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Improving the identification and monitoring of cirrhosis

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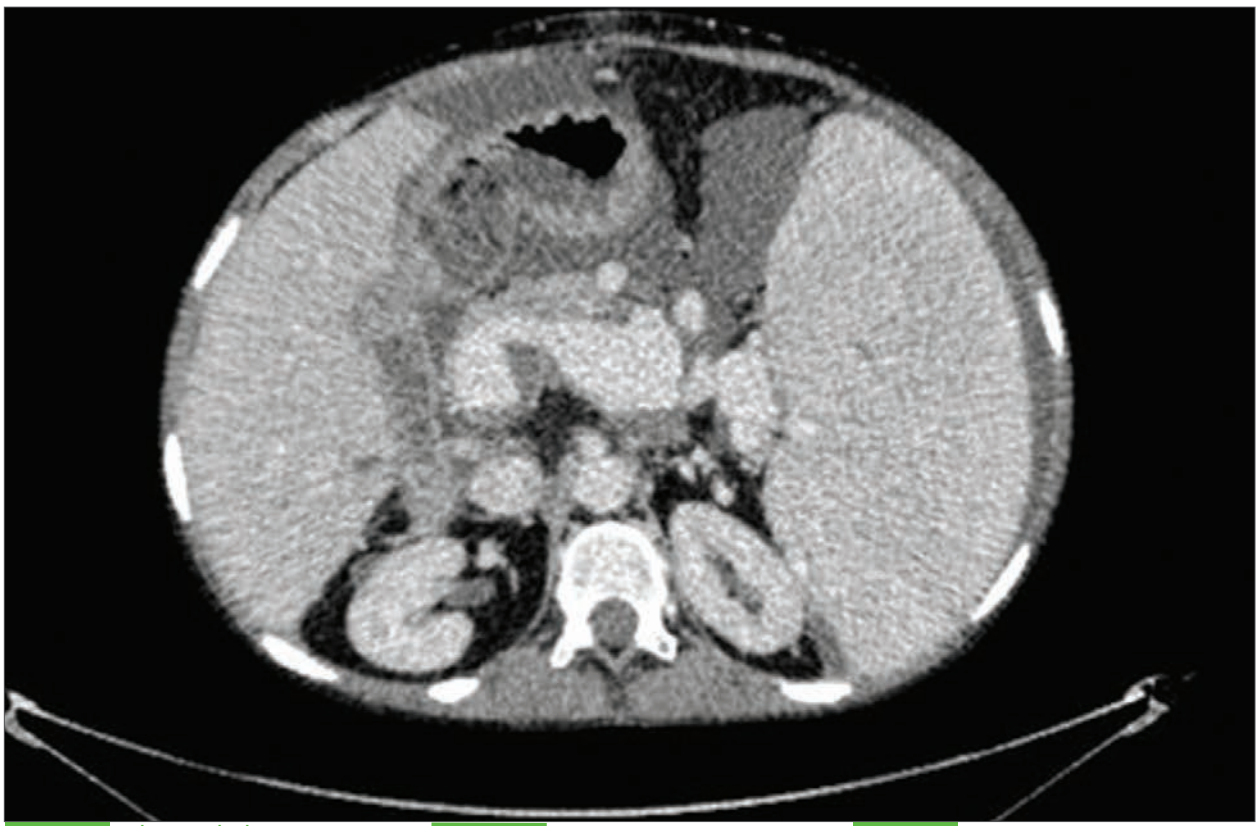
Improving the identification and monitoring of cirrhosis

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CT scan showing decompensated liver disease with portal hypertension and ascites

How should cirrhosis be diagnosed?

BOTH THE MORBIDITY AND MORTALITY ASSOCIATED WITH CIRRHOSIS ARE ON THE INCREASE.

In a recent UK cohort study the incidence of cirrhosis increased by 50.6% between 1998 and 2009. By 2009 the authors estimated there to be approximately 17,000 new cases per year with a disease burden greater than the fifth leading cause of cancer. Although all causes of liver disease increased during this period, this trend was primarily attributed to rising levels of alcohol misuse and obesity.[1]

By 2012, cirrhotic patients admitted to hospital were six times more likely to die compared with patients admitted for any other reason. Nearly half of liver disease admissions were for alcohol-related liver disease and were associated with a 12.3% mortality.[2]

What are the potential complications?

Cirrhosis is more common in urban and socially deprived areas.[3] The NHS Atlas of Variation in Healthcare for People with Liver Disease found that the highest rates of hospital admission for end-stage liver disease due to chronic hepatitis C virus were in central London and the North West of England. Admissions for alcohol-related liver disease were also most common in the North West.[4]

Consequently, the Chief Medical Officer has advised that liver disease should be one of the key issues for health in England and earlier this year NICE published an evidence-based guideline on assessment and management of cirrhosis (NG50).[2]

How should patients be monitored?

DIAGNOSIS

Cirrhosis generally results from chronic liver damage over many years. It is characterised by fibrosis and nodularity of the liver parenchyma, which interferes with the synthetic, metabolic and excretory functions of the liver.

Common causes include: alcohol misuse, hepatitis B (± delta) and C, and non-alcoholic fatty liver disease (NAFLD). Less common causes include: primary or secondary biliary cirrhosis; autoimmune hepatitis; primary sclerosing cholangitis: haemochromatosis; Wilson's disease; alpha 1-antitrypsin deficiency; cystic fibrosis; certain drugs e.g. methotrexate, isoniazid, amiodarone; right-sided heart failure, tricuspid regurgitation, pericarditis and veno-occlusive disease e.g. Budd-Chiari syndrome. »

INVESTIGATIONS

Abnormal liver function tests (LFTs) are a common finding in primary care but correlate poorly with the presence of cirrhosis. Alanine amino transaminase (ALT) is only elevated in 1-4% of asymptomatic patients with cirrhosis,[5] and therefore routine blood tests cannot rule out cirrhosis.[2]

Ultrasound

Abdominal ultrasonography is a good first-line investigation in patients with suspected liver disease. It has a high sensitivity (91%) and specificity (94%) for the detection of the gross features of cirrhosis,[6] can detect > 90% of gallstones,[7] and differentiate between solid and cystic lesions within the liver parenchyma.

Biopsy

The gold standard test for the diagnosis of cirrhosis remains a liver biopsy. However, it is associated with adverse events such as sub-capsular haemorrhage in up to 1% of cases. Liver biopsy samples < 1/50,000 of the liver parenchyma,[8] so sampling errors are possible. It is also relatively expensive, invasive and disliked by patients, making serial measurements challenging.

Noninvasive serum markers have therefore been developed to improve identification of patients with advanced fibrosis or cirrhosis who require further assessment or referral to secondary care.

Enhanced liver fibrosis panel

The most commonly used serum biomarker is the enhanced liver fibrosis panel, see box 1, below.[9] When interpreting these tests it is recognised that extra-hepatic inflammation may result in a false-positive result and alternatively significant fibrogenesis may go undetected if there is minimal hepatic inflammation. Overall these markers are becoming increasingly reliable at detecting fibrosis although they correlate poorly with the stage of fibrosis and may be less specific if there is concurrent hepatitis.[10]

'Compared with a standard biopsy, transient elastography will assess a much larger proportion of the liver and therefore sampling errors should be reduced'

Transient elastography

This is a specialist radiological test, which 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.

Compared with a standard biopsy, transient elastography will assess a much larger proportion of the liver and therefore sampling errors should be reduced. The measurements are painless and quick and as a consequence serial measurements for monitoring treatment response e.g. in chronic viral hepatitis, are feasible and acceptable to patients. Although reproducibility is generally very good, intraobserver variation still exists and its sensitivity is reduced in obese patients, those with significant ascites or active hepatitis — in these patients liver biopsy remains the optimal method of detecting cirrhosis.

Acoustic radiation force impulse (ARFI) imaging

ARFI is similar to transient elastography as it measures the propagation speed of an acoustic wave produced by the probe, that is increased in fibrotic tissue. Unlike transient elastography this technique uses a standard ultrasound machine but with an additional probe.[11] A meta-analysis comparing ARFI and transient elastography found that there was no significant difference in reliability between the techniques.[12]

RISK FACTORS

Nearly 50% of patients with cirrhosis are asymptomatic.[13] As a result the condition may only be discovered incidentally as a result of abnormalities in LFTs or imaging of the abdomen performed for other reasons, or by the targeted screening of high-risk groups. In the UK the most common risk factors for developing cirrhosis, and therefore the patients who should be targeted for screening include those with: hepatitis B or C infection, alcohol misuse, obesity (BMI ≥ 30 kg/m^2) or type 2 diabetes. NICE guidelines recommend that this is done with transient elastography in patients with hepatitis C, men who drink > 50 units or women who drink > 35 units of alcohol per week and have done so for several months and in patients who have been diagnosed with alcohol-related liver disease.[2]

In patients who are at risk of NAFLD i.e. those who are obese, have diabetes or metabolic syndrome, there is limited evidence to support routine screening, but they are recognised to be at a higher risk of developing cirrhosis. Therefore initially screening should be performed with an enhanced liver fibrosis panel, see box 1, left, to stratify those patients who potentially have advanced liver fibrosis. In patients with an enhanced liver fibrosis score > 10.51 further investigation by transient elastography or ARFI is recommended.[2,14]

If initial screening tests for cirrhosis are negative in high-risk groups (alcohol-related liver disease, chronic hepatitis C which has not shown a

Box 1

Enhanced liver fibrosis (ELF) panel [28]

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 moderate 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[2]

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

Table1

Risk factors for the development of hepatocellular carcinoma (HCC)

Risk factor	
Age	> 60[29]
Gender	Male[29]
Hepatitis B and C	Worldwide approximately half of cases of HCC are attributed to hepatitis B and a third to hepatitis C[29] Co-infection with HIV further increases risk[30]
Cirrhosis	One third of cirrhotic patients will develop HCC during their lifetime[31]
Alcohol	Alcohol misuse is a risk factor for HCC independent of cirrhosis[29,32]
Metabolic syndrome	Diabetes, obesity and fatty liver[32,33]
Smoking[32,34]	
Haemochromatosis	Up to half of patients with iron overload will develop HCC in their lifetime, although most will be cirrhotic at the time of HCC diagnosis[35]
Toxins	Aflatoxin B,[36] anabolic steroids [37]
Genetic predisposition	BRCA 1/ BRCA 2/ EGF gene [38,39]

Table 2a

Calculating the Child-Pugh score

Score	1	2	3
Bilirubin (μmol/L)	< 34	34-51	> 51
Prothrombin time in seconds (INR)	< 4 (< 1.7)	4-6 (1.7-2.3)	> 6 (> 2.3)
Albumin (g/L)	> 35	28-35	< 28
Ascites	Absent	Mild-moderate (diuretic responsive)	Severe (diuretic refractory)
Encephalopathy	Absent	Grade 1-2 (or precipitant induced)	Grade 3-4 (or chronic)

Table 2b

Three-year survival based on Child-Pugh score

The Child-Pugh score ranks the severity of cirrhosis into three classes

Disease severity	Child-Pugh score	Three-year survival[40]
Class A	≤ 6	73%
Class B	7 to 9	59%
Class C	≥ 10	46%

sustained virological response to antiviral therapy and those with NAFLD and an elevated enhanced liver fibrosis panel), repeat testing should be performed with transient elastography every two years.

ASSESSMENT FOR COMPLICATIONS

Patients with confirmed cirrhosis should be assessed for potential complications (ascites, encephalopathy, oesophageal varices or hepatocellular carcinoma). Decompensation or complications of cirrhosis should be detectable by all clinicians. Screening and surveillance for hepatocellular carcinoma and varices is the responsibility of secondary care. GPs should ensure patients are getting the appropriate investigations when they see patients with known cirrhosis for any reason.

In patients with compensated disease the risk of developing complications can be predicted using clinical scoring systems such as the Model for End-Stage Liver Disease (MELD). In patients with cirrhosis, MELD scores should be repeated six monthly; those with a MELD score > 12 are at an increased risk of developing complications. Once the MELD score is > 30, patients have a mortality of > 50% at three months.[15] All patients with cirrhosis and especially those who have decompensated disease and/or an elevated MELD score (> 12) should be under the care of a specialist hepatology centre.[2]

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide, with an estimated 750,000 new cases per year. Incidence varies globally with the highest prevalence in China, South East Asia and sub-Saharan Africa where carriage of chronic viral hepatitis is high. In the UK, there has also been an increase in the incidence of primary liver cancers in the past decade. The trend has been more profound in men than women.[16] Ninety per cent of cases are associated with one or more risk factors, see table 1, above left.

HCC is often asymptomatic until late in the disease. The European Association for the Study of the Liver (EASL) therefore recommends HCC surveillance in the following high-risk groups to enable earlier detection of these lesions:[17]

- Cirrhotic patients, Child-Pugh stage A and B (see table 2a and 2b, left) and Child-Pugh stage C awaiting liver transplantation
- Non-cirrhotic hepatitis B carriers with active hepatitis or family history of HCC

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key points

SELECTED BY

Dr Matthew Lockyer
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Morbidity and mortality associated with cirrhosis are on the increase. In a recent UK cohort study the incidence of cirrhosis increased by 50.6% between 1998 and 2009. By 2009 the authors estimated there to be around 17,000 new cases per year with a disease burden greater than the fifth leading cause of cancer. Although all causes of liver disease increased during this period, this trend was primarily attributed to rising levels of alcohol misuse and obesity.

Cirrhosis generally results from chronic liver damage over many years. It is characterised by fibrosis and nodularity of the parenchyma, which interferes with the synthetic, metabolic and excretory functions of the liver. Common causes include: alcohol misuse, hepatitis B (± delta) and hepatitis C and non-alcoholic fatty liver disease.

Abnormal liver function tests are a common finding in primary care but correlate poorly with the presence of cirrhosis. Alanine amino transaminase is only elevated in 1-4% of asymptomatic patients with cirrhosis, and so routine blood tests cannot rule out cirrhosis. Abdominal ultrasonography is a good first-line investigation in patients with suspected liver disease. The most commonly used serum biomarker is the enhanced liver fibrosis panel. Transient elastography is a specialist radiological test, which quantifies liver compliance or stiffness. Compared with a standard biopsy, it will assess a much larger proportion of the liver and therefore sampling errors should be reduced. The measurements are painless and quick and serial measurements for monitoring treatment response e.g. in chronic viral hepatitis, are feasible and acceptable to patients.

In the UK, the most common risk factors for developing cirrhosis, and therefore the patients who should be targeted for screening, include those with: hepatitis B or C infection, alcohol misuse, obesity (BMI $\geq$ 30 kg/m^2) or type 2 diabetes. NICE recommends that this is done with transient elastography in patients with hepatitis C, men who drink > 50 units or women who drink > 35 units of alcohol per week, and have done so for several months, and in people who have been diagnosed with alcohol-related liver disease.

Patients with confirmed cirrhosis should be assessed for potential complications (ascites, encephalopathy, oesophageal varices or hepatocellular carcinoma). Reviewing cirrhotic patients regularly in primary care provides a valuable opportunity to ensure hepatocellular carcinoma and variceal surveillance is being undertaken and enables further opportunities to provide lifestyle advice such as losing weight or reducing alcohol intake. One in four patients with oesophageal varices will develop a variceal haemorrhage within two years. Acute variceal haemorrhage is associated with a mortality of up to 50%. Patients with a new diagnosis of cirrhosis should be offered a gastroscopy for detection of varices.

and non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis

NICE guidelines also suggest surveillance in all patients with established cirrhosis who do not have hepatitis B infection and are not receiving end of life care. NICE, the British Society of Gastroenterology (BSG) and EASL all recommend that surveillance should be performed by abdominal ultrasound every six months.[18] NICE and the BSG also suggest ultrasound can be combined with serum alpha fetoprotein (AFP).[19] In up to 90% of small HCCs the AFP will be normal so it cannot be used alone for surveillance.[19,20]

'Patients with a new diagnosis of cirrhosis should be offered a gastroscopy for detection of varices'

Despite multiple surveillance guidelines HCC surveillance continues to be performed poorly even in large centres.[21,22] Therefore reviewing cirrhotic patients regularly in primary care provides a valuable opportunity to ensure HCC and variceal surveillance is being undertaken and enables further opportunities to provide lifestyle advice such as losing weight or reducing alcohol intake.

Oesophageal varices

Oesophageal varices are present in approximately one-third of patients with compensated cirrhosis and two-thirds of those with decompensated disease at diagnosis.[23] In those with established cirrhosis 5-7% will develop oesophageal varices annually. Once established, small oesophageal varices progress to large varices at a rate of approximately 8% per year.

Risk factors for variceal rupture include: size of varix, severity of liver disease, sepsis, HCC and an elevated portal pressure gradient. One in four patients with oesophageal varices will develop a variceal haemorrhage within two years.[24] Acute variceal haemorrhage is associated with a mortality of up to 50%.[25]

Patients with a new diagnosis of cirrhosis should be offered a gastroscopy for detection of varices. Surveillance endoscopy should be repeated three yearly if no varices are detected.[2] If moderate to large varices are seen, endoscopic variceal band ligation should be performed and in cases of variceal haemorrhage antibiotic prophylaxis should be commenced in addition to standard resuscitation and endoscopic management.

The management of small varices is controversial and has been omitted from the current NICE guidelines because of lack of evidence.

Ascites

A further complication of cirrhosis leading to portal hypertension and subsequent activation of the renin-angiotensin-aldosterone system is the development of ascites and fluid retention. Ascites is usually managed with diuretics in combination with a low-salt diet and fluid restriction. If ascites is unresponsive to this initial management or the patient develops complications such as hepatorenal syndrome, then transcatheter intrahepatic portosystemic shunt (TIPS) should be considered.

Encephalopathy, cardiac failure and severe liver disease are contraindications to TIPS and in these cases regular large volume paracentesis is an alternative. When the ascitic protein concentration is < 15 g/L prophylactic ciprofloxacin or norfloxacin is recommended until the ascites has resolved, to prevent spontaneous bacterial peritonitis.[2]

Hepatic encephalopathy

Hepatic encephalopathy is defined as a spectrum of neuropsychiatric abnormalities in patients with cirrhosis, after exclusion of other causes.

The condition is characterised by changes in personality, intellectual impairment and drowsiness. It can be subdivided into two main categories: overt and minimal.

Overt hepatic encephalopathy is evident clinically, whereas minimal hepatic encephalopathy requires neuropsychological testing for confirmation. Overt hepatic encephalopathy occurs in around 30-45% of cirrhosis patients in their lifetime, although it is suspected that up to 70% may experience a subclinical minimal encephalopathy state at some point.[26] Patients with cirrhosis have an annual risk of developing overt hepatic encephalopathy of approximately 20%.[27]

Common precipitants include non-compliance with hepatic encephalopathy therapy, increased protein ingestion, gastrointestinal bleeding, constipation, renal failure, electrolyte imbalance e.g. hyponatraemia, hypovolaemia, drugs (e.g. opiates, benzodiazepines, diuretics) and sepsis.[17]

CONCLUSIONS

Noninvasive markers to detect advanced fibrosis are increasingly available allowing better differentiation of those with advanced liver disease from the much larger population with abnormal liver enzymes or risk factors for liver disease. In light of these markers becoming more available in routine practice, the recent NICE guideline provides clinicians with a framework for identifying those at risk of cirrhosis and who should be further assessed by enhanced liver fibrosis panel and/or transient elastography and ultimately who warrants referral to secondary care hepatology services.

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