CIRRHOSIS: REVIEWING THE LITERATURE AND FUTURE PERSPECTIVES

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ABSTRACT

Cirrhosis is the final stage of chronic liver disease and has many causes, including viral hepatitis, excessive alcohol intake, and non-alcoholic steatohepatitis. When decompensated cirrhosis develops, complications occur that affect quality of life and patient survival. Cirrhosis has a large burden of disease and is responsible for almost 2% of deaths in Europe. Cirrhotic patients are in need of early diagnosis and a careful follow-up for the prevention and detection of complications. The ultimate treatment for end-stage cirrhosis is liver transplantation. This review will cover clinical aspects of cirrhosis and uncover future trends in the care of these patients.

Keywords: Cirrhosis, diagnosis, treatment.

INTRODUCTION

Cirrhosis is the final stage of chronic liver disease. It results in distortion of the hepatic architecture by fibrosis, and the formation of regenerative nodules.[1] It is the result of progressive liver fibrosis caused by chronic liver diseases, including viral hepatitis, alcoholic liver disease, non-alcoholic steatohepatitis (NASH), autoimmune liver disease, and genetic disorders, amongst others. Recent reports support the finding that the early stages of cirrhosis are reversible on a microscopic level with adequate treatment of the underlying liver disease.[2] However, at more advanced stages, cirrhosis is considered irreversible. Cirrhosis is the source of a variety of complications, which result in a reduction in the life expectancy of these patients.[3] At this stage, liver transplantation is the only curative treatment option.[4]

EPIDEMIOLOGY AND AETIOLOGY

Cirrhosis has a large burden of disease. It is the eighth leading cause of death and is responsible for 1.2% of all deaths in the USA.[5] According to the Global Burden of Disease study, the worldwide prevalence of cirrhosis is increasing.[6] In the USA, the most common causes of cirrhosis are chronic hepatitis C virus (HCV), alcoholic liver disease, and non-alcoholic liver disease.[7] In Europe, liver cirrhosis accounts for 1.8% of all deaths, amounting to 170,000 deaths per year.[3] Worryingly, the reported incidence of cirrhosis remains stable or is increasing in several countries, including both the UK[8] and Ireland.[3] In Europe, the main causes are alcoholic liver disease, NASH, and HCV.[3] The four most frequent causes of cirrhosis worldwide are chronic hepatitis B virus (HBV) and HCV, alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), and haemochromatosis. A variety of other diseases can result in cirrhosis, although these are less frequent.[9]

Alcohol

Excessive alcohol intake remains the number one cause of cirrhosis in Western countries. A daily intake of ≥60 g/day for men, and ≥40 g/day for women is considered harmful. Chronic intake of alcohol can also accelerate the natural progression of chronic HBV or HCV,[10] and haemochromatosis. Alcohol abstinence is the cornerstone of treatment and can reverse the disease course.[11]

Viral Hepatitis

Chronic HBV and HCV are leading causes of cirrhosis, especially in endemic regions like South

East Asia and Sub-Saharan Africa. According to the disease stage, finite treatment with pegylated interferon or long-term therapy with nucleos(t)ide analogues is appropriate in HBV patients.[12] The introduction of interferon-free treatment for HCV has been important, as it has resulted in improved treatment response without significant side effects.[13] However, access to these new direct-acting agents remains a challenge due to high costs. Hepatitis A and E do not develop into chronic hepatitis in immunocompentent patients and are not considered risk factors for cirrhosis.

Non-Alcoholic Fatty Liver Disease

NAFLD is related to the presence of metabolic syndrome in association with obesity, diabetes, and/or arterial hypertension. A subset of these patients will develop signs of NASH, which can lead to the development of fibrosis and subsequently cirrhosis.[14,15] It is an increasing health problem, especially in the Western world.[6] Treatment is based on dietary measures and exercise.[14]

Haemochromatosis

Hereditary haemochromatosis is an autosomal recessive disorder characterised by excessive intestinal absorption of dietary iron, which results in a pathological increase in total body iron stores.[16] End-organ liver damage can occur, in turn leading to cirrhosis. Phlebotomy has been indicated to remove excessive iron stores.[17]

Autoimmune Hepatitis

Autoimmune hepatitis is a rare disease affecting 16–18 cases per 100,000 inhabitants in Europe. More than 30% of adult patients and ~50% of children have cirrhosis at diagnosis, due to an insidious disease course.[18] Treatment is based on immunosuppressive agents including corticosteroids and azathioprine.[18]

Primary Biliary Cholangitis and Primary Sclerosing Cholangitis

Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are autoimmune diseases that affect the small and the large bile ducts, respectively. PBC can lead to progressive fibrosis resulting in cirrhosis. In PSC patients, prolonged extrahepatic cholestasis can induce the development of portal fibrosis leading to cirrhosis.[19] Ursodeoxycholic acid can slow down disease progression in PBC and can be used in PSC.[20] In PBC, newer agents, like obeticholic acid, are promising treatment options.[21]

Rare Causes of Cirrhosis

Other causes of cirrhosis include a reaction to drugs, Budd-Chiari syndrome, Wilson's disease, alpha-1 antitrypsin deficiency, granulomatous liver diseases, right-sided heart failure, and veno-occlusive disease amongst others.[9] A specific aetiology can be determined in 85–90% of patients.[22]

CLINICAL MANIFESTATION

Cirrhosis can be compensated without overt complications, or decompensated with the appearance of complications. The three major complications of cirrhosis are the consequences of portal hypertension (e.g. ascites, variceal bleeding, etc.), hepatocellular insufficiency (e.g. icterus), or the appearance of hepatocellular carcinoma (HCC).

Patients with compensated cirrhosis may present with nonspecific symptoms or may even be asymptomatic. They can complain of anorexia, weight loss, or fatigue. When decompensation develops, patients may present with jaundice, pruritus, signs of upper gastrointestinal bleeding, abdominal distension due to ascites, or confusions due to hepatic encephalopathy.[23] Hypogonadism may occur in men, which can manifest as impotence, infertility, or loss of libido.[24] In women, amenorrhoea or irregular menstrual bleeding are common.[25] Typical signs at clinical examination include jaundice, stellate angiomas, palmar erythema, foetor hepaticus, asterixis, signs of hypogonadism, and feminisation in males. Other signs include indicators of portal hypertension such as ascites, cutaneous collateral venous circulation, and splenomegaly.[23]

DIAGNOSIS

Laboratory Findings

Laboratory abnormalities may be the first indication of liver cirrhosis. Though bilirubin levels may be normal in compensated cirrhosis, the levels rise as cirrhosis progresses. Levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are moderately elevated in cirrhosis; however, normal aminotransferase levels do not exclude cirrhosis. Alkaline phosphatase is usually mildly elevated in cirrhosis. Levels higher than 2 or 3-times the upper limit of normal suggest an underlying cholestatic liver disease, such as

PSC or PBC.[20] Gamma-glutamyl transpeptidase levels correlate well with alkaline phosphatase, but are more elevated in alcohol induced chronic liver disease.[26]

Once the synthetic function of the liver is affected, albumin levels decrease and prothrombin time levels increase as key proteins involved in the coagulation cascade are produced in hepatocytes. Low platelets can appear in the case of hypersplenism.[27]

Imaging

Ultrasonography is the first step in liver imaging. It is non-invasive, widely available, affordable, and well accepted by patients. Liver volume can be normal, enlarged, or diminished, especially in advanced cirrhosis.[28] Often a nodular deformation of the liver can be observed. Other typical signs include atrophy of the right lobe of the liver, and hypertrophy of the caudate or left lobes.

When portal hypertension develops, Doppler imaging can reveal an enlarged portal vein, enlarged collateral veins, and decreased portal flow.[29] Ultrasonography is useful for the detection of hepatic nodules and is the backbone of screening programmes for the early detection of HCC.[30,31] Detection of hepatic nodules demands further characterisation using computed tomography or magnetic resonance imaging.

Non-Invasive Markers of Cirrhosis

Hepatologists are increasingly adopting the use of non-invasive markers of fibrosis and cirrhosis. These include biological markers and transient elastography (TE). Liver fibrosis can be staged using 1-dimensional ultrasound (FibroScan®, Echosens, France),[32] which measures the velocity of a low-frequency (50 Hz) elastic shear wave propagating through the liver. The stiffer the tissue, the faster the shear wave propagates. Ultrasound elastography can currently be performed based on two physical principles: strain displacement/imaging, and shear wave imaging and quantification.[33] The latter includes point shear wave elastography (pSWE), also known as acoustic radiation force impulse imaging (ARFI; Virtual touch tissue quantification™, Siemens Healthcare; elastography point quantification, ElastPQ™, Philips) and 2D-shear wave elastography (2D-SWE; Aixplorer™ Supersonic Imagine, France). A major advantage of pSWE/ARFI is that it can be easily implemented on modified commercial ultrasound machines (Acuson 2000/3000 Virtual Touch™ tissue quantification, Siemens Healthcare, Germany; ElastPQ, iU22xMATRIX, Philips, Netherlands). This results in a combined approach of conventional ultrasonography with TE.[34] Correct interpretation of pSWE/ARFI results should systematically take into account potentially confounding parameters: fasting for at least 2 hours, levels of transaminases (<5-times the upper limit of normal), absence of extrahepatic cholestasis, and absence of right heart failure.[33] According to the European Association for the Study of the Liver (EASL) clinical practice guidelines, TE is a reliable method for the diagnosis of cirrhosis in patients with chronic liver diseases. TE is generally better at ruling-out rather than suggesting cirrhosis and has a negative predictive value >90%.[34]

FibroTest©, a patented biomarker (combining six serum markers with the age and gender of the patient: alpha-2-macroglobulin, haptoglobin, apolipoprotein A1, gamma-glutamyl transpeptidase, total bilirubin, and ALT), and APRI (AST to Platelet Ratio Index calculator) are the most widely used and validated biological markers.[35] Fibrotest and APRI show an area under a receiver operating characteristic curve (AUROC) of 0.86 and 0.84,[36] respectively, for the diagnosis of cirrhosis.

