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Review Article

Cirrhosis and end-stage chronic liver disease: The changing scenes on etiopathogenesis

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A B S T R A C T

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Liver cirrhosis and its most serious complication hepatocellular carcinoma (HCC) together make up for a substantial proportion of human diseases carrying high morbidity and mortality. Years of sustained research efforts involving clinical, epidemiological and laboratory studies have succeeded in sequential unraveling of the etiological factors for the vast majority of these two diseases. Unfolding the scenarios on these through time will help to understand and logically analyze the current situation on cirrhosis and HCC and to plan effective control and management strategies on them in the coming years.

Even though Laennec who first gave the name cirrhosis had noted its occurrence in alcoholics, for more than a century the disease seen all around the world was considered to be caused by nutritional deficiency. In the Asian and African countries many of these livers had hepatocellular carcinoma (HCC), a rapidly fatal tumor. In the 1950s it was confirmed that alcohol directly injures the liver and prolonged alcohol abuse leads to cirrhosis. By the end of twentieth century three other major etiologic factors for cirrhosis were identified, hepatitis B virus (HBV), hepatitis C virus (HCV) and nonalcoholic fatty liver disease (NAFLD). HBV and HCV were also found to be carcinogenic to the liver and causally related to the vast majority of HCC. HBV was considered to bear the largest share in causing the global burden of cirrhosis and HCC and the most dominant of the four major causes in Asian and African countries. Preventive measure for the parenterally transmitted HBV and HCV infections were implemented and a highly effective HBV vaccine was administered universally to newborns and children in some countries.

Presently, the etiologic factors for more than 90% cases of cirrhosis and HCC, their sources and ways of controlling exposure to them are known. In all parts of the world these diseases caused by HBV are on the decline to variable extents, resulting largely from the wide use of control measures including the universal vaccination programs, the latter to a limited degree. Cirrhosis and HCC caused by HCV and NAFLD which is associated with metabolic syndrome are steadily increasing while the ones related to alcohol abuse have remained steady at earlier levels or are mildly increasing in developed countries but progressively increasing in the developing countries. Increasing use of adequately effective anti-viral medications for HBV and HCV infection and wider introduction of liver transplantation are helping reduce the virus carrier pools and diseases caused by these viruses.

Since all four major etiologic factors are from the living human environment, diseases related to them are potentially preventable. If circumstances countering the exposure to and operation of these factors are favorable and an effective HCV vaccine becomes

available soon, a likely scenario for prevalence of cirrhosis and HCC around the middle of this century can be visualized. The total global burden of these diseases will come down significantly, most of it involving the developing countries in Asia and Africa mainly because of marked reduction in the HBV related segments. The major share of diseases will be those related to alcohol and NAFLD, the latter dominating the scene in developing countries. HCV related disease will also reduce to reasonable extents, more so in developed countries.

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1. Introduction

Considered in a global context, chronic liver disease (CLD) and cirrhosis rank high among diseases that pose significant social and community health problems. They carry a high morbidity and, given time, are potentially fatal because of serious complications like massive gastro-intestinal bleeding consequent to portal hypertension, critical infections, liver failure and hepatocellular carcinoma (HCC) – one of the most dreaded human malignancies. During the last four decades our understanding on the etiology, pathogenesis, biologic progression, curative and preventive therapy and management of cirrhosis and HCC have advanced so rapidly that from a point of knowing almost nothing except their existence we are now poised not only to largely reduce these disease loads but also to even eradicate some of them in not so distant future. Over the years our knowledge on the etiopathogenesis of CLDs and cirrhosis has witnessed frequent changes as newer findings are continually being unveiled. Establishment of liver transplantation and increasing world wide use of cadaveric as well as living donor liver transplants have unraveled several new facets of these diseases that were unknown only a few years back. Some risk factors are currently showing a decline, others remain stable or show some increase in different regions, while CLD caused by other new factors are emerging and fast increasing in incidence.

All etiologic factors incriminated for the vast majority of CLD, cirrhosis and HCC are of environmental origin and therefore eliminating exposure to them is possible. In addition, effective treatments of individuals already exposed to most of these agents are available now. However, implementation of the various preventive and therapeutic measures is hindered by differing economic, socio-cultural, political and logistic issues continuing to prevail in different countries and geographic regions. Liver transplantation which remains the only answer to end stage chronic liver disease is not accessible to large segments of populations world wide because of the high cost involved, restricted availability of donor liver and, prioritization of cases given transplant on the basis of cost-effectiveness, and the category of recipient's native liver disease. Several recent reports from different developed and developing countries document the current status of cirrhosis, end stage chronic liver disease and HCC in their regions and advocate modalities of containing these serious health problems.^{1–10} Resulting from a

process of continuing or intermittent injury followed by repair, over a prolonged period covering years, these diseases are generally encountered in adults and older individuals over 30 years age. When seen in children and adolescents they are due to inherited metabolic abnormalities or developmental defects. The present review, therefore, will be largely devoted to consideration of cirrhosis and end stage CLD in adults and only few of such diseases occurring in children will be discussed. The report will begin with a journey through time recounting the evolution of our understanding cirrhosis and end stage CLD and reviewing the changing scenes on their etiopathogenesis which have helped in formulation of proper strategies for preventive and therapeutic intervention programs. This will be followed by a critical evaluation of the current scenario on different etiologic types and finally by a foresight of the future global picture of these diseases in the years to come. A panoramic view of these dynamic changes will help to highlight the great potential of preventive and therapeutic strategies already available or going to be available, in controlling and largely eliminating the menace of chronic liver disease and its fatal complications.

2. Historical perspective

Awareness on ill health attributable to the liver has existed since the earliest organized human civilization. All ancient forms of medicine, Mesopotamian, Egyptian, Greek, Roman, Indian and Chinese not only recognized the importance of liver diseases but also formulated different therapeutic measures for them, several centuries before the birth of Christ (3000 BC onwards).^{11–14}

2.1. Early period of modern medicine (upto end of 19th century)

The first documentation of fatal chronic liver disease and the appearance of these livers at autopsy in writings on modern medicine were done during the mid 18th and early 19th century by physicians in England (John Brown, 1642–1700, Mathew Baillie, 1761–1823), Italy (Geovanni Morgagni, 1682–1771) and France (Theophile Laennec, 1781–1826).¹⁵ It was however, Laennec, the inventor of stethoscope, who first christened the name 'Cirrhose' derived from the Greek word 'Kirrhos' meaning tawny or

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