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• REVIEW •

Current research of hepatic cirrhosis in China

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Abstract

Hepatic cirrhosis is a common disease that poses a serious threat to public health, and is characterized by chronic, progressive and diffuse hepatic lesions preceded by hepatic fibrosis regardless of the exact etiologies. In recent years, considerable achievements have been made in China in research of the etiopathogenesis, diagnosis and especially the treatment of hepatic fibrosis, resulting in much improved prognosis of hepatic fibrosis and cirrhosis. In this paper, the authors review the current status of research in hepatic fibrosis, cirrhosis and their major complications.

Key words: Hepatic cirrhosis; China

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ETIOLOGY OF HEPATIC CIRRHOSIS

In China, virus hepatitis B and C remain the primary etiological factors for hepatic cirrhosis, and a recent increase in alcoholic cirrhosis has also been noted[1,2]. But in the past years, approximately 25% to 40% of HBsAg-, antiHBc and antiHBe-positive cases failed to receive due attention[3] for the potential risk of hepatic cirrhosis, and carcinoma in relatively rare cases. With the development of public hygiene, schistosomal liver cirrhosis has greatly decreased, and other etiologies such as biliary cirrhosis, hemochromatosis and Wilson's disease are now hardly seen.

STUDY ON HEPATIC FIBROSIS

Hepatic fibrosis is a reversible pathological process[4] and chronic hepatic disease has become a widespread concern of researchers. Recently, significant results have been obtained in research of the pathogenesis of hepatic fibrosis in view of the role of hepatic stellate cells (HSCs)[5-7], formation of extracellular matrix (ECM), hyperoxidation, cytokine network, Na^+/H^+ exchange pump and calcium channel.

Pathogenic mechanism of hepatic fibrosis

HSCs, the main source of ECM[8,9], play important roles in the formation of hepatic fibrosis[2,12-16]. Pathogenic research of hepatic fibrosis is now focused on the following respects: peroxidation mechanism, cytokine network, signal transduction pathways, and cell apoptosis, as examined briefly in the following.

Peroxidation mechanism Chronic hepatic damage by inflammation, toxins, immunity, and malnutrition, *etc.*,can activate HSCs. The process of activation is closely related to peroxidation[10-13]. It has been shown that lipid peroxidation occurs in injured hepatic cells[14], which may further activate HSCs. In the event of hepatic inflammatory reaction, neutrophilic granulocytes are the main source of reactive oxygen species (ROS)[15] that have been proved to be able to promote HSC activation and proliferation *in vitro*[16]. Some anti-oxidants can inhibit the activation of HSCs, suggesting that peroxidation accompanies the progression of hepatic fibrosis.

Cytokine network Kupffer cells can initiate the progress of hepatic fibrosis[17]. After being activated, Kupffer cells release a variety of cytokines closely related to hepatic fibrosis such as transforming growth factors (TGF)α and β, tumor necrosis factor (TNF)α, interleukin-1 (IL-1) and platelet-derived growth factor (PDGF). In addition, Kupffer cells, which can be regarded as important "coefficients", help maintain the kinetic equilibrium of hepatic fibrosis, and mediate the feedback mechanism of some biological messages during the progression of hepatic fibrosis. HSCs have both paracrine and autocrine functions, the activation of which can be triggered via a reaction cascade of cytokines and biochemical factors[18-20]. Two major changes occur after the activation of HSC, that is, proliferation and phenotypic transition[21]. PDGF and TGFβ1 play an important role in the proliferation and transformation of HSCs[22]. The key role of PDGF, a most effective mitogen during the synthesis of HSC DNA[23], is to convert HSC from G_0 to G_1 and S phases, whereas TGFβ1 promotes the synthesis of collagen and inhibitors of tissue metalloproteinases (TIMPs) in activated HSCs[24]. Moreover, PDGF and TGFβ1 can interact with each other. PDGF is capable of inducing HSCs to express and secrete PDGF receptors. PDGF and TGFβ1 can also interact with IL-1 and TNFα[25], leading to the formation of cytokine network with HSCs at the crucial center.

