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Early treatment can arrest or reverse cirrhosis

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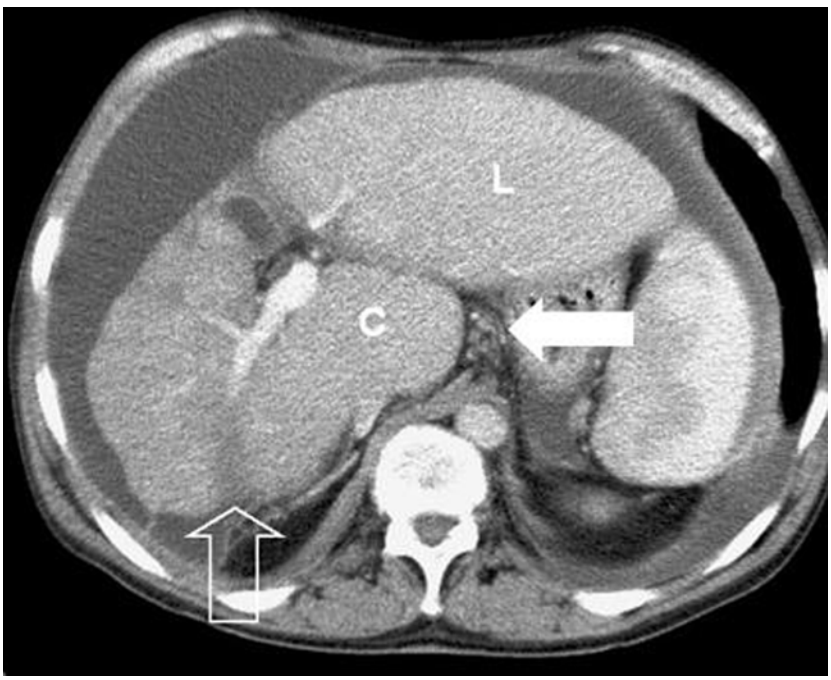

FIGURE 1
Advanced cirrhosis. CT scan with a portal venous-phase image showing a markedly enlarged left lobe (L) and caudate (C), with an area of focal fibrosis and atrophy of the posterior right lobe, deforming contour (open arrow). Incidental note of prominent collaterals in lesser curvature region (white arrow)

What are the presenting symptoms?

How should patients be assessed?

How should patients be followed up?

LIVER DISEASE CAUSES 2 MILLION DEATHS PER YEAR WORLDWIDE WITH INCIDENCE PREDICTED to double in the UK within 20 years.[1] Around 60,000 people in the UK are estimated to have cirrhosis.

In contrast to other common diseases in the UK, mortality rates have increased 400% since 1970 and cirrhosis is now the third most common cause of premature death.[2] Indeed, liver disease is predicted to overtake ischaemic heart disease in the next two years as the leading cause of working life years lost in the UK.[2]

Alcohol remains the primary driver for the vast majority of cirrhosis-related hospital admissions with a median age of presentation in the early 50s.[3] However, obesity is rapidly rising and non-alcoholic steatohepatitis (NASH) will also drive the increasing liver disease mortality.[2]

All patients with cirrhosis should undergo thorough investigation to exclude treatable causes (e.g. Wilson's disease or autoimmune hepatitis). Causes of cirrhosis are listed in table 1, p12.

Cirrhosis represents the final common pathway for liver disease and is characterised by progressive fibrosis of the liver parenchyma, which leads to portal hypertension and deterioration of liver function, see figure 1, above.

'Cirrhosis is now the third most common cause of premature death'

Decompensation represents a watershed moment for patients with cirrhosis, with the median survival falling from > 12 years for compensated cirrhosis to around two years, which is a far worse prognosis than for many cancers.[4] Decompensated cirrhosis is defined as an acute deterioration in liver function in a patient with cirrhosis and is characterised by jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome or variceal haemorrhage.

PRESENTATION

Patients may be asymptomatic or experience nonspecific symptoms, particularly weakness, anorexia and fatigue. Therefore, a high index of suspicion is important when monitoring patients known to have non-cirrhotic liver disease or those with significant risk factors e.g. drinking at a harmful level or alcohol dependency.

Specific symptoms include:

- Right hypochondrial pain from liver distension
- Abdominal distension caused by ascites
- Ankle swelling due to fluid retention
- Haematemesis and melaena from gastrointestinal haemorrhage. In patients with liver cirrhosis, variceal haemorrhage is the most common source of acute upper gastrointestinal bleeding. It is a serious complication of portal hypertension, and an important cause of morbidity and mortality in these patients. Bleeding from portal hypertensive gastropathy and other lesions seen in the general population such as gastric ulcers may also occur
- Pruritus due to cholestasis – often an early symptom of primary biliary cholangitis
- Gynaecomastia, loss of libido and amenorrhoea resulting from endocrine dysfunction
- Confusion and drowsiness resulting from neuropsychiatric complications (portosystemic encephalopathy)
- Recurrent nosebleeds in those with portal hypertension

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EXAMINATION AND ASSESSMENT

Physical examination is often normal. However, there are a number of clinical signs that may be present, as discussed below.

The skin

The chest and upper body may show spider naevi. These are telangiectases that consist of a central arteriole with radiating small vessels (resembling a spider's legs). They are found in the distribution of the superior vena cava and more than five are a strong pointer to cirrhosis. They may also occur in pregnancy.

In haemochromatosis the skin may have a slate grey appearance. The hands may show palmar erythema, indicative of a hyperdynamic circulation. Palmar erythema is also seen in pregnancy, thyrotoxicosis and rheumatoid arthritis.

Clubbing occasionally occurs, and a Dupuytren's contracture is often seen in alcoholic cirrhosis, though the association is with alcohol consumption rather than liver disease itself.

Xanthomas (cholesterol deposits) are seen in the palmar creases or above the eyes in primary biliary cholangitis.

Jaundice (icterus) is detectable clinically when the serum bilirubin is > 50 μmol/L.

The abdomen

Initial hepatomegaly will be followed by a small liver in well established cirrhosis.

Table 1

Causes of cirrhosis

Common causes
- Alcohol
- Hepatitis B ± D
- Hepatitis C
- Non-alcoholic fatty liver disease (NAFLD)

Other causes
- Primary biliary cholangitis
- Secondary biliary cirrhosis
- Autoimmune hepatitis
- Hereditary haemochromatosis
- Hepatic venous congestion
- Budd-Chiari syndrome
- Wilson's disease
- Drugs (e.g. methotrexate)
- Alpha-1 antitrypsin deficiency
- Cystic fibrosis
- Galactosaemia
- Glycogen storage disease
- Veno-occlusive disease
- Idiopathic (cryptogenic)

Splenomegaly occurs with portal hypertension. Ascites and peripheral oedema occur in very advanced cirrhosis, sadly many patients will present for the first time in this manner.

The endocrine system

Gynaecomastia, occasionally unilateral, and testicular atrophy may be found in males. It probably relates to altered oestrogen metabolism, often combined with spironolactone treatment.

As patients with cirrhosis are often asymptomatic, many will first be identified as having liver disease following liver blood test abnormalities. In particular, an AST:ALT ratio > 1 and low platelet count are suggestive of cirrhosis in the context of confirmed or strongly suspected liver disease,[5] although these can occur in alcohol misuse without cirrhosis.

Furthermore, cirrhosis may be detected following imaging of the abdomen for another reason such as pain or gastrointestinal symptoms.

DIAGNOSIS

Investigations aim to assess the severity and type of liver disease.

Assessing disease severity

Liver function: Serum albumin and INR are the best indicators of liver function; the outlook is poor if serum albumin is < 28 g/L. The degree to which the INR is prolonged correlates with disease severity.

Liver biochemistry: This may be normal, depending on the severity of cirrhosis. In most cases, there is a slight elevation in the serum ALP and aminotransferases. In decompensated cirrhosis, all biochemistry indices are deranged.

Serum electrolytes: A low sodium level in the presence of cirrhosis and ascites indicates severe liver disease due to a defect in free water clearance or excess diuretic therapy. Coexistent renal dysfunction e.g. creatinine > 130 μmol/L is a marker of poor prognosis.

Biomarkers: The enhanced liver fibrosis (ELF) test score is derived from quantitative serum concentration

Table 2

Useful blood and urine tests in the investigation of liver cirrhosis

Test	Disease
Antimitochondrial antibody	Primary biliary cholangitis
Antinuclear, smooth muscle (actin), liver/kidney microsomal antibody	Autoimmune hepatitis
Raised serum immunoglobulins:	
● IgG	Autoimmune hepatitis
● IgG4	Autoimmune hepatitis/cholangiopathy and pancreatitis
● IgM	Primary biliary cholangitis
Viral markers	Hepatitis A, B and C
Alpha-fetoprotein	Hepatocellular carcinoma
Serum iron, transferrin saturation, serum ferritin	Hereditary haemochromatosis
Serum and urinary copper, serum caeruloplasmin	Wilson's disease
Alpha-1 antitrypsin	Alpha-1 antitrypsin deficiency
Antinuclear cytoplasmic antibodies (ANCA)	Primary sclerosing cholangitis
Enhanced liver fibrosis test (ELF) – serological marker of liver fibrosis	All
Genetic analyses	HFE gene (hereditary haemochromatosis) Alpha-1 antitrypsin deficiency

key points

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Liver disease causes 2 million deaths per year worldwide with incidence predicted to double in the UK within 20 years. Around 60,000 people in the UK are estimated to have cirrhosis. In contrast to other common diseases in the UK, mortality rates have increased 400% since 1970 and cirrhosis is now the third most common cause of premature death. Liver disease is predicted to overtake ischaemic heart disease in the next two years as the leading cause of working life years lost in the UK.

Cirrhosis represents the final common pathway for liver disease and is characterised by progressive fibrosis of the liver parenchyma, which leads to portal hypertension and deterioration of liver function. Decompensation represents a watershed moment for patients with cirrhosis, with the median survival falling from > 12 years for compensated cirrhosis to approximately two years. Decompensated cirrhosis is defined as an acute deterioration in liver function in a patient with cirrhosis and is characterised by jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome or variceal haemorrhage.

Ascites is the most common complication of cirrhosis or a decompensation event, with 5-10% of uncomplicated (compensated) liver cirrhosis patients per year developing this. Other common complications include variceal bleeding, jaundice, alcoholic hepatitis, hepatic encephalopathy and sepsis and require urgent hospital admission. Development of any of these complications significantly worsens prognosis and these patients require referral for assessment for liver transplantation.

Aspirin and NSAIDs, which may precipitate gastrointestinal bleeding or renal impairment, should be avoided. Patients should undergo six-monthly ultrasound to screen for the early development of primary hepatocellular carcinoma, as all therapeutic strategies work best with small, single tumours. Patients should also undergo an initial upper gastrointestinal endoscopy to screen for varices.

Patients with compensated cirrhosis should be encouraged to lead a normal life. Many will be able to work normally and have an excellent quality of life and should not feel restricted in terms of activity or travel. Decompensated cirrhosis is associated with a very poor quality of life, recurrent hospital admissions, high mortality and high cost. Currently palliative care is used infrequently in these patients and this is an area of increasing need. Potential barriers to increased uptake include the possibility of a liver transplant and the challenges of accurate prognostication. However, a liver transplant, although life-saving, is only actually appropriate in a small number of patients.

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measurements of three fibrosis markers, tissue inhibitor of metalloproteinase 1 (TIMP-1), amino terminal peptide of type III procollagen (PIIINP) and hyaluronic acid (HA), see box 1, right.[6]

The score shows a good correlation with fibrosis stages in chronic liver disease with values < 7.7 indicating none to mild, 7.7- < 9.8 moderate, and ≥ 9.8 severe. NICE suggests that the ELF test should be considered in people who have been diagnosed with non-alcoholic fatty liver disease (NAFLD) to test for advanced liver fibrosis. Routine liver blood tests should not be used to assess these patients for advanced liver fibrosis. An ELF score ≥ 10.51 indicates advanced liver fibrosis in the presence of NAFLD. Retesting can be offered every three years.[7]

Box 1

Enhanced liver fibrosis (ELF) panel [6]

ELF score calculation

ELF = 2.494 + 0.846 ln([HA]) + 0.735 ln([PIIINP]) + 0.391 ln([TIMP-1])

Cut-off values
< 7.7 = No fibrosis to mild fibrosis
7.7 to < 9.8 = Moderate fibrosis
≥ 9.8 = Severe fibrosis

*NB: In patients with NAFLD NICE guidelines suggest using a cutoff of 10.51 for further investigation of cirrhosis[13]

HA = hyaluronic acid PIIINP = procollagen III amino terminal peptide
TIMP-1 = tissue inhibitor of metalloproteinase 1

Further assessment
Blood and urine tests that may help determine the underlying cause of liver cirrhosis are listed in table 2, opposite.

Imaging is key in diagnostic assessment. Ultrasound can demonstrate changes in the size and the shape of the liver. In established cirrhosis, there may be marginal nodularity of the liver surface and distortion of the arterial vascular architecture. Splenomegaly (spleen > 12 cm) occurs with portal hypertension.

Transient elastography is increasingly used. This radiological test quantifies liver compliance or stiffness using a probe that produces a shear ultrasound wave that passes through the liver.

The velocity of the wave moving through liver tissue acts as a proxy for fibrotic change. A measurement > 7 kPa is indicative of significant fibrosis (METAVIR grade F2-F4) and > 11-14 kPa is consistent with cirrhosis.

Technical limitations preclude its use in patients with ascites or morbid obesity, but it is suitable for most patients.

Arterial phase contrast-enhanced scans are useful for detecting primary hepatocellular carcinoma. Magnetic resonance (MR) angiography can demonstrate the vascular anatomy, and MR cholangiography the biliary tree.

Endoscopy detects and can treat gastro-oesophageal varices and portal hypertensive gastropathy.

Liver biopsy remains the gold standard for confirming the type and severity of liver disease.

POTENTIAL COMPLICATIONS

Ascites is the most common complication of cirrhosis or a decompensation event, with 5-10% of patients with uncomplicated (compensated) liver cirrhosis developing this each year.[4]

Other common complications include variceal bleeding, jaundice, alcoholic hepatitis, hepatic encephalopathy and sepsis and require urgent hospital admission. Development of any of these complications significantly worsens prognosis and these patients require referral for assessment for liver transplantation.

MANAGEMENT

Treatment of the underlying cause, especially chronic hepatitis C virus (HCV), may arrest or reverse cirrhosis. In particular, identification of the major risk factors associated with liver disease, alcohol misuse, obesity and a history of intravenous drug abuse is very important as it can lead to early diagnosis of liver disease and prevent the development of cirrhosis.

In the absence of any specific therapies that directly target fibrosis, early diagnosis and modification of associated risk factors remains the most effective treatment for the majority of people with liver disease.

The highly effective oral antiviral regimens against HCV have led to campaigns to identify and treat all patients with HCV.[8] The WHO has set targets for reducing the prevalence of HCV by 80% and HCV related mortality by 65% by 2030. NHS England aims to achieve the WHO goals by 2025.

It is never too late to abstain from alcohol as even following hospital admission with alcoholic hepatitis or ascites, patients who stop drinking alcohol may return to a good quality »

of life. NICE recommends psychosocial support for all patients seeking abstinence and undergoing alcohol withdrawal.[9]

Pharmacotherapies such as disulfiram, naltrexone and acamprosate have been approved to reduce alcohol intake, promote abstinence and prevent relapse in alcohol dependent patients. However, these drugs have not been tested in patients with advanced liver disease and are therefore contraindicated in severe hepatic failure. To date, baclofen represents the only anti-craving medication formally tested in randomised clinical trials in alcoholic patients affected by liver cirrhosis as it is principally metabolised by the kidneys. Results from these small trials have been conflicting. It is not licensed for this indication and additional studies are needed.

Vitamin B_1 supplementation is required to prevent development of Wernicke-Korsakoff's syndrome.

Weight loss may improve established NASH cirrhosis and the associated cardiovascular complications.

'Weight loss may improve NASH cirrhosis and associated cardiovascular complications'

The farnesoid X receptor agonist obeticholic acid significantly improved fibrosis in NASH patients with stage F2-F3 fibrosis in a planned month-18 interim analysis of a multicentre, randomised, double-blind phase III trial. Just over 300 patients were randomised to each arm.

The fibrosis improvement primary endpoint (≥1 stage with no worsening of NASH) was met by 12% of patients in the placebo group, 18% of patients receiving obeticholic acid 10 mg ($P = 0.045$) and 23% of patients receiving obeticholic acid 25 mg ($P = 0.0002$). An alternative primary endpoint of NASH resolution with no worsening of fibrosis was not met. The study is ongoing to assess clinical outcomes.[10]

Antifibrotic therapies are awaited but currently liver transplantation is the only available treatment for liver failure.

The aldosterone antagonist spironolactone is used to treat ascites with response rates of around 60%.[11] The loop diuretic furosemide is added if response is poor but has several potential disadvantages, including hyponatraemia, hypokalaemia and volume depletion.

Treatment with the beta-blockers carvedilol or propranolol is used for primary or secondary prophylaxis for variceal bleeding. Lactulose is given to prevent hepatic encephalopathy and rifaximin added if a patient has required hospitalisation for this.

FOLLOW-UP

Overall, the prognosis for cirrhosis is extremely variable, depending on the stage at which diagnosis is made. The median five-year survival rate is approximately 50%.[4]

Those at risk should receive hepatitis A and B vaccination and all patients should receive seasonal influenza vaccination.[12] The only dietary restriction is to reduce salt intake (≤ 2 g sodium per day). Aspirin and NSAIDs, which may precipitate gastrointestinal bleeding or renal impairment, should be avoided.

Patients should undergo six-monthly ultrasound to screen for the early development of primary hepatocellular carcinoma, as all therapeutic strategies work best with small, single tumours. Patients should also undergo an initial upper gastrointestinal endoscopy to screen for varices.[13]

'Patients should undergo ultrasound to screen for primary hepatocellular carcinoma every six months'

Importantly patients with compensated cirrhosis should be encouraged to lead a normal life. Many will be able to work normally and have an excellent quality of life and should not feel restricted in terms of physical or mental activity or travel.

Decompensated cirrhosis is associated with a very poor quality of life, recurrent hospital admissions, high mortality and high cost. Currently palliative care is used infrequently in these patients and this is an area of increasing need. Potential barriers to increased uptake include the possibility of a liver transplant and the challenges of accurate prognostication. However, a liver transplant, although life-saving, is only actually appropriate in a small number of patients. There are few prospective studies that describe the impact of palliative care in liver disease and these are small and not randomised. However, studies of palliative care in cancer demonstrate that prospective, randomised trials of palliative care can be performed. It is hoped that these can be replicated in advanced liver cirrhosis.

Competing interests: None

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Useful information

British Liver Trust
https://britishlivertrust.org.uk

PSC Support
For patients with primary sclerosing cholangitis
www.pscsupport.org.uk

The Hepatitis C Trust
www.hepctrust.org.uk