension, nausea, vomiting, hypertension, headache, tremors, dysuria and muscle weakness. There are no cutaneous symptoms. Attacks are precipitated when ALAS1 activity is induced, for example, by alcohol, certain drugs, steroids, low calorie intake and stress. Approximately 3–5% of patients with AHP suffer from severe or recurrent acute attacks, associated with impaired quality of life. Long-term complications of AHP, especially AIP, include hepatocellular carcinoma, chronic pain and chronic renal failure.

Management of acute hepatic porphyrias involves avoiding known triggers and treating symptoms, for example, using analgesics for abdominal pain, and phenothiazines for nausea and vomiting. In mild attacks, intravenous glucose should be given. For patients who do not respond, or who have a moderate/severe attack, intravenous hemin therapy should be administered. In patients with frequent attacks, which are unresponsive to treatment, treatment options include off-label use of prophylactic haemin infusions and hormonal suppression therapy. Liver transplant can be considered as a last resort. The drug ‘Givosiran’ is an aminolevulinate synthase 1 (ALAS1)-directed small interfering RNA (siRNA) covalently linked to a ligand that enables targeted delivery to hepatocytes. It has recently been approved in the USA for the treatment of AIP, based on findings in a phase III (ENVISION) clinical trial [1]. In this trial, Givosiran treatment was associated with significantly reduced frequency of attacks in patients with AIP, although this was accompanied by an increased risk of hepatic and renal adverse events [1]. Other strategies are aimed at enhancing expression of the deficient protein; for example, through administration of porphobilinogen deaminase (PBGD) mRNA packaged into nanoparticles [2], or via adenovirus-mediated transfer of PBGD cDNA [3].

In the cutaneous porphyrias, excess porphyrins and porphyrinogens are deposited in the upper dermal capillary walls. Porphyria cutanea tarda (PCT) is a hepatic cutaneous

porphyria, characterised by cutaneous symptoms without neurological features. Patients develop vesicles on sun-exposed areas of the skin, with crusting, superficial scarring, hypertrichosis and hyperpigmentation. Whilst severe liver disease is unusual in PCT, mild abnormalities of liver function tests are common, with 50% of patients demonstrating raised serum transaminases [4]. Up to 90% of patients with PCT have mild-moderate iron overload with hepatic siderosis, and this is implicated in the disease pathogenesis [4]. Management of PCT includes avoidance of risk factors, such as sunlight, alcohol, oestrogens and iron supplements. Repeated venesection to reduce hepatic iron almost always achieves a good response. Oral iron chelating agents can be considered in patients with anaemia or those who do not tolerate venesection; however, their efficacy is inferior to venesection, and they are associated with hepatic and renal side effects. Alternatively, use of low-dose chloroquine can be used to promote porphyrin excretion (as high doses of chloroquine are hepatotoxic). This is of similar efficacy to venesection [5]; although more costly. There is a very rare condition called hepatoerythropoietic porphyria (HEP), also caused by a mutation in the UROD (uroporphyrinogen decarboxylase) gene. HEP does not typically respond to low-dose chloroquine or phlebotomy, and therefore the priority of management is photoprotection.

There are **three erythropoietic cutaneous porphyrias**: congenital erythropoietic porphyria (CEP), X-linked protoporphyria (XLP) and erythropoietic porphyria (EPP). These usually present with cutaneous photosensitivity in childhood. In CEP, patients develop bullae, vesicles, altered skin pigmentation and hypertrichosis. The increase in erythrocyte porphyrins causes haemolysis and splenomegaly. Regular blood transfusions to suppress erythropoiesis can reduce porphyrin accumulation, but are associated with iron overload. Patients should also be advised to avoid sunlight. XLP and EPP have similar clinical features, with severe pain, erythema and itching following exposure to sunlight. Vesicles and bullae are uncommon in these conditions, and haemolytic anaemia is