Na^+/H^+ exchange pump and calcium/calmodulin Messages in cytokines could pass to HSC nuclei through the membrane or intracellular pathways. Svegliati Baroni *et al*[14] found that the HSCs exposed for 24 h to the culture medium of hepatocytes subjected to oxidative stress could increase the proliferation of HSCs and accumulation of collagen I. The mechanism is related to the increased intracellular pH of HSCs and enhanced activation of Na^+/H^+ exchanger. Actually, Na^+ influx is the key element that initiates the proliferative reaction[26]. PDGF can activate Na^+/H^+ exchanger by activating IP3-calcium/calmodulin and protein kinase C[27]. Synthesis of ECM promoted by TGFβ1 may be modulated by the activity of calcium channel[28]. Therefore, activation of IP3-calcium/calmodulin-Na^+/H^+ exchanger in succession induces proliferation of HSCs and synthesis of ECM, which serves as the theoretical basis for therapy of hepatic fibrosis.

HSC apoptosis Concerning the apoptosis of HSCs, consensus has been reached over the occurrence of HSC apoptosis, which takes place in α-SMA-positive but not static HSCs, in parallel with phenotypic transition[29]. CD95 (APO-1/Fas) receptor and

its ligand have been recognized for their important role in inducing HSC apoptosis[30], and the therapeutic strategy against hepatic fibrosis is maneuvered to target at promoting the apoptosis of HSCs. Realization that activation is the premise of apoptosis of HSCs is not meant to confirm the seemingly natural cause-effect relationship between monophasic HSC activation and apoptosis, and the reversibility of phenotype transformation of HSCs is still worthy of further exploration.

Diagnosis of hepatic fibrosis

Currently, the diagnosis of hepatic cirrhosis depends mainly on needle biopsy of the liver, and ultrasonic examination can hardly define the degree of hepatic fibrosis. Through consistent effort, researchers have made encouraging progress in serological diagnosis of hepatic cirrhosis[31-34].

Pathological diagnosis In May 1995, the *Prevention and Treatment of Virus Hepatitis* was revised at the 5th Congress of Parasite and Infectious Diseases, and chronic hepatitis was then classified into mild, moderate and severe degrees and pathologically graded into G0-G4 degrees and S0-S4 stages. Wang *et al*[35], after observing 1 000 hepatic biopsy specimens, proposed a classification protocol of the inflammatory activity and fibrosis, which was an improved version of the criteria given by Knodell *et al*[36] and Chevallier *et al*[37]. This protocol has now been accepted in clinical practice.

Serological diagnosis Needle biopsy of the liver has its inherent limitations in diagnosis and curative effect assessment[38]. Currently, great progress has been made in the serological diagnosis of hepatic fibrosis[39,40]. Many useful indices have been set up to reflect the metabolism of ECM, including PCIII/ PIIIP, CIV, PIIIP, and LN[41,42], of which HA is the most sensitive. CIV, the main ingredient of basal membrane, was found to elevate during capillarization of the hepatic sinusoid. After comprehensive analysis, HA and CIV were established as the most significant indices during S3 and S4 stages[38]. Our hospital developed a "quadruple detection" protocol combining CIV, PIIIP, LN and HA, which proved to be highly specific and sensitive. However, its value should not be overemphasized while comprehensive judgment is still needed including that derived from biochemical examinations.

Treatment of hepatic fibrosis

So far, no satisfactory treatment protocol with western drugs is available for hepatic fibrosis because of their severe side effects. Meanwhile, we have obtained promising results with traditional Chinese medicines, and a number of drugs have been found to reverse the progression of hepatic fibrosis. Antifibrotic therapy targets at the inhibition of HSC proliferation[43-46], cytokine activity[47-49] and ECM degradation. Calmodulin antagonists belong to HSC proliferation inhibitors, working to inhibit the pathway of IP3-calcium/calmodulin-Na^+/H^+ exchangers, but relevant studies[50-52] conducted in China have so far achieved no significant breakthrough in this aspect. The apoptosis of HSC was another interest of study in recent years[31-33,53-55]. Gene therapies using antisense oligonucleotides, nucleases and gene carriers promise optimistic results of treatment, but the problems of gene targeting and expression modulation have yet to be solved. Studies have shown that traditional Chinese medicines can inhibit the deposition of collagen fibers[56-63] and promote the reversion of fibrosis, which was also confirmed by experimental evidence that *Radix Salviae Miltiorrhizae*, *Radix Angelicae Sinensis*, *Radix Astragali seu Hedysari*, *Radix Paeoniae Rrbra*, *Semen Persicae*, *Hirudo*, *Flos Carthami*, *Radix Notoginseng*, *Rhizoma Sparganii*, *Rhizoma Zedoariae*, *etc* could obviously inhibit the formation of collagen fibers. The agent 861[56,59], *Qianggan* capsule, *Fuzhenghuayu* 319[58], *Dahuangzhechong* pill[59], *Yigan* infusion[60], and the traditional Chinese medicinal formula *Xiaochaihu* decoction *etc*., could eliminate clinical symptoms, improve liver function, decrease liver collagen content and improve the histologic picture of the liver without obvious side effects, all of which seem to suggest a bright future of traditional Chinese medicine in treating hepatic fibrosis. Problems, however, do exist in traditional Chinese medicines, in the standardization and purification methodology. Currently no standardized criteria are available to compensate for the geographical variation in the content of effective components of drugs, and the methods of harvest and refinement are also controversial. The methodology employed for animal experiments needs standardization, and strict double-blind, multi-center studies have yet to be performed.

STUDY OF LIVER CIRRHOSIS

In China, histological diagnosis of liver cirrhosis is not a universal practice and liver puncture is performed in a very small portion of patients suspected of the disease. The clinical diagnosis of liver cirrhosis still depends on the presence of enlarged and hardened liver and spleen, and manifestations of portal hypertension. Non-invasive B type ultrasound provides a convenient means for the diagnosis of liver cirrhosis, the typical manifestations of which include sharp or wave-like margins of the liver and disproportional right and left lobes of the liver with uneven echoes from the hepatic parenchyma. The indirect signs include enlarged spleen, dilated portal (>1.4 cm) or splenic veins (>0.9 cm) and ascites. The treatment of cirrhotic patients is directed against the complications including ascites, gastrointestinal bleeding, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, hepatic encephalopathy, cirrhosis-induced carcinoma and thrombosis, *etc*. Current interests of research are devoted predominantly to bleeding gastroesophageal varices, early diagnosis of SBP, recognition and treatment of subclinical hepatorenal syndrome, treatment of ascites especially refractory ascites, diagnosis of subclinical hepatoencephalopathy, early detection of liver cancer, and hypertensive gastrointestinal diseases.

Esophageal variceal bleeding (EVB)

Critical factors and prediction of EVB Degree of liver damage, size of varices, endoscopic red color signs and elevated portal vein pressure (PVP) or hepatic vein pressure gradient (HVPG) are the major risk factors for bleeding[64]. In China, patients with PV$\geqslant$1.70 cm, SPV$\geqslant$1.20 cm and EV$\geqslant$6.0 mm especially those with red color signs are at high risk for bleeding[65]. Impaired liver function is the dominant factor threatening bleeding, as the blood flow rate in cases of extrahepatic hypertension with normal liver function, in spite of the presence of severe varices and higher PVPs, is decidedly lower than that in liver cirrhosis patients with portal hypertension[66]. The more relevant factors are the red color signs on the varices seen on endoscopy and hemodynamic changes with portal pressure[67]. Recently, much attention has been paid to bacterial infection for its potential to cause bleeding[68-70], possibly because in patients with severe varices and a high esophageal wall tension, the release of endotoxin into the systemic circulation during the episodes of bacterial infection resulted in a further increase in the portal pressure induced by endothelin and possibly vasoconstrictive cyclo-oxygenase products. The subsequent contraction of HSC caused a rise in intrahepatic vascular resistance. Furthermore, endotoxin-induced nitric oxide and prostacyclin, and prostacyclin induced by endothelin could inhibit platelet aggregation, which may result in further deterioration of the already existent bleeding[64].

Strategies of management Correct use of Sengstaken-Blakemore tube, knot and sclerosis of esophageal varices, and uses of new hemostatics such as somatostatin and thrombin, have improved the prognosis of EVB[71-74]. The rebleeding and mortality rates have been greatly reduced by use of β-receptor blockers as the first-line drugs; the combination of β-receptor blockers, calmodulin antagonists, and nitroesters can enhance the efficacy; vasopressin should be used with nitroglycerin or to reduce the side effects, somatostatin and octreotide are better options than vasopressin and have no obvious side effects. Traditional Chinese herbal drugs such as *Radix Salviae Miltiorrhizae*, *Radix Angelicae Sinensis*, may promote the blood flow and remove blood stasis, and are effective for lowering the PVP and HVPG. The slow but relatively long-lasting effects of the herbal drugs help prevent bleeding[75,76]. Sclerosis and knot of the varices also effectively prevent the primary bleeding and decrease the rate of rebleeding. Porto-systemic shunt, however, is not recommended for the prevention of the primary bleeding. TIPSS could prevent the primary bleeding, but the rebleeding rate and long-term effect need further assessment.

Refractory ascites and hepatorenal syndrome

The ascites in cirrhotic patients usually indicates the progression of the disease into the decompensatory stage. Patients with a small amount of ascites should receive active and adequate treatment when they respond favorably to diuretics and have sufficient renal function without electrolyte disturbance. Rest, restricted salt intake, protein-rich food or application of herbal drugs that promote blood flow, removing stasis, invigorating the spleen and refreshing *Qi* (such as *Rhizoma Alismatis, Polyporus Umbellatus*, *Semen Plantaginis* and the preparation of *Weiling* decoction), could help eliminate the ascites. For patients with a large amount of ascites that failed to be resolved by exclusive use of traditional Chinese drugs, spirolactone should be given with short-term use of dihydrochlorothiazide. Diuretic abuse should be avoided for potential drastic reduction in systemic blood volume and development of hepatorenal syndrome. Close relationship has been identified between ascites and renal function. Patients with refractory ascites are often characterized by increased resistance index (RI) of the interlobar and cortical vessels in comparison with patients with responsive ascites. The RI decreases physiologically from the hilum of the kidney to the outer parenchyma in healthy subjects and patients with responsive ascites, but this difference vanishes in patients with refractory ascites[76]. Examination of renal blood distribution may help identify hepatorenal syndrome at early stages and make correct therapeutic decisions on responsive ascites. In clinical practice, elimination of ascites should be considered in line with the evaluation of the renal function. Spontaneous ascites discharge with intravenous albumin[77] or dextran infusion[78] and ascites autoperfusion[79] have achieved good results. Close monitoring of the renal function needs to be carried out when attempt is made to lower the portal pressure and eliminate the ascites. Radionuclide renal dynamic imaging can be performed for diagnosis of subclinical hepatorenal syndrome[80], and a thorough understanding of the status of the renal blood dynamics and perfusion of the glomeruli may hold much significance for the prognosis of hepatorenal syndrome and refractory ascites.

Splanchnic hyperdynamics and SBP

Most cirrhotic patients suffer from disturbance of the intestinal flora. The overgrowth of aerobic Gram-negative bacteria may play an important role in endotoxemia[81]. The diagnosis of SBP is based mainly on the results of cell counting, and differential or bacterial culture of the ascites greatly helps the description of SBP. So far, the knowledge about endotoxemia, endothelin and NO has revealed a new scope of splanchnic hyperdynamics and SBP: endotoxin evokes the release of endothelin, which in turn increases the PVP, and promotes the synthesis of NO and other vasodilators such as VEGF[82] derived from the residue cells induced by IL-1 and TNFα as well. These dilators cause the dilation of the splanchnic vascular beds, and the arterioles and microarteries are especially responsive to these substances, to result in the decreased blood RI followed by lowered blood pressure and increased heart output. This low RI and hyperdynamics, along with the high CI and low blood flow velocity[76] at the portal system, are further deteriorated by SBP, resulting in variceal bleeding for more elevated PVP and heat shock or hepatorenal syndrome. Close relationship was found among the four episodes: SBP, portal hypertension with splanchnic hyperdynamics, esophageal venous bleeding and hepatorenal syndrome. For those who were not responsive to diuretics, diagnostic abdominocentesis and bacterial culture should be performed even in the absence of abdominal signs of SBP. The treatment of SBP include (1) strengthening the trophotherapy, (2) using antibiotics according to the bacterial culture, (3) treatment with intravenous antibiotics for more than 7 d or continuous use for 3-6 d after the abdominocentesis becomes negative, and (4) intravenous antibiotics combined with ascites discharge and intraperitoneal injection of drugs, which may produce better effect than exclusive use of intravenous antibiotics.

Hepatic encephalopathy

Severe liver diseases may lead to functional disturbance of the central nervous system with a high mortality rate, which can be relieved by early detection of the condition. In recent years, the diagnosis of subclinical hepatic encephalopathy has witnessed great improvement in China. The examination of nerve-evoked potentials offers a means of objective and sensitive diagnosis of the disease[83]. Several factors may contribute to the occurrence of encephalopathy, including (1) blood accumulation in the intestines after bleeding or intake of substances containing nitrogen, (2) water and electrolyte disturbance for iatrogenic reasons, (3) endotoxemia and infections, (4) *Helicobacter pylori* (*H pylori*) infection, (5) use of anesthetics or sedatives, and (6) decompression of the portal vein such as by TIPSS or porto-systemic shunt. Elimination of these factors may reduce or even prevent the occurrence of encephalopathy. When the disease occurs, treatments with defecation and intestinal acidification, use of arginine or glutamate, branch-chain amino acids, and levodopa are often effective. Antibiotics for *H pylori* can be used to reduce the absorption of ammonia from the intestine for treatment of hepatic encephalopathy.

Others

Ultrasonic examination and AFP dynamic methods are reliable for early diagnosis of primary liver cancer. Hepatic arterial radiography, CT and needle biopsy should be used in suspected cases to raise the diagnostic accuracy. Gastrointestinal disease with portal hypertension is no longer a concept of simple pathology, but a disease with specific clinical and endoscopic presentations secondary to liver cirrhosis[84-86]. Low blood oxygen capacity in liver cirrhosis, or hepatopulmonary syndrome, is closely related to the portopulmonary shunt, inflammation of the lungs, hydrothorax and atelectasis at the base of the lung[87]. Hepatic hydrothorax is most often found on the right side of the pleural cavity, but so far its causes have not been fully understood. Hypoalbuminemia

could accelerate the formation of hydrothorax in cirrhotic cases. Budd-Chiarry syndrome, which is found much more frequently than ever, is likely to be confused with liver cirrhosis. Color Doppler ultrasound or infravenacavography, if necessary, could identify most of the causes of the disease. It is worth noticing that splanchnic hyperdynamics and hypoalbuminemia may lead to hepatic myocardiopathy and heart insufficiency[88].

We believe that the incidence of liver cirrhosis can be lowered with its prognosis improved, when more effort is made in research of the complex mechanism of fibrosis and cirrhosis and their molecular biology, serological diagnosis, complications in relation to liver cirrhosis, application of integrated Chinese and western medicine, and especially the study of the curative mechanism of Chinese herbs, their serological pharmacology and the extraction of effective components.

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