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The Patient, the Doctor, and the System: Underdiagnosis and Undertreatment of Hepatitis B

Cohen C, Holmberg SD, McMahon BJ, Block JM, Brosgart CL, Gish RG, et al. Is chronic hepatitis B being undertreated in the United States? J Viral Hepat 2011;18:377-383. (Reprinted with permission.)

Abstract

Chronic infection with the hepatitis B virus (HBV) is a major risk factor for the development of end-stage liver disease, including cirrhosis, liver failure, and primary liver cancer. There are now 7 antiviral agents approved by the US Food and Drug Administration for the management of chronic HBV infection. Despite the fact that there are between 1.4 and 2 million chronic HBV infections in the United States, fewer than 50,000 people per year receive prescriptions for HBV antiviral medications. This report discusses possible explanations for the disparity between the number of people who are chronically infected and the number of people who receive treatment. Explanations for this incongruence include the potentially large number of infected persons who are unscreened and thus remain undiagnosed, and lack of access, including insurance, education, and referral to appropriate medical care, particularly for disproportionately infected populations.

Comment

The incidence of acute hepatitis B (HBV) infection has decreased since the implementation of universal screening of pregnant women and vaccination of newborns.[1] However, there still exists a substantial number of Asian Americans, Africans, and other groups immigrating from areas of high prevalence, men who have sex with men (MSM), and IV injection drug users (IVDU) who are already infected or are at risk of infection. Once chronic, HBV increases the risk of cirrhosis, as well as hepatocellular carcinoma (HCC). Unfortunately, even with the success of preventative strategies there still exist 730,000 to 2 million people in the United States who are already chronically infected with HBV,[2] with the largest proportion being MSM, IVDU, and Asian Americans. Of the chronically infected, Cohen et al. suggest only 50,000 patients are receiving antiviral treatment.[3] Although not all infected persons require therapy, understanding why this large disparity exists requires understanding the individual, specific community, health care provider-related, and health care systems-based barriers that may exist.

One group affected by HBV infection is the Asian American/Pacific Islanders (AAPI), who comprise approximately 4% of the US population and are expected to be 9.2% of the population by 2050.[1] This group is disproportionately affected by chronic HBV compared to the rest of the US population as an estimated 1 in 10 AAPIs have chronic HBV. Of new cases of chronic HBV diagnosed in the United States, approximately 24% of those cases are found in AAPIs.[4] This is in contrast to the prevalence of chronic HBV among whites, which is estimated at 0.2%.[5] Many of these chronically infected AAPIs are immigrants from countries where the prevalence of hepatitis B surface antigen positivity may be as high as 10% to 20% of the population, which is seen in many parts of Southeast Asia.[5] Contributing to the issue is that two-thirds of immigrants from high-prevalence areas such as Southeast Asia do not know they are infected.[1] Many of the countries with the highest prevalence of HBV worldwide are also countries with limited resources for mandatory screening programs; therefore, increasing opportunities for screening this population are critical to decreasing the impact of chronic HBV infection.

Other populations at risk include MSM and intravenous drug abusers. These 2 groups have the highest incidence of acute HBV infection in the United States,[6] which equates to an annual incidence of chronic HBV infection within these groups of 1.1% and ~2.4% to 11%,[7] respectively. Although some of these individuals may have access to the health care system, studies have shown that these groups may also be underscreened for HBV.

The reasons for the lack of screening and treatment in high-risk groups often involve a patient's educational status, belief systems, and cultural barriers to screening. These factors can influence the willingness of an individual to seek screening or comply with screening recommendations. Philbin et al. recently surveyed immigrant and native-born Chinese, Vietnamese, and Korean individuals about their knowledge of hepatitis and associated liver diseases. In this study, the responses showed that many individuals felt that lack

of education about the disease, as well as limited access to health care were barriers to screening.[8] Studies among AAPIs who have lower levels of education and socioeconomical status revealed that they were the least likely to be vaccinated and screened.[1,9] These patients were asked about their health care in a questionnaire, which showed that health care provider recommendations as well as family suggestion were the leading reasons for a person to seek screening.[9] Overcoming these barriers as well as the social stigma of infection and treatment will be essential in improving screening and treatment acceptance.

