ABC of diseases of liver, pancreas, and biliary system
Other causes of parenchymal liver disease

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Autoimmune hepatitis

Autoimmune hepatitis is a relatively uncommon disease that mainly affects young women. The usual presentation is with fatigue, pain in the right upper quadrant of the abdomen, and polymyalgia or arthralgia associated with abnormal results of liver function tests. Other autoimmune diseases are present in 17% of patients with classic autoimmune hepatitis, predominantly thyroid disease, rheumatoid arthritis, and ulcerative colitis.

Autoimmune hepatitis is an important diagnosis as immunosuppressive drugs (prednisolone and azathioprine) produce lasting remission and an excellent prognosis. Although the condition can produce transient jaundice that seems to resolve totally, the process can continue at a subclinical level producing cirrhosis and irreversible liver failure. The diagnosis is based on detection of autoantibodies (antinuclear antibodies (60% positive), antismooth muscle antibodies (70%)) and high titres of immunoglobulins (present in almost all patients, usually IgG).

About 40% of patients with autoimmune hepatitis present acutely with jaundice

Metabolic causes of liver disease

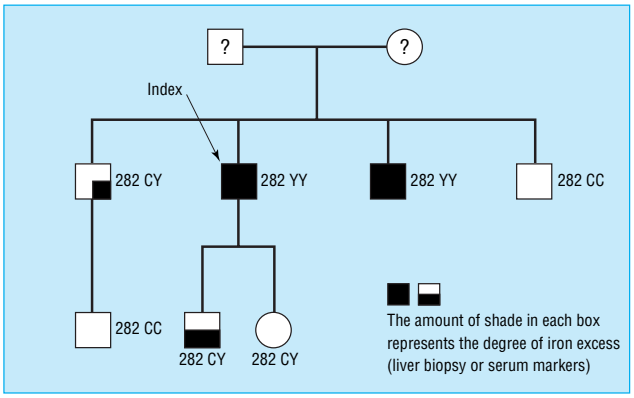
Metabolic liver disease rarely presents as jaundice, and when it does the patient probably has end stage chronic liver disease.

Haemochromatosis

Haemochromatosis is the commonest inherited liver disease in the United Kingdom. It affects about 1 in 200 of the population and is 10 times more common than cystic fibrosis.

Haemochromatosis produces iron overload, and patients usually present with cirrhosis or diabetes due to excessive iron deposits in the liver or pancreas. The genetic defect responsible is a single base change at a locus of the HFE gene on chromosome 6, with this defect responsible for over 90% of cases in the United Kingdom. Genetic analysis is now available both for confirming the diagnosis and screening family members. The disease typically affects middle aged men. Menstruation and pregnancy probably account for the lower presentation in women.

Patients who are homozygous for the mutation should have regular venesection to prevent further tissue damage. Heterozygotes are asymptomatic and do not require treatment. Cardiac function is often improved by venesection but diabetes, arthritis, and hepatic fibrosis do not improve. This emphasises the need for early recognition and treatment.



Use of genetic analysis to screen family members for haemochromatosis. The index case was a 45 year old man who presented with cirrhosis. His brothers were asymptomatic and had no clinical abnormalities. However, the brother who had inherited two abnormal genes (282YY) was found to have extensive iron loading on liver biopsy

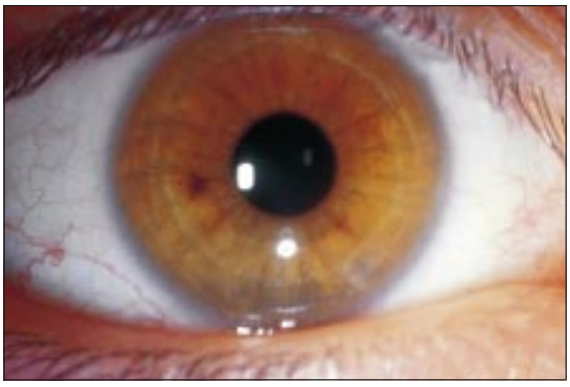
Presenting conditions in haemochromatosis

- Cirrhosis (70%)
- Diabetes (adult onset) (55%)
- Cardiac failure (20%)
- Arthropathy (45%)
- Skin pigmentation (80%)
- Sexual dysfunction (50%)

Wilson's disease

Wilson's disease is a rare autosomal recessive cause of liver disease due to excessive deposition of copper within hepatocytes. Abnormal copper deposition also occurs in the basal ganglia and eyes. The defect lies in a decrease in production of the copper carrying enzyme ferroxidase. Unlike most other causes of liver disease, it is treatable and the prognosis is excellent provided that it is diagnosed before irreversible damage has occurred.

Patients may have a family history of liver or neurological disease and a greenish-brown corneal deposit of copper (a Kayser-Fleischer ring), which is often discernible only with a slit lamp. Most patients have a low caeruloplasmin level and low



Kayser-Fleischer ring in patient with Wilson's disease

serum copper and high urinary copper concentrations. Liver biopsy confirms excessive deposition of copper.

Treatment is with penicillamine, which binds copper and increases urinary excretion. Patients who are unable to tolerate penicillamine are treated with trientene and oral zinc acetate. Asymptomatic siblings should be screened and treated in the same way.

Wilson's disease should be suspected in any patient presenting with chronic hepatitis or cirrhosis under the age of 35

Drug related hepatitis

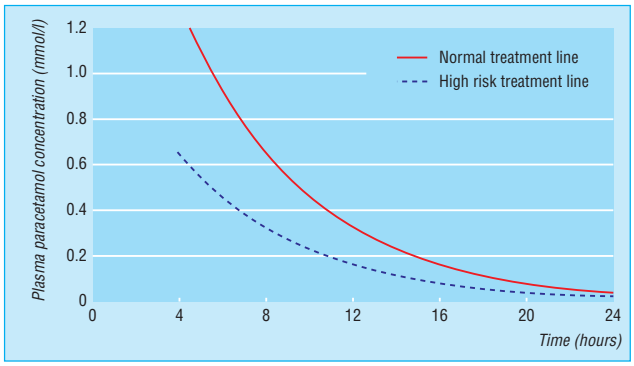
Most drugs can cause liver injury. It is relatively uncommon for drug reactions to present as acute jaundice, and only 2-7% of hospital admissions for non-obstructive jaundice are drug related. Different drugs cause liver injury by a variety of mechanisms and with differing clinical patterns. In general terms, drug related jaundice can be due to predictable direct hepatotoxicity, such as is seen in paracetamol overdose, or idiosyncratic drug reactions.

Paracetamol poisoning

Paracetamol is usually metabolised by a saturable enzyme pathway. When the drug is taken in overdose, another metabolic system is used that produces a toxic metabolite that causes acute liver injury. Hepatotoxicity is common in paracetamol overdose, and prompt recognition and treatment is required. The lowest recorded fatal dose of paracetamol is 11 g, but genetic factors mean that most people would have to take considerably higher doses to develop fulminant liver failure.

Overdose with paracetamol is treated by acetylcysteine, which provides glutathione for detoxification of the toxic metabolites of paracetamol. This is generally a preventive measure, and decision to treat is based on the serum concentrations of paracetamol. It is important to be certain of the time that paracetamol was taken in order to interpret the treatment nomogram accurately. If there is doubt over the timing of ingestion treatment should be given.

Paracetamol poisoning is by far the commonest cause of fulminant liver failure in the United Kingdom and is an accepted indication for liver transplantation. As this is an acute liver injury, patients who survive without the need for transplantation will always regain normal liver function.



Thresholds for treatment of paracetamol poisoning in normal and high risk patients. Adapted from *British National Formulary*

Idiosyncratic drug reactions

The idiosyncratic drug reactions are by their nature unpredictable. They can occur at any time during treatment and may still have an effect over a year after stopping the drug. The management of acute drug reactions is primarily stopping the potential causative agent, and if possible all drugs should be withheld until the diagnosis is definite. Idiosyncratic drug reactions can be severe, and they are an important cause of fulminant liver failure, accounting for between 15% and 20% of such cases. Any patient presenting with a severe drug reaction will require careful monitoring as recovery can be considerably delayed, particularly with drugs such as amiodarone, which has a long half life in blood.

The drug history must also include non-prescribed medications. Fulminant liver failure is well described in patients who have taken Chinese herbal medicine.

Common drugs producing hepatic idiosyncratic reactions

- Sodium valproate
- Non-steroidal anti-inflammatory drugs (diclofenac)
- Amiodarone
- Aspirin
- Methyldopa
- Isoniazid
- Minocycline

Complementary medicines may account for as much as 5% of all drug induced liver disease

Cholestatic non-obstructive jaundice

Initial investigation of patients with jaundice and a cholestatic pattern on liver function tests is by ultrasonography. This will detect dilatation of the bile duct in most cases of extrahepatic biliary obstruction caused by tumour or stones and will also detect most metastatic liver tumours, the other main cause of

Common drugs producing cholestatic reactions

- Chlorpromazine
- Oestrogens (hormone replacement therapy or contraceptive pill)
- Co-amoxiclav or flucloxacillin
- Chlorpropamide

cholestatic malignant jaundice. Dilatation of the biliary tree may not always be present in early biliary obstruction, and if doubt exists, either repeat ultrasonography or endoscopic retrograde cholangiopancreatography is advisable. Particular attention is required in patients with no apparent drug cause for their jaundice and in whom serological tests for other causes of cholestasis give negative results.

Primary biliary cirrhosis

Primary biliary cirrhosis is relatively common and mainly affects middle aged women. It typically presents as cholestatic jaundice, but with more widespread use of liver enzyme tests it is increasingly found at a presymptomatic stage because of raised alkaline phosphatase and γ-glutamyltransferase activities during investigation of associated symptoms such as pruritus. When patients present with jaundice, it is usually associated with cutaneous signs of chronic liver disease, xanthoma, and other extrahepatic features such as Sjögren's syndrome.

Primary biliary cirrhosis is immunologically mediated, and the presence of M2 antimitochondrial antibodies is diagnostic. Immunoglobulin titres, particularly IgM, are often raised. Liver biopsy is used to stage the disease rather than to confirm the diagnosis. Treatment with ursodeoxycholic acid has been shown to slow disease progression. Patients with advanced liver disease require liver transplantation.

Primary sclerosing cholangitis

Sclerosing cholangitis is characterised by progressive fibrosing inflammation of the bile ducts. The changes are often diffuse, but symptoms usually arise from dominant strictures at the hilum or within the extrahepatic bile ducts. Primary sclerosing cholangitis usually occurs in men younger than 50 years old and is associated with inflammatory bowel disease in 70-80% of cases. The incidence of primary sclerosing cholangitis in patients with ulcerative colitis is 2-10%. Cholangiocarcinoma develops in 20% to 30% of patients with primary sclerosing cholangitis and is an important cause of death in patients with ulcerative colitis.

Sclerosing cholangitis may be asymptomatic but usually presents with fluctuating jaundice, nausea, and pruritus. The diagnosis is suggested by cholangiography (endoscopic retrograde cholangiopancreatography, percutaneous transhepatic cholangiography, or magnetic resonance cholangiopancreatography). Multiple strictures with beading of ducts, duct pruning (scanty ducts), irregularities of the duct wall, and diverticula are typical features. Liver biopsy is a supplementary investigation that shows characteristic histological features in 30-40% of patients. Raised serum titres of smooth muscle antibody (70% of patients) and perinuclear antineutrophil cytoplasmic antibody (60%) may help diagnosis. Raised concentrations of serum CA19-9 tumour marker are highly suspicious of cholangiocarcinoma.

Treatment of primary sclerosing cholangitis is at present limited to the management of recurrent cholangitis. Treatment with ursodeoxycholic acid (7 mg/kg/day) may improve symptoms and liver function, but no strong evidence exists for its effectiveness. Dominant strictures may be improved with endoscopic dilatation or surgical resection. Liver transplantation is required for patients with deteriorating liver function with progressive secondary biliary cirrhosis.

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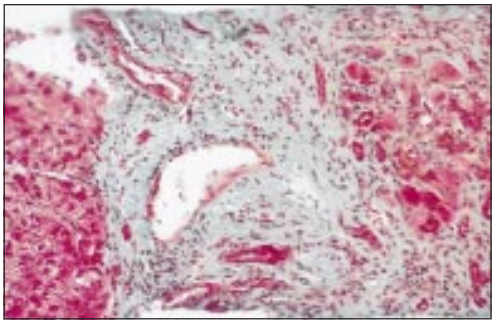
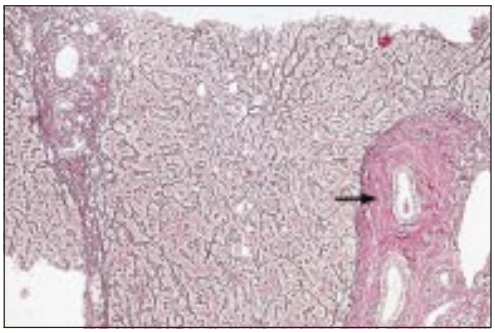
The ABC of diseases of liver, pancreas, and biliary system is edited by I J Beckingham, consultant hepatobiliary and laparoscopic surgeon, department of surgery, Queen's Medical Centre, Nottingham (Ian.Beckingham@nottingham.ac.uk). The series will be published as a book later this year.



Broad fibrosis band in patient with primary biliary cirrhosis

Endoscopic retrograde cholangiopancreatogram in patient with primary sclerosing cholangitis showing irregular stricturing and dilatation of intrahepatic bile ducts



Liver biopsy specimen of patient with primary sclerosing cholangitis. Characteristic "onion skin" fibrosis is visible round portal tracts

Summary points

- Most drugs have potential to cause liver injury, and 2-7% of admissions with non-obstructive jaundice are for drug related hepatitis
- Herbal remedies and illegal drugs can also cause jaundice and liver damage
- Primary biliary cirrhosis typically presents as cholestatic jaundice in middle aged women
- Primary sclerosing cholangitis is associated with ulcerative colitis in 75% of cases, although the two may develop at different times
- Haemochromatosis is the commonest inherited liver disease in the United Kingdom, and a gene probe for clinical testing is now available

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