mild or absent. Because protoporphyrins are lipid soluble, they can be taken up by the liver and excreted in bile, with potential for causing hepatic parenchymal damage and biliary stones. In around 5% of patients, protoporphyrin accumulation causes severe liver disease, which may progress to cholestatic liver failure. Treatment includes avoiding sunlight. There is limited benefit with use of oral beta-carotene. In patients with liver disease, cholestyramine may promote faecal excretion, and plasmapheresis is sometimes helpful. In patients who have liver transplantation for EPP-mediated liver failure, overall survival is comparable to patients having liver transplant for other diseases. However, as the source of the excess protoporphyrins is the bone marrow rather than the liver, disease recurrence is common (69%), and the increased risk of post-operative biliary complications may cause graft damage. In such patients, bone marrow transplant should also be considered to reduce the incidence of graft loss.

Novel treatment strategies under investigation for erythropoietic porphyrias include the use of afamelanotide, an alpha-melanocyte stimulating hormone analogue, which is a melanin inducer. In phase III trials (NCT01605136), afamelanotide was associated with reduced photosensitivity, fewer phototoxic reactions and improved quality of life, although there was no change in protoporphyrin or hepatic enzyme levels. Pre-clinical studies are also investigating the potential of anti-sense oligonucleotides to restore normal activity of the hypomorphic FECH allele (IVS3-48C), which is implicated in >95% of cases of EPP [6].

Alpha-1-Antitrypsin Deficiency

Overview

Alpha-1-antitrypsin (A1AT) is a large glycoprotein produced mainly by hepatocytes. It is a serine protease inhibitor and is the predominant inhibitor of neutrophil elastase in the lungs.

A1AT is also an acute phase protein, and therefore levels are elevated in inflammatory states. A1AT deficiency is the most common genetic cause of metabolic liver disease in neonates and children [7]. It is caused by a mutation on the SERPINA1 gene (previously known as the Pi gene), which has been localised to chromosome 14q32. The abnormal A1AT undergoes spontaneous polymerisation and thus cannot be exported from hepatocytes. The resulting A1AT deficiency in the lungs causes proteolytic connective tissue damage, predisposing to early-onset panlobular emphysema. In the liver, accumulation of A1AT causes cell apoptosis, hepatic inflammation and cirrhosis.

Genetics and Epidemiology

A1AT deficiency is an autosomal recessive disorder with codominant expression. Whilst over 100 alleles have been identified, only some of these cause liver disease. Based on migration properties on isoelectric testing, the normal allele is identified M, which accounts for 95% of alleles. Common abnormal variants include S (with 50–60% protein activity) and Z (with 10–20% protein activity), which account for 2–3% and 1% of alleles, respectively. It is estimated that 1:10 individuals are carriers of the ‘S’ or the ‘Z’ variant. The ZZ genotype is associated with severe A1AT deficiency and occurs in 1:3500 births, being more common in Europeans and North Americans and very rare amongst Asian and Mexican Americans [7]. In mutations where there is absence of A1AT production, there is lung disease without associated liver disease.

Clinical Presentation

In patients with the ZZ genotype, there is a bimodal distribution in the clinical presentation, with one peak in infancy and another in adults aged in their 50s. In infancy, presentation is

usually with jaundice secondary to acute cholestasis or neonatal hepatitis. Around 10% of infants with A1AT deficiency develop neonatal hepatitis, but most make a clinical recovery.

When the rate of accumulation of abnormal folded protein in the hepatic endoplasmic reticulum exceeds the liver's capacity to degrade/remove it, this can trigger a series of reactions that ultimately result in the development of liver fibrosis, cirrhosis and HCC [8]. Only 2–3% of ZZ infants develop cirrhosis requiring transplantation in childhood [9].

Around one-third of adult patients with the ZZ genotype develop liver cirrhosis [10]. Risk factors for disease progression include male sex, age >50 years, viral hepatitis and diabetes. Unfortunately, adults often present late in the course of their disease, frequently due to a lack of symptoms or misdiagnosis [11]. Heterozygotes for A1AT deficiency are often asymptomatic, but heterozygosity can be a co-factor in development of chronic liver disease [12]. Indeed, retrospective studies have revealed that a large number of patients undergoing liver transplant for A1AT were in fact heterozygotes, who had a 'second hit' that accelerated progression to end-stage liver disease [13].

Diagnosis

Summarised in Box 14.1 are clinical features which should prompt suspicion of A1AT deficiency, as recommended by guidelines from the American Thoracic Society [14].

Abdominal examination may reveal signs of end-stage liver disease, and ultrasound can assess liver structure. Although changes in serum transaminases may be seen, the degree of liver injury is often out of proportion to the level of transaminitis. Diagnosis of A1AT deficiency can involve quantification of A1AT, phenotyping or genotyping. Initial testing usually involves measuring serum A1AT, using nephelometry. Serum A1AT concentration <10–20%

Box 14.1 Conditions in Which Alpha-1-Antitrypsin Deficiency Should Be Suspected [14]

- Early-onset emphysema (aged 45 years or less)
- Emphysema in the absence of a recognised risk factor (smoking, occupational dust exposure, etc.)
- Emphysema with prominent basilar hyperlucency
- Otherwise unexplained liver disease
- Necrotising panniculitis
- Antiproteinase-3 positive vasculitis
- Family history of: emphysema, bronchiectasis, liver disease or panniculitis
- Bronchiectasis without evident aetiology

of normal is suggestive of A1AT deficiency. Current methods of A1AT quantification tend to overestimate A1AT levels. Transiently higher levels A1AT levels are associated with systemic inflammation, because A1AT is an acute phase protein. In heterozygotes, A1AT levels may even be normal and therefore cannot be used to exclude A1AT deficiency. Phenotyping using isoelectric focusing migration patterns is the gold standard for diagnosis. However, results can be challenging to interpret, because of the variety of existing alleles. Genotyping can provide definitive diagnosis of known phenotypic variations. Liver biopsy is not necessary for diagnosis but the A1AT aggregates give rise to the hallmark findings of PAS-positive diastase resistant granules in patients with the Z alleles and some other alleles. Liver biopsy may be used for staging disease severity in establishing liver disease secondary to A1AT deficiency.

Treatment

Unfortunately, currently there is no specific treatment available for A1AT deficiency affecting the liver. In patients with

end-stage liver disease, liver transplantation can correct the underlying disorder as well as replacing the diseased liver. In children, A1AT deficiency is the leading metabolic cause for liver transplant, with 3 year survival rates of around 85% [15, 16]. In adults, A1AT deficiency represents only 1% of transplants performed, but 5-year graft and patient survival rates are excellent [17]. Although liver transplant recipients have normalisation of A1AT levels, it is unclear whether this can delay progression of lung disease.

According to American Thoracic Society guidelines, patients with A1AT related liver disease should have regular follow-up for assessment of symptoms, examination, liver function tests and ultrasound to screen for the presence of fibrosis or HCC [14]. Patients should be advised to avoid alcohol, eat a healthy diet, lose weight if necessary, avoid NSAIDs and get vaccinated against hepatitis. In the absence of liver disease, patients with A1AT deficiency should have regular blood tests to monitor liver function tests.

Supportive treatments for patients with lung disease secondary to A1AT deficiency include avoidance of smoking, use of bronchodilators, pulmonary rehabilitation, nutritional support, consideration of supplementation oxygen, vaccination against influenza and pneumococcus, and prompt treatment of exacerbations with steroids and antibiotics. Whilst IV ‘augmentation’ therapy with pooled human plasma has been shown to raise serum A1AT levels, there is less evidence that it causes a significant reduction in decline of FEV1 [18].

A number of novel treatment approaches are currently under investigation. Some approaches have focused on preventing accumulation of the abnormal A1AT. For example, current phase I and II trials are investigating the ability of siRNA to downregulate production of the Z mutant A1AT, and the use of adenoviral vectors to transfer normal A1AT to muscle cells. Other studies have focused on using chemicals, such as 4-phenylbutyric acid, to stabilise the abnormal A1AT to promote its excretion; although results from animal studies were promising, this failed to demonstrate efficacy in clinical

trials. A third approach is to enhance degradation of abnormal A1AT via autophagy. In this regard, carbamazepine has shown promise in a mouse model of hepatic fibrosis and is now in phase II clinical trials.

Cystic Fibrosis and Liver Disease

Overview

Cystic fibrosis is the most commonly occurring genetic disease in the Caucasian population. It is caused by abnormalities in the cystic fibrosis transmembrane regulator (CFTR) gene. This affects chloride and sodium transport across membranes, which results in difficulty in efflux of water, causing dehydrated secretions. Over 2000 mutations have been identified, but the delta F508 mutation is responsible in around two-thirds of cases.

Mild CFLD is common and usually asymptomatic. It is estimated that up to 45% of patients with CD have asymptomatic raised serum transaminases and up to 60% of patients have hepatic steatosis [19]. Around one-third of patients with cystic fibrosis develop clinically significant cystic fibrosis liver disease (CFLD). It has been estimated that 2–4% of patients with cystic fibrosis die from CFLD, making it the third most common cause of mortality in CF, after lung disease and complications of liver transplant [20]. The development of liver disease in cystic fibrosis is not related to the severity of cystic fibrosis or the underlying mutation, which suggests that other factors must influence risk. These include male sex, severe lung disease, Hispanic ethnicity, heterozygosity for the PiZ allele of alpha-1 antitrypsin, neonatal meconium ileus and pancreatic insufficiency [21, 22].

There is a range of clinical presentations of CFLD, including cholelithiasis, neonatal cholestasis, hepatitis, hepatic steatosis, hepatic fibrosis or cirrhosis with or without portal hypertension.

The most common manifestation is hepatic steatosis, occurring in approximately 67% of patients with cystic fibrosis, although the mechanism of this is not clearly understood [23]. Even in cases of widespread steatosis, features of steatohepatitis are normally absent. Neonatal cholestasis occurs in less than 10% of infants with CF, presenting with prolonged conjugated hyperbilirubinaemia. The clinical features tend to regress during the first few months of life, and this condition is not a predictor of cirrhosis in later life [19].

However, the most clinically significant manifestation of CFLD is biliary cirrhosis with portal hypertension. CFTR genes are expressed on epithelial cells lining the intrahepatic and extrahepatic bile ducts and the gallbladder. In cystic fibrosis, bile is more viscous and less alkaline. The dehydrated secretions can block bile ducts, predisposing to gallstones, infection and damage from toxins. This process also causes injury to cholangiocytes and hepatocytes, thus triggering periductal inflammation and fibrosis and eventually multilobular cirrhosis with portal hypertension. Patients with cirrhosis and portal hypertension usually present in childhood. In a large cohort of 561 patients with CFLD with cirrhosis and portal hypertension, the mean age of presentation was only 10 years of age, with 90% of patients presenting by 18 years [24]. Once patients develop liver failure, transplant is the only curative option. Non-cirrhotic portal hypertension is also recognised in CFLD. This is characterised by nodular hypoplasia and is associated with microscopic obliterative portal venopathy, although the detailed mechanisms of this condition are not completely understood [25]. Other biliary problems include development of gallstones in 12–24% of patients, which are relatively more common in adults. The majority of transplants performed for CFLD are in children. Approximately 25–30% of patients with CF have microgallbladder, which is defined as a gallbladder measuring <35 mm in the longest axis [19].

Investigations

In suspected CFLD, patients require examination for hepatosplenomegaly, abdominal ultrasound and measurement of liver enzymes. There may be asymmetrical hepatomegaly in CFLD due to the presence of focal regenerative nodules. Clinical signs of advanced liver disease, such as splenomegaly or caput medusae, are usually subtle or present at a very late stage of disease. Significant liver disease is considered if any liver enzyme is over 1.5 times the upper limit of normal on at least two occasions 6 months apart. However, changes in biochemical parameters have a low sensitivity and specificity for CFLD with cirrhosis. Thrombocytopaenia should be monitored closely as it may suggest splenic sequestration.

Ultrasound can demonstrate any hepatomegaly, steatosis, hepatic texture, splenomegaly and gallbladder problems. Combined with Doppler, ultrasound allows assessment of portal hypertension. Although a significantly abnormal ultrasound has a 84% positive predictive value for advanced CFLD, it is less useful for excluding CFLD when it is normal. Non-invasive liver elastography (Fibroscan) is useful for diagnosing CFLD and establishing its severity. MRI offers high quality images of the pancreatic and hepatobiliary structures and is less operator-dependent than ultrasound. If there is any doubt about the diagnosis, liver biopsy can help to assess whether the predominant problem is steatosis or biliary disease, the severity of the disease and response to treatment. It should also be used to confirm the presence of cirrhosis prior to liver transplant. However, it is important to consider that lesions in CFLD tend to be distributed non-uniformly across the liver; therefore, liver biopsy may underestimate disease severity.

Patients with established CFLD also require regular follow-up. This includes using annual examination for hepatosplenomegaly and biochemical assessment (liver enzymes, prothrombin time and platelet count) and abdominal US. Due to the presence of regenerative nodules, hepatomegaly in CFLD may be asymmetric.

Treatment

In terms of general supportive measures, for patients with CFLD it is important to optimise nutrition. Patients with CFLD may require higher doses of fat-soluble vitamins than those without, due to abnormalities in bile acid quantity/function in the intestine. Patients should be advised to be vaccinated against hepatitis A and B and to avoid alcohol and medications with hepatotoxic effects.

Patients with abnormal ultrasound findings or persistently deranged LFTs are commenced on ursodeoxycholic acid (UDCA) at 20 mg/kg/day in two or three divided doses. This is a hydrophilic bile acid, which stimulates bile flow and displaces toxic hydrophobic bile acids. The main side effect of UDCA is diarrhoea, which usually responds to dose reduction. Its use is controversial, whilst some studies suggest that it improves biochemical parameters, there is little evidence that it influences the likelihood of needing a liver transplant.

CF patients with portal hypertension should have endoscopic screening for the presence of oesophageal varices and band ligation considered if needed. Beta-blockers should not be given in adults with varices, due to their potential to cause bronchoconstriction.

In patients with end-stage liver disease liver transplant can be considered. The 5-year survival rate for children and adults is 85.8% and 72.7%, respectively [26]. Compared with patients having liver transplant for other reasons, patients with CFLD have a lower post-operative survival. This may be because CF patients are more likely to have poor nutrition status and concomitant lung disease. The prognosis of combined lung and liver transplant is poor, with a 5 year survival of only 49% [27].

Recently, the drug 'Kaftrio' has recently been licensed in the UK for treatment of patients with cystic fibrosis. It is indicated in patients who are aged 12 and over, and homozygotes for the delta F508 mutation, or heterozygotes for F508 with a minimal function mutation. In these groups of patients, phase III clinical trials showed improvements in lung function (FEV1) of 10% and 14%, respectively [28, 29]. Kaftrio is a

combination of ivacaftor, tezacaftor and elexacaftor and should be taken together with another medicine containing ivacaftor alone. Elexacaftor and tezacaftor work to increase the number of CFTR proteins on the cell surface, whilst Ivacaftor enhances the activity of the defective CFTR protein.

Abnormalities in liver function tests, particularly serum transaminases, are common during Kaftrio treatment. Therefore, patients need regular monitoring of liver function tests. Kaftrio can be used in patients with mild hepatic impairment (Child's Pugh A). In patients with severe hepatic impairment (Child's Pugh C), Kaftrio should be avoided. In patients with moderate hepatic impairment (Child's Pugh B), Kaftrio should only be used if there is a clear medical need, and the expected benefit outweighs the risks.

Answers to Case Study Questions

1. Alpha-1-antitrypsin deficiency, with liver failure
2. Serum phenotyping and genotyping
3. The use of purified human alpha antitrypsin for treatment of pulmonary disease associated with alpha-1-antitrypsin deficiency

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