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Research Progress on Serum Porphyrin and Chronic Liver Disease

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Abstract: Liver cirrhosis is an important cause of chronic liver cancer. At present, a breakthrough has been achieved in the development of chronic hepatitis C treatment, but there is no effective measure to completely cure chronic hepatitis B. Porphyrins are a class of macromolecular heterocyclic compounds formed by interconnecting the α-carbon atoms of four pyrrole-like substituents through hypomethyl bonds. Porphyrins and their derivatives widely exist in organelles related to energy transfer in organisms. They are mainly involved in the synthesis of heme in human body. Heme is an iron-containing porphyrin compound, 15–20% of which is synthesized and utilized in the liver. Studies have found that porphyrin metabolism disorder can occur in patients with chronic liver disease. The early stage of viral hepatitis is accompanied by increased production of porphyrins and their compounds, increased levels of peripheral circulating porphyrins, porphyrin cholestasis, and biochemical changes of free porphyrins which precede the histological changes. The accumulation of serum and liver protoporphyrins and the oxidative stress can cause liver and extrahepatic damage. On the one hand, porphyrin metabolism disorder can aggravate chronic liver disease, and even progress to liver cirrhosis and liver cancer. On the other hand, chronic liver disease can also aggravate porphyrin metabolism disorder, recurrent attacks, and damage to liver and extrahepatic tissues and organs.

Keywords: Viral hepatitis; Chronic hepatitis B; Hemoglobin; Protoporphyrin; Porphyrin

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1. Introduction

Viral hepatitis is one of the most important public health problems in the world. The World Health Organization has proposed the complete elimination of viral hepatitis by 2030. At present, new drugs are developed to treat hepatitis C. However, no effective measures have been taken to completely cure hepatitis B. To achieve the goal of completely eliminating viral hepatitis by 2030, reducing the incidence of chronic hepatitis B and hepatitis C cases and reducing the mortality rate by 65%, it is necessary to carry out further basic and clinical research about hepatitis, and the status quo of the diagnosis and treatment of hepatitis is still not optimistic. Therefore, it is of great significance to carry out early warning, treatment timing and clinical evaluation based on the condition of abnormal porphyrin metabolism after hepatocyte damage in

viral hepatitis.

At present, there are about 70 million cases of chronic hepatitis B virus (HBV) infection in the whole population in China, including 20–30 million cases of chronic hepatitis B (CHB) infection. The medical burden caused by HBV-related diseases is very heavy [1]. Although nucleoside antiviral drugs play a definite role in the treatment of hepatitis B, they are unable to completely eliminate the virus. At present, there are about 10 million patients with chronic hepatitis C [2], but less than 3% of the patients have been diagnosed, and only about 50% of the patients have received antiviral treatment [3]. The current situation of prevention and treatment is not optimistic.In recent years, the prevalence of adult nonalcoholic fatty liver disease (NAFLD) in China has increased rapidly. The meta-analysis based on 392 epidemiological studies on a total of 2054554 people from 2008 to 2018 shows that the prevalence of NAFLD in China is now as high as 29.2%. NAFLD has become the most common form of chronic liver disease in China, accounting for 50% of the total cases of all etiologies of chronic liver disease [4]. NAFLD heavily burdens the society and families. Therefore, early diagnosis and treatment are of great significance to prevent disease progression and improve prognosis.

2. Course of chronic HBV infection and antiviral strategy

2.1. Course of HBV infection

According to the natural course, the natural history of chronic HBV infection can be generally divided into four stages [5-7], namely immune tolerance stage (chronic HBV carrying state), immune clearance stage (HBeAg positive CHB), immune control stage (inactive HBsAg carrying state), and reactivation stage (HBeAg negative CHB). Not all patients with chronic HBV infection go through the above-mentioned four stages.

2.2. Antiviral strategies for chronic HBV infection

The Guidelines for Prevention and Treatment of Chronic Hepatitis B (2019 Edition) points out that patients with positive serum HBV DNA and normal alanine aminotransferase (ALT) have a high risk of disease progression if they have one of the following conditions, and antiviral treatment is recommended: (i) Liver histology showed obvious liver inflammation (≥ G2) or fibrosis (≥ S2); (ii) Family history of liver cirrhosis/liver cancer and age > 30 years; (iii) There is no family history of liver cirrhosis/liver cancer, but the patient's age is > 30 years old. It has been reported that obvious liver inflammation or fibrosis were detected in liver fibrosis patients by noninvasive diagnostic technique or liver histology; (iv) There are HBV-related extrahepatic manifestations, such as glomerulonephritis, vasculitis, nodular polyarteritis, peripheral neuropathy, etc.; (v) Patients with compensatory cirrhosis. It is generally considered that HBV replication is more active in patients with hepatitis B during the immune tolerance period, positive or negative HBeAg in serum, HBV-DNA content ≥ 104 copies /ml, and normal serum levels of ALT and AST. During the immune tolerance period, the immune system in the body of patients with hepatitis B can neither recognize the HBV virus nor effectively clear the HBV virus. The effect of antiviral treatment during this period is poor, and antiviral treatment is not recommended [1]. There is a consensus that the immune clearance period is the best timing to treat chronic hepatitis B with antiviral therapy. Some patients in the immune tolerance period may enter the immune clearance period and have hepatitis activity. Inactive HBsAg carrier status is in immune control stage, but it is still possible to develop into HBeAg negative CHB, and there is still a risk of hepatocellular carcinoma (HCC) in long-term follow-up. The treatment is limited to the immune clearance stage, which is unfavorable for the prevention and termination of the occurrence and development of liver cirrhosis and liver cancer [1]. Based on a large number of clinical treatment studies and follow-up data, massive liver puncture demonstrates the presence of ≥G2 inflammatory necrosis in 90% of the liver tissue in patients with high hepatitis B viral load but with ALT

< 2×UIN, which requires antiviral therapy [8]. Studies have shown that tens of millions of hepatitis B patients in immune tolerance period in China refuse to undergo liver biopsy and fail to receive antiviral treatment in time, so these patients will become a high-risk source of hepatitis B virus infection and do great harm to other people [1]. This problem has been discussed many times at the national liver disease conferences in recent two years, but there is a lack of effective monitoring indicators. Therefore, it is of great significance to find a sensitive biomarker that can predict liver function damage in patients with immune tolerance.

3. Porphyrin metabolism in chronic liver disease

3.1. Porphyrin metabolism disorder

Studies have found that porphyrin metabolism disorder often occurs in chronic liver disease. Porphyrins are a class of macromolecular heterocyclic compounds formed by interconnecting the α-carbon atoms of four pyrrole-like substituents through hypomethyl bonds (=CH-). The parent compound is porphin ($C_{20}H_{14}N_4$), and the porphin with substituent is called porphyrin. A molecule of porphin combines with a metal ion to form porphyrin. Porphyrins and their derivatives widely exist in important organelles related to energy transfer in organisms. It is mainly involved in the synthesis of heme in human body. Heme is an iron-containing porphyrin compound, 15–20% of which is synthesized and utilized in the liver. Liver is also prone to porphyrin metabolic abnormalities. Porphyria can be divided into 8 types according to the defect of enzyme [9]. Heme is synthesized through a series of enzymatic reactions: Glycine and succinyl coenzyme A are synthesized into δ-ALA by the action of 5-aminolevulinic acid synthase (ALAS), which is catalyzed by ALA dehydratase to form bilirubinogen (PBG). Most PBGs synthesize uroporphyrinogen under the action of hydroxymethylbilin synthase (HMBS) and uroporphyrinogen synthase, and then convert into fecal porphyrinogen and protoporphyrinogen IX to form protoporphyrin IX, which is combined with divalent iron to synthesize heme under the catalysis of ferrous chelatase. In some pathological conditions, some parts of the heme metabolism pathway may be disturbed, leading to abnormal metabolism of heme or porphyrins in the body and resulting in increased levels porphobilinogen and porphyrin precursors in blood, urine and feces, which offers the possibility of using porphyrins as biomarkers [10]. Animal experiments confirmed that when the liver parenchyma was damaged, the level of metalloporphyrin in the liver decreased, while the biochemical changes of free porphyrin increased and preceded the histological changes [11]. Our previous clinical studies also found that the porphyrin metabolism of patients with chronic hepatitis B was abnormal, while that of patients with nonalcoholic fatty liver was basically unchanged. According to the results of this study, combined with the fact that there is no clear demarcation index between immune tolerance period and immune clearance period of chronic hepatitis B in clinic settings, the application index of antiviral drugs remains unclear.

3.2. Causes of porphyrin metabolic disorder

The cause of disorders of porphyrin metabolism in chronic liver disease is unclear and could be the result of multiple factors leading to increased production of porphyrins and their compounds, increased peripheral circulating porphyrins, porphyrin cholestasis, or a combination thereof.

3.2.1. Increased synthesis of porphyrin and its compounds

Liver δ-aminolevulinic acid synthase 1 (ALAS1) is a rate-limiting enzyme responsible for hepatic heme synthesis. Missense or nonsense mutations in susceptible genes involved in the process of hepatic heme biosynthesis, such as hydroxymethylbisalkane synthase (*HMBS*) mutation, could cause significant decrease of hepatic HMBS activity. In coordination with other environmental, nutritional, hormonal and genetic factors, it may lead to the serious defect of heme, the final product of this pathway. The de-inhibition of the

rate-limiting enzyme 5-aminolevulinic acid (ALA) synthase-1 is significantly upregulated, leading to the overproduction of ALA in the liver, and the downstream intermediate of ALA, i.e., porphyrinogen (PBG), in the synthesis chain will become in excess [12]. Due to chronic liver disease, the chronic consumption of heme in the body increases, and the feedback inhibition of the rate-limiting enzyme ALAS1 of heme synthesis is weakened, resulting in the production of excessive porphyrins and porphyrin precursors. ALA and PBG released into the blood circulation through the liver have toxic effects on the liver, extrahepatic tissues and neurons, and can cause neurological and endocrine clinical manifestations, which are often accompanied by severe abdominal pain, vomiting, tachycardia and hypertension. Severe cases could also become comorbid with hyponatremia, peripheral neuropathy, and even paralysis, seizures and psychiatric symptoms. The stimulation of long-term toxin can develop into primary liver cancer [13]. In chronic liver disease, glucagon and deacetylase-dependent molecules activated by hepatocytes under stress and insufficient cell energy enhance this process and form a vicious circle through the enhancement and prolongation of automatic generation of ALA [14].

3.2.2. Increased peripheral circulating porphyrins

During chronic hepatitis B virus infection and hepatitis C virus infection, the estrogen level in the body fluctuates, iron is overloaded, and iron regulatory protein is downregulated. When iron accumulation reaches a threshold, uroporphyrinogen decarboxylase (UROD) is inhibited. Following the reduced activity of UROD, porphyrins and their precursor compounds are increased, leading to liver damage. Some precursor compounds are released into the bloodstream, causing increased skin fragility and blistering lesions in sun-exposed areas [15]. Krivosheev et al. found that among 101 patients with hepatitis virus infection, 29 patients with chronic viral hepatitis had no porphyrin dissolution. Of the 13 patients with hepatic cirrhosis (HC), 11 cases (84.6%) detected elevated porphyrin scores in urine and/or feces. 19 of the 59 patients (32.2%) had obvious late cutaneous porphyria. Nonspecific porphyrin metabolic disorder occurs in HC stage, which is more common in the presence of chronic hepatitis B virus infection. Chronic hepatitis C virus infection is associated with significant advanced skin porphyria [16]. A Norwegian study found that patients with delayed cutaneous porphyria (PCT) had an increased risk of liver, gallbladder and biliary cancers as well as premature death. However, some inherent factors of PCT may contribute to the development of HCC [17]. The increase of ferritin in patients with long-term stimulation of toxic substances is related to liver function damage, and fibrosis and cirrhosis with HCC occasionally occur. It is speculated that the toxic effect of iron plays a certain role in the pathogenesis of liver damage caused by porphyrin [18]. Studies from Spain have shown that PCT is closely related to hepatitis C virus infection in southern Europe. The treatment of hepatitis C virus in infected patients with active delayed skin porphyria using direct acting antiviral drugs (DAA) showed that urinary porphyrin disappeared rapidly after the virus is cleared. This indicates that the virus is directly involved in the oxidation mechanism leading to the inhibition of uroporphyrinogen decarboxylase [19]. In addition, the presence of hepatitis C virus core protein increased the mRNA expression of porphyrin transport export proteins ABCG2 and FLVCR1, promoting the output of excessive porphyrinogen III and/or porphyrin III. Nakano et al. believe that hepatitis C virus core protein has a functional effect on mitochondria, resulting in the production of host reactive oxygen species (ROS), lipid peroxidation, increased mitochondrial Ca^{2+} uptake, reduced concentration of glutathione (GSH), reduced nicotinamide adenine dinucleotide phosphate (NADPH), and reduced activity of mitochondrial complex I; hepatitis C virus core protein upregulates the absorption of iron by mitochondria, aggravating oxidative stress and hepatotoxicity and further affecting the synthesis of heme [20].

3.2.3. Porphyrin cholestasis

Partial deficiency of iron chelatase, specific liver δ-mutations in the function of aminolevulinate synthase

2 (ALAS2) will lead to the accumulation of erythrocyte protoporphyrin. Iron chelatase is the terminal enzyme of heme pathway. Both diseases can lead to the accumulation of erythrocyte protoporphyrins, mainly metallo-free protoporphyrins. Erythrocyte protoporphyrin is released into the plasma and absorbed by liver and vascular endothelium. High levels of plasma lipophilic protoporphyrin activate the skin, causing burning pain and erythema. Because protoporphyrins are deposited in bile and/or hepatocytes, protoporphyrins in bile can lead to gallstones, cholestasis, fibrosis and eventually liver failure. About 2–5% of patients develop clinically significant liver dysfunction, which can develop into cholestatic liver failure requiring transplantation [21,22]. A study in the United States found that 266 patients with erythropoietic protoporphyria (EPP) and X-linked protoporphyrin (XLP) had related symptoms, such as anemia, liver dysfunction, gallstones, etc. [23]

4. Discussion

At present, there are two mechanisms of liver and extrahepatic damage caused by porphyrin metabolic disorder. The accumulation of protoporphyrin in the liver can hinder the excretion of bile, resulting in cholestasis and the formation of micro bile thrombus. The oxidative stress response induced by protoporphyrin [24] produces free radicals and reactive oxygen species, such as superoxide anion (O2•-), hydrogen peroxide (H_2O_2), hydroxyl (• OH) and ALA alkenyl (• ALA), which are oxidants in vivo and in vitro [25], so as to cause swelling and degeneration of hepatocytes, which then progress to end-stage liver diseases such as liver cirrhosis [26]. Porphyrin metabolism disorder can aggravate chronic liver disease, and even progress to liver cirrhosis and liver cancer. Chronic liver disease can also aggravate porphyrin metabolism disorder, recurrent attacks, and damage to extrahepatic tissues and organs.

The treatment of porphyrin metabolic disorder in chronic liver disease is a challenge. It is generally believed that in chronic liver disease, it may be more beneficial to correct porphyrin metabolic disorder on the basis of antiviral and primary disease treatment. According to Phillips JD, givosiran is a kind of directional small interfering RNA (siRNA), which can inhibit the expression of ALAS1 and covalently connect with ligands, so that the siRNA can be specifically delivered to hepatocytes. Triggering *ALAS1* gene silencing leads to downregulation of *ALAS1* mRNA and prevents neurