DEFINITION

1. Cirrhosis is an irreversible disorder of the liver characterised by diffuse hepatic fibrosis and the conversion of normal liver architecture into abnormal nodules. It represents a sustained healing response to chronic injury from a wide variety of causes.

2. The condition often develops insidiously without giving rise to symptoms and it is thought that about 30-40% of cases are clinically latent. It may therefore be categorised on clinical grounds as:

    2.1. **Compensated cirrhosis**, in which the patient is asymptomatic and the condition is discovered during biochemical screening, routine clinical examination, or abdominal surgery for another condition.

    2.2. **Decompensated cirrhosis**, in which the most frequent manifestations are jaundice, ascites, encephalopathy and gastric or oesophageal haemorrhage.

CLINICAL MANIFESTATIONS

3. The commonest clinical presentation initially is of general malaise, with anorexia, weight loss, muscle weakness and fatiguability. Examination may reveal the characteristic features of palmar erythema, spider naevi, foetor hepaticus and hepatic enlargement.

4. Obstruction of the portal venous system causes portal hypertension, with gastric and oesophageal varices and the development of periumbilical collateral vessels. The distended gastric and oesophageal vessels may produce life-threatening haemorrhage.

5. Anaemia is common, and impaired coagulation due to decreased production of hepatogenic coagulation factors. Various endocrine effects such as diabetes mellitus may occur, and feminisation and hypogonadism in the male.

6. Pulmonary and cardiac complications may be present and around 50% of cirrhotic patients develop a circulatory hyperdynamic state with increased cardiac output and reduced exercise capacity.

7. Hepatocellular cancer occurs in 10-25% of cases, especially in those whose cirrhosis is due to viral and alcohol-related causes. It may become evident before the underlying cirrhosis is diagnosed.

8. As the condition progresses liver failure may supervene, with jaundice, ascites and hepatic coma.

AETIOLOGY

9. A wide variety of agents and diseases produce the common end result of cirrhosis of the liver. These may be categorised as; alcohol, chronic viral hepatitis, drugs and toxins, autoimmune diseases, metabolic disorders, biliary disease, venous outflow obstruction and nutritional abnormalities. In addition, a significant proportion of cases have no identifiable cause; so-called “cryptogenic” cirrhosis.

10. The aetiology of cirrhosis varies both geographically and socially but in the western world the frequencies of the major categories are:

    10.1. Alcoholic liver disease: 60-70%

    10.2. Viral hepatitis: 10%

    10.3. Biliary diseases: 5-10%

    10.4. Metabolic disorders: 5%

    10.5. Cryptogenic cirrhosis: 10-15%

    10.6. Other causes 2%

11. **Alcohol** The exact mechanism whereby alcohol results in parenchymal liver damage is unclear. The process may be attributable to free radical generation, to hypoxia due to the increased oxygen requirement in ethanol acetaldehyde metabolism, or to neo-antigen production in the form of acetaldehyde-protein adducts.

    11.1. Progression to cirrhosis generally pursues a course from fatty liver, which resolves completely 4 to 6 weeks after alcohol ingestion is discontinued, to alcoholic hepatitis, which may resolve if underlying fibrosis is minimal and the patient stops drinking; otherwise the process continues to cirrhosis. In patients with established cirrhosis abstinence is a crucial determinant of prolonged survival.

    11.2. Not all alcohol abusers develop cirrhosis, and the predisposition of some individuals to develop it is as yet unexplained. Susceptibility to liver damage is probably caused not by a single gene defect but through a cumulative interaction of a number of genes.

12. **Chronic viral hepatitis** Chronic hepatitis B virus (HBV) and chronic hepatitis C virus (HCV) infections are an important cause of cirrhosis in the western world.

    12.1. In chronic HBV infection the rate of progression to cirrhosis depends upon the replicative activity of the virus and whether there has been superinfection with hepatitis delta virus (HDV).

12.2. The hepatitis delta virus (HDV) is unable to replicate on its own and is dependent upon the presence of HBV to render it capable of infecting the human host; the interaction between the two viruses is very complex. Infection with HDV is uncommon in Western countries and is largely confined to intravenous drug users. Fresh and florid cases of the disease are now rare, but in most chronic carriers subversion of the liver architecture is seen early and cirrhosis – often clinically stable – occurs within a few years.

12.3. In chronic HCV infection, progression to cirrhosis is also dependent on the age at exposure and the duration of infection. Previous liver damage, for example due to alcohol, will increase the degree of inflammation and the rate of progression to cirrhosis.

12.4. Type A hepatocellular viral infection (HAV) does not cause cirrhosis.

13. **Other infections** A number of infective agents affect the liver but do *not* cause cirrhosis; these include schistosomiasis, amoebiasis, malaria, yellow fever and infectious mononucleosis.

    13.1. **Brucellosis** This disease is transmitted from animals and may enter a chronic phase in which the liver is involved.

14. **Drugs and toxins** A wide variety of drugs and toxins may be implicated in the development of cirrhosis. However their contribution is small compared with that of alcohol and viral hepatitis.

    14.1. **Methotrexate** Signs of hepatotoxicity may appear following long-term therapy for rheumatoid arthritis, psoriasis or leukaemia.

    14.2. **Amiodarone** This drug, used in certain cardiac arrhythmias, is known to possess hepatotoxic effects and may result in cirrhosis after prolonged use.

    14.3. **Vitamin A** Increasingly encountered in dermatology, vitamin A is only slowly metabolised in the liver and toxicity may develop with the ingestion of as little as 50,000 IU over two years.

    14.4. **Isoniazid** The toxicity of this anti-tuberculous drug is enhanced by anaesthetic drugs, paracetamol and alcohol.

    14.5. **Methyldopa** This antihypertensive drug may result in hepatotoxic effects, either related to metabolites of the active substance or in some cases due to an immunological effect.

15. **Autoimmune hepatitis** This is a poorly defined, ill-understood condition, previously known as ‘lupoid’ hepatitis. It is more common in females (female:male = 4:1) and is characterised by a low rate of spontaneous remission and a high mortality. Unless treated by immunosuppression it usually progresses to active cirrhosis.

15.1 A number of agents have been regarded as possible triggers for this self-perpetuating autoimmune process, including viruses, bacteria, toxic substances and genetic factors. The recent emphasis has been on viral causes, including hepatitis A, B, C, and D; herpes simplex virus type 1 and Epstein-Barr virus.

16. **Metabolic diseases** A number of metabolic disorders may lead to cirrhosis. They include conditions in which there is defective metabolism and storage of specific substances, such as haemachromatosis (iron) and Wilson's disease (copper).

16.1. **alpha$_1$-antitrypsin deficiency** is a genetically determined disorder in which this liver-produced protein is deficient, allowing the unopposed action of proteases. The main effects are on the lungs and liver.

16.2. **The glycogenoses** Different forms of the glycogen-storage diseases produce different enzymatic effects. Most affect the liver and usually result in poor physical growth in childhood. All varieties seem to be inherited.

16.3. **Galactosaemia** In this disorder, the liver lacks the specific enzyme galactose-1-phosphate-uridyl transferase, essential for the metabolism of galactose. It is inherited as an autosomal recessive.

16.4. **Hereditary fructose intolerance** This autosomal recessive condition produces severe metabolic derangement due to inability to break down fructose-1-phosphate.

16.5. **Hereditary tyrosinaemia** This condition is due to the lack of the enzyme fumaryl acetoacetate hydrolase, which catalyses the last step of the breakdown of tyrosine. Abnormal hepatotoxic metabolites of tyrosine develop.

16.6. **Hereditary haemorrhagic telangiectasia** In this rare autosomal dominant disease there are mutations in endothelium-related proteins which may cause vascular dysplasia, causing interference with the nutrition of liver cells and ensuing cirrhosis.

16.7. **Byler's disease** (Progressive familial intrahepatic cholestasis). This is a rare cause of intrahepatic cholestasis. Conjugated bile acids cannot be excreted and death is usual before the age of 8 years. There is accumulating evidence that it is in fact a genetically and phenotypically heterogeneous group of disorders.

16.8. **Abetalipoproteinaemia** This autosomal recessive disorder is characterised by virtual absence of apolipoprotein B-containing lipoproteins and very severe fat malabsorption. There is a clear preponderance of male victims of this disease (male:female=2:1). The cause is unknown.

16.9. **The porphyrias** These conditions are caused by defects in the biosynthesis of haem. Most are inherited as autosomal dominant conditions. The majority of carriers are asymptomatic, and attacks are precipitated by drugs, hormonal factors and endogenous metabolic changes.

17. **Biliary disease** Biliary disease of various types may lead to cirrhosis. Bile duct obstruction – intrahepatic or extrahepatic – leads to cholestasis and the harmful retention of bile salts. Liver cell damage occurs due to their detergent effect.

    17.1. **Extrahepatic biliary obstruction** includes any anatomical obstruction to the common bile duct, common hepatic duct and major bile ducts. Causes include calculi, malignant and benign tumours and benign strictures.

    17.2. **Intrahepatic biliary obstruction** This may occur due to a wide variety of conditions, e.g. infective hepatitis, liver infiltrations due to lymphoma, amyloid, and sickle cell crises.

    17.3. **Primary biliary cirrhosis** This is a disease of uncertain cause in which intrahepatic bile ducts are progressively destroyed. It is associated with severe immunological disturbance. 90% of patients are female, usually in the 5^{th} to 7^{th} decade. It is considered likely that environmental factors, including infections acting on a genetically predisposed host may cause the condition.

    17.4. **Primary sclerosing cholangitis** Underlying this condition is a chronic fibrosing inflammatory process involving all parts of the biliary tree, which is ultimately destroyed, resulting in biliary cirrhosis. The cause of the condition is not known although in about 70% of cases the patient also suffers from ulcerative colitis. It is thought that the process occurs in immunologically susceptible individuals when an infective agent penetrating the abnormally porous bowel wall reaches the liver by haematogenous spread.

18. **Veno-occlusive disease** In this group of conditions there is narrowing of the lumen of hepatic veins by loose connective tissue. Cirrhosis may ensue if the condition is sufficiently prolonged. A number of agents and conditions may be responsible.

    18.1. **Pyrrolizidine alkaloids** These substances have a worldwide occurrence in certain plants, e.g. crotolaria and senecio. Epidemic outbreaks may occur due to the ingestion of contaminated flour.

    18.2. **Therapeutic radiation** Signs of liver damage may occur some weeks after therapeutic abdominal irradiation; so-called radiation hepatitis. The pathology of the condition is that of veno-occlusive disease. Sensitivity to therapeutic radiation varies between individuals, but damage rarely occurs at doses of less than 0.3Gy. (For comparison, the dosage from a chest X-ray is about 0.0001Gy and from a CT scan about 0.008Gy).

    18.3. **Budd-Chiari syndrome** This syndrome comprises hepatomegaly, abdominal pain and ascites. It is caused by obstruction of the venous outflow from the liver at any site from the efferent veins of the hepatic lobule to the entry of the inferior vena cava into the right ventricle.

        18.3.1. Budd-Chiari syndrome may be caused by such diverse agents as myeloproliferative diseases, pregnancy, the use of oral contraceptives, sickle cell disease, malignancy and blunt trauma.

18.4. **Anti-neoplastic drugs** Many of these drugs are hepatotoxic and prolonged use may result in veno-occlusive disease and ensuing cirrhosis. They include azathioprine, 6-mercaptopurine, vincristine and doxorubicin.

19. **Nutritional factors** Although malnutrition does not cause hepatic cirrhosis, certain disturbances of nutrition have been implicated in chronic liver damage and cirrhotic change. For example, in obesity the liver exhibits varying degrees of fatty change, even progressing to fibrosis and cirrhosis. In patients who have undergone jejuno-ileal bypass for morbid obesity a similar sequence of events may occur.

20. **Cryptogenic cirrhosis** In this heterogeneous group the cause of the cirrhosis is unknown. Since the clarification of the role of hepatitis C virus however the number of cases falling into this category has dropped considerably. Some 75% of cases of cryptogenic cirrhosis have features of autoimmunity.

CONCLUSION

21. Cirrhosis is a process of diffuse fibrosis of the liver parenchyma with nodule formation. There are numerous causes, the most important of which are alcohol abuse and chronic hepatocellular viral infection.

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