The MSM community is often perceived as having a higher socioeconomic status than AAPIs; however, when this community was studied by the Young Men's Survey Phase II, Weinbaum et al. reported the prevalence of immunization at only 17.2% among MSM surveyed. Many of these individuals had access to health care or had been screened for HIV, another commonly associated disease among MSM, but many had no knowledge they were susceptible to HBV or that a vaccine existed.[6]

Aside from individual patient factors, the health care practitioner's role in screening, diagnosis, and treatment of HBV is of obvious importance. With the expansion of the treatment armamentarium and the effectiveness of vaccination, it would be expected that physicians would be highly proactive in screening and treating those meeting treatment guidelines. Unfortunately, this has not been the case as data published on physicians' adherence to The Centers for Disease Control and Prevention guidelines for screening showed that only 60% of physicians correctly screened at-risk patients.[10] In fact, many physicians who practice in areas with large at-risk populations such as AAPIs actually underestimate the impact of HBV on this population. Misidentifying the population to screen was determined to be the main reason for lack of screening among physicians in a recent survey.[1] Many clinicians feel they only need to screen those with abnormal liver tests, such as transaminitis or when presenting with symptoms, when in fact many patients may not have symptoms or abnormal lab tests.

The approval of new first-line oral therapies have shown effective viral suppression, low resistance, and good safety profiles with evidence of biochemical normalization and moderate rates of hepatitis B e antigen seroconversion.[11] The result of decreasing disease activity with antiviral suppressive therapy is decreased risk of cirrhosis and theoretical decrease of HCC risk as well.[12,13] Despite the availability of these medications, recent interviews with physicians who treat patients in AAPI populations show that close to 60% of these physicians are not aware of current treatments.[14]

In the article by Cohen et al.—"Is Chronic Hepatitis B Being Undertreated in the United States?"[3]—the authors show how patients, doctors, and health care systems are the primary factors for the lack of screening and treatment of HBV. Screening is cost effective even in population centers with as little as 0.3% prevalence when the expense of hospitalizations for cirrhosis and transplantation are considered.[15] The authors make the case that only 4% to 5% of chronic HBV-infected patients are screened, enter into a health care system, and obtain treatment. So what can we do? One large AAPI community intervention in San Francisco using a comprehensive citywide program utilizing HBV education, screening, and treatment showed that within 1 year of being screened, the individual diagnosed with chronic HBV (67%) had accessed health care, and many (78%) have encouraged family members to undergo screening.[1] This article makes a point that we probably all know: that hepatitis B is underdiagnosed and undertreated. The more difficult task will be how to mobilize stronger and more persistent patient, physician, and community advocacy to increase the numbers of patients screened, diagnosed, and treated.

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Exploring Beyond Cirrhosis

Hytiroglou P, Snover DC, Alves V, Balabaud C, Bhathal PS, Bioulac-Sage P, et al. Beyond "cirrhosis": a proposal from the International Liver Pathology Study Group. Am J Clin Pathol 2012;137:5-9. (Reprinted with permission.)

Abstract

"Cirrhosis" is a morphologic term that has been used for almost 200 years to denote the end stage of a variety of chronic liver diseases. The term implies a condition with adverse prognosis due to the well-known complications of portal hypertension, hepatocellular carcinoma, and liver failure. However, recent advances in the diagnosis and treatment of chronic liver diseases have changed the natural history of cirrhosis significantly. This consensus document by the International Liver Pathology Study Group challenges the usefulness of the word cirrhosis in modern medicine and suggests that this is an appropriate time to consider discontinuing the use of this term. The role of pathologists should evolve to the diagnosis of advanced stage of chronic liver disease, with emphasis on etiology, grade of activity, features suggestive of progression or regression, presence of other diseases, and risk factors for malignancy, within the perspective of an integrated clinicopathologic assessment.

Comment

The last 30 years have witnessed profound changes in the understanding and interpretation of chronic liver diseases (CLD). Although the birth of hepatology in the 1950s corresponds with the identification of defined clinical syndromes and with the increasing adoption of liver biopsy as a key diagnostic tool, the development of this area of medicine has reached maturity only with the progressive identification of hepatitis viruses, immune- and toxicity-mediated mechanisms, genetic mutations, and the relative pathophysiological events leading to chronic damage, inflammation, fibrogenesis, and carcinogenesis. In spite of these major advancements, the term *cirrhosis*, introduced almost 200 years ago, to highlight the presence of profoundly abnormal structure of the liver in current clinical usage indicates an irreversible end-stage condition. However, it is increasingly evident that the term cirrhosis does not reflect accurately the modern understanding of chronic fibrogenic liver diseases, which demands an integrated clinical-pathological assessment; a readjustment of perspective is urgently required. This necessity is clearly expressed in the well-timed article by the International Liver Pathology Study Group.[1] The key suggestion of this article is to abolish the term cirrhosis and to introduce a more rational and clinically useful approach to identify different stages of the evolution of advanced-stage CLD. This is in complete agreement with the increasing awareness of the hepatology community concerning the need for a pathophysiological classification of cirrhosis.[2] In any case, it is remarkable that this suggestion comes from pathologists at the same time that clinicians have increasing difficulties in categorizing advanced liver disease after realizing that fibrosis in a cirrhotic liver (and even early cirrhosis itself) is at least partially reversible following appropriate treatment. In addition, the term cirrhosis is generally sensed as absolutely fatal by patients and many physicians, whereas by modern standards, all cases of cirrhosis do not inevitably result in clinically significant portal hypertension and hepatocellular failure leading to liver transplantation or death.

In addition to these considerations, in their article this group of pathologists make a vibrant analysis of several morphological, clinical, and pathophysiological matters strictly connected with the overall concept of cirrhosis. A first important issue is related to the contrast between the definition of cirrhotic liver as the morphological end stage common to all types of chronic liver disease, regardless of the different patterns and mechanisms of fibrogenesis or the culpable fibrogenic cell types (ie, portal myofibroblasts vs hepatic stellate cells) relevant to different etiologies of chronic liver disease.[3] In other words, the natural history of

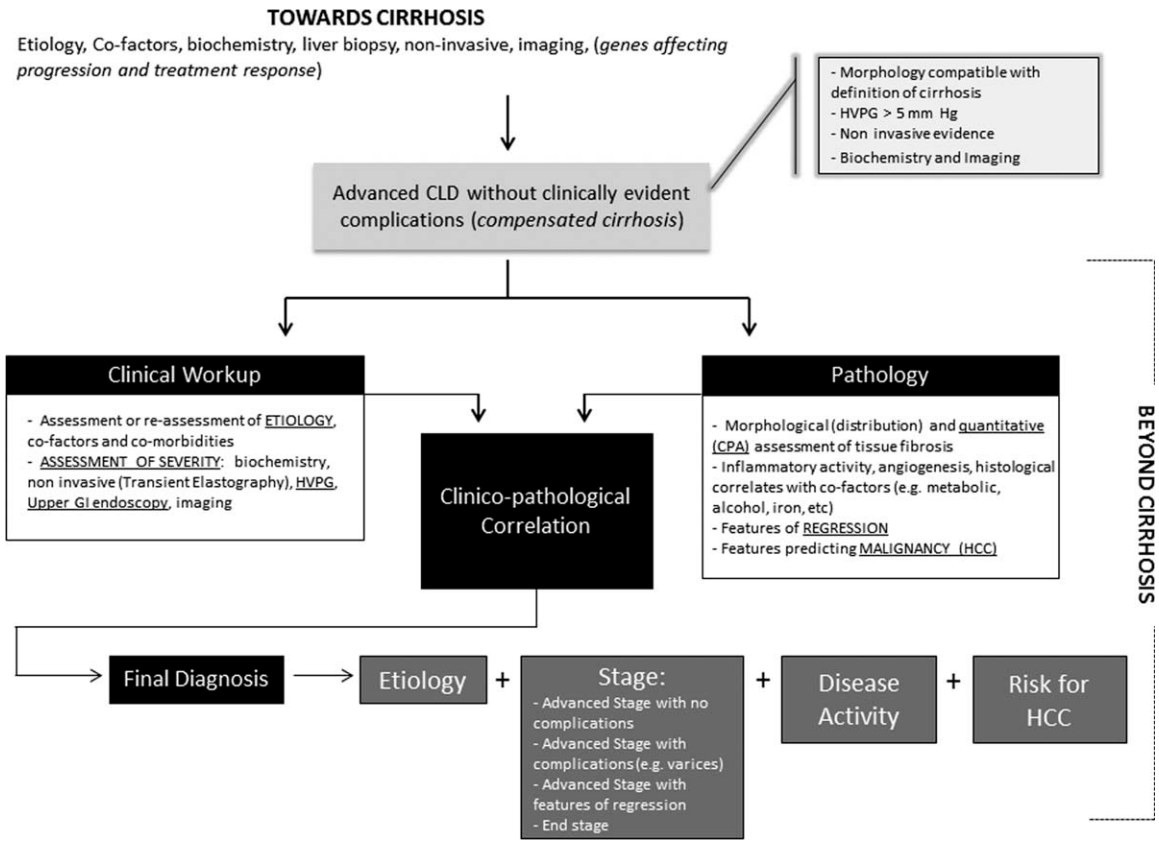

Fig. 1. Proposed working scheme for future studies investigating the relationships between pathological aspects and clinical data in the setting of advanced chronic liver disease (CLD) without clinically evident complications. CPA, collagen proportionate area; GI, gastrointestinal; HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient.

disease associated with a cirrhotic liver caused by chronic alcohol abuse could be markedly different when compared to a cirrhotic liver caused by chronic viral hepatitis. In addition, the potential for disease progression and regression following abstinence and treatment will also be different. Along these lines, the results of a recently published study[4] analyzing fibrosis distribution in explanted cirrhotic liver indicated that a case of alcoholic cirrhosis requiring liver transplantation is characterized by a collagen content, assessed with recently introduced collagen proportionate area (CPA) method,[5] which is on average double that of a case of HCV-related cirrhosis. These observations affirm the idea that cirrhosis, or more precisely advanced-stage CLD, should be primarily framed according to etiology. It is indeed rare in modern medicine to find a term equivalent to cirrhosis that serves as a blanket term to denote end-stage fibrous disease of other organs.

The evaluation of CPA as well as of other morphological aspects, such as nodule size and thickness of fibrous septa,[6,7] may help in establishing a pathophysiological link, possibly etiology driven, with the progression of portal hypertension particularly in the stage of advanced CLD known as *compensated cirrhosis*, which should be accordingly renamed *advanced-stage CLD without clinically evident complications*. Overall, the considerations made in this article apply mainly if not exclusively to this stage of CLD. Along these lines, measurement of hepatic venous pressure gradient (HVPG) associated with transjugular liver biopsy could be proposed at this clinical juncture, although these procedures are available only in highly specialized centers. More importantly, studies investigating the relationship between liver morphology, CPA, HVPG, and some of the available noninvasive methodologies, particularly liver stiffness, could increase the possibility for noninvasive monitoring of disease progression within a phase of the disease currently interpreted as end stage but not yet characterized by clinical complications.

As suggested by the authors, a more insightful morphological analysis of the liver of patients with advanced-stage CLD may also add important information on key pathophysiological aspects that are currently neglected, such as the degree of

necroinflammation (still representing the main profibrogenic stimulus), the extent of neoangiogenesis in fibrous septa, the characteristics of liver regeneration (particularly the contribution of mature hepatocytes versus hepatocyte precursor cells), and the occurrence of preneoplastic features and features of neoplasia risk (such as small and large cell changes). As further stressed in the article, all of these features, and particularly the predictors of hepatocellular carcinoma, may be significantly different according to different etiologies.

Certainly, the definition of these morphological aspects would have a positive impact in the interpretation of fibrosis regression and architectural improvement following etiological and/or antifibrotic therapy, especially if linked with significant changes in portal pressure and in parameters obtained with noninvasive methodologies.[8] In addition, considering that 1 of the most highly anticipated revolutions in medicine is the introduction of bioimaging techniques able to link cellular and molecular mechanisms with changes in tissue structure and clinical manifestations, a more precise definition of these aspects will help to set morphological standards of disease progression and regression to be targeted by new imaging technologies.

Although the content and the spirit of the proposal formulated in this article by the International Liver Pathology Study Group are innovative and represent a solid base for a constructive debate among hepatologists, the plan proposed to put these concepts into clinical practice is complex and of uncertain success. The main difficulty for the clinician is the central role of liver biopsy in this process of reclassifying advanced-stage CLD in times when the utility and the accuracy of liver biopsy are being continuously challenged even for initial and intermediate stages of disease progression. In other words, although this may be applicable in major specialized centers, it will be difficult to convince the hepatology community to introduce liver biopsy as a routine procedure in patients with advanced-stage CLD, who will still be seen as cirrhotics and therefore as subjects bearing a high risk of postbiopsy complications. In any case, Figure 1 proposes a working scheme complementing the outline provided in the article by Hytiroglou and colleagues[1] that may represent the basis for future work aimed at a more detailed investigation of the relationships between pathological aspects and clinical data in the setting of advanced CLD without clinically evident complications.

In conclusion, what is the real impact of the International Liver Pathology Study Group proposal? The answer is that it is time to change our mentality and professional approach toward cirrhosis. The message of these pathologists converges with that of clinicians and scientists and calls for a new classification of advanced-stage CLD (not just cirrhosis!) incorporating etiology, prevalent cellular and molecular mechanisms, specific changes in tissue architecture and biology, and invasive (HVPG) and noninvasive diagnostic approaches, bearing in mind that fibrosis and even early cirrhosis could be reversible. At the same time, it becomes clear that we should look also at earlier stages with new eyes, because the traditional histopathological systems for staging CLD become more and more obsolete with the progress in understanding fibrogenesis. On the other hand, it is clinically crucial to know which patients will progress to cirrhosis. Therefore, the article by the International Liver Pathology Study Group is a stimulus to an overall rethink of the systems we use to assess the risk of progression of CLD. In other words, exploring beyond cirrhosis but also toward cirrhosis could create a platform for a future rich in noninvasive diagnostic and prognostic methods and advanced bioimaging.

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