Liver Biopsy

The gold standard for the diagnosis of cirrhosis is a histological examination. However, this should not be performed in all cirrhotic patients. A biopsy should be considered in patients in whom the diagnosis is in question, and when knowledge of a specific diagnosis is likely to alter the management of the disease.[37] A liver biopsy can be performed percutaneously, transjugularly, or laparoscopically. There is an inherent risk of bleeding, and severe bleeding occurs in between 1 in 2,500 and 1 in 10,000 biopsies performed using an intercostal percutaneous approach.[37]

MAJOR COMPLICATIONS

Cirrhotic patients are at risk for the development of complications, therefore cirrhotic patients should be observed more closely for decompensated cirrhosis. Once decompensation develops, the patient should be considered for liver transplantation.[4] Many complications of cirrhosis develop as a result of portal hypertension, an increased pressure in the portal circulation defined as an elevation of the hepatic venous pressure

gradient to >5 mmHg.[38] The haemodynamic abnormalities associated with portal hypertension cause the most severe complications of cirrhosis, including ascites, hepatic encephalopathy, and bleeding from gastro-oesophageal varices.

Ascites is the accumulation of fluid in the peritoneal cavity. It is treated with diuretics and sodium restriction. Some patients require repeated therapeutic paracentesis, or transjugular intrahepatic portosystemic shunt (TIPS) placement.[39] In patients with ascites, spontaneous bacterial peritonitis (SBP) may occur. Patients may be asymptomatic, present with altered mental status, or be seriously ill with a high fever, abdominal tenderness, and pain. The diagnosis is established by an elevated ascitic fluid absolute polymorphonuclear leukocyte count (≥250 cells/mm^3). The mortality is high if prompt antibiotic treatment and albumin substitution are not initiated.[39]

Hepatorenal syndrome (HRS) can develop in patients with advanced cirrhosis. HRS is the development of renal failure in patients with advanced chronic liver disease who have portal hypertension and ascites.[40] Around 40% of these patients will develop HRS during the natural history of their disease. It is caused by vasoconstriction of the renal circulation and intense systemic arteriolar vasodilatation, which results in reduced systemic vascular resistance and arterial hypotension. Following liver transplantation, the histological appearance of the kidneys is normal and the kidneys often resume normal function.[39] Treatment of HRS is based on the treatment of the precipitating factors; adequate volume replacement with albumin and vasoconstriction therapy with vasopressin analogues, such as terlipressin.[39]

Variceal haemorrhage is a dramatic event that typically presents as haematemesis and/or melaena. The mortality rate is high (20%, 30-day mortality) and treatment requires a multidisciplinary approach[41] including antibiotic treatment and endoscopic haemostasis. In selected patients, early TIPS placement can increase survival.[42]

A typical complication of cirrhosis is the occurrence of portal vein thrombosis (PVT). According to a large prospective trial in France, the 5-year cumulative incidence of PVT was 10.7%.[41] PVT is associated with the severity of liver disease at baseline and anticoagulation is indicated in patients waiting for liver transplantation.[43]

Hepatic encephalopathy encompasses a spectrum of potentially reversible neuropsychiatric abnormalities including confusion, altered level of consciousness, and coma.[44] Signs can easily be overlooked when they are limited to psychomotor slowing, a lack of attention, or sleep disturbances. Hepatic encephalopathy can be scored using the West Haven criteria. A typical sign of encephalopathy is the presence of asterixis. Treatment is based upon addressing the precipitating factors using synthetic disaccharides (e.g. lactulose) and nonabsorbable antibiotics (e.g. rifaximin).[44]

Liver cirrhosis is the most important risk factor for the development of HCC. HCC represents up to 85% of the primary liver cancer burden.[45] In patients with compensated cirrhosis the annual incidence of HCC ranges from 1–8%.[46] It is mandatory for an ultrasonography to be taken every 6 months to ensure early detection of HCC.[47,48]

FOLLOW-UP, PREVENTION OF COMPLICATIONS, AND TREATMENT

The natural course of cirrhosis is variable and can be well tolerated for many years. In these patients the primary goal should be to prevent the occurrence of complications. Slowing or even reversing the progression of liver disease can be achieved by addressing the underlying liver disease. Abstinence from alcohol improves survival in alcoholic cirrhosis.[49] Achieving a sustained viral response in HCV with antiviral treatment lowers liver-related mortality.[50]

The presence of impaired hepatic metabolism and renal excretion denotes a need for caution with many medications, which may subsequently necessitate dose adjustments or should even be avoided.[49,51] Nephrotoxic agents can precipitate HRS and should be used cautiously. Careful monitoring for the development of complications and, if possible, the prevention of complications, is the cornerstone of the treatment of a cirrhotic patient. Cirrhotic patients should undergo screening for oesophageal varices with upper endoscopy. However, according to the recent Baveno VI guidelines, patients with a liver stiffness <20 kPa, and a platelet count >150,000 can avoid screening.[52] Patients with medium or large varices require primary prevention with non-selective beta blockers or endoscopic band ligation. The role of carvedilol remains unclear.[52] Furthermore, platelet levels <100,000 can increase risk for surgery.

In a study, it was demonstrated that in patients with ascitic fluid protein <15 g/L and without prior SBP, norfloxacin (400 mg/day) reduces the risk of SBP and improves survival. In these patients, long-term primary prophylaxis should be considered.[41] Empirical antibiotics should be started immediately following the diagnosis of SBP. Furthermore, albumin (1.5 g/kg at diagnosis and 1 g/kg on Day 3) should be administered in order to decrease the risk of HRS.[41]

The presence of hepatic encephalopathy can be extremely subtle. Precipitating factors including dehydration, infection, and variceal bleeding should be avoided or addressed as soon as possible. The ultimate treatment for cirrhosis is liver transplantation, and excellent long-term results have been demonstrated.[53] It should be considered in patients with decompensated cirrhosis. The final decision depends upon the severity of the liver disease and the absence of contraindications.[4]

Patients who develop HCC should be managed according to the Barcelona Clinic Liver Cancer (BCLC) staging system.[31] Single HCC lesions in Child–Pugh A patients are eligible for resection or ablation. Intermediate stage disease patients are offered locoregional therapy including transarterial chemoembolisation or radioembolisation. In advanced or metastatic disease, sorafenib is the only remaining option; it improves median overall survival from 6 to 9 months. In patients with lesions that meet the 'Milan criteria' liver transplantation should be considered.[31]

PROGNOSIS

The prognosis of patients with compensated cirrhosis is excellent. Transition from the compensated to the decompensated stage occurs at a rate of 5–7% per year.[11] The median survival rate in compensated cirrhosis is >12 years.[11] Once patients develop complications of cirrhosis, such as ascites, variceal bleeding, or HRS, they are considered to have decompensated cirrhosis and their prognosis is worse.

Two models are commonly used for prognosis evaluation: the Child–Pugh classification and the Model for End-Stage Liver Disease (MELD). The Child–Pugh classification includes the variables serum albumin and bilirubin, ascites, encephalopathy, and prothrombin time.[54] The ranges from 5 to 15, and patients are divided into Child–Pugh A (score 5–6), B (score 7–9), or C (score 10–15). One-year survival rates for Child–Pugh A, B, and C patients are 100%, 80%, and 45%, respectively.[55] MELD score is calculated using bilirubin levels, creatinine, and international normalised ratio.[56] It is now used for prioritising patients on the liver transplant waiting list. Patients with a MELD score of >10 should be referred to a liver transplant centre for evaluation.

There is a growing interest in the use of non-invasive tests for the prognosis of chronic liver disease, particularly for TE in patients with cirrhosis.[34] The Baveno VI consensus paper[52] introduced the term 'compensated advanced chronic liver disease' (cACLD). This term applies to patients with chronic liver disease at increased risk of developing clinically significant portal hypertension, defined as a hepatovenous pressure gradient of ≥10 mmHg. TE values <10 kPa in the absence of other known clinical signs rule out cACLD. Values between 10–15 kPa are suggestive of cACLD but need confirmation. Values >15 kPa are highly suggestive of cACLD. Patients with cACLD are at an increased risk for complications and should be referred to a liver disease specialist.[52]

CONCLUSION

Cirrhosis is the final stage of chronic liver disease. The aim of a clinician dealing with cirrhosis should be to prevent the development of major complications. A new trend in this field is the adoption of non-invasive techniques, e.g. TE for diagnosis of cirrhosis and follow-up of cirrhotic patients, as they are an emerging tool for risk stratification. In cirrhotic patients the performance of an ultrasonograph every 6 months remains of utmost importance for early detection of HCC. Decompensated patients have a dismal prognosis and should be referred to a specialised hepatological centre, as liver transplantation should be considered in these patients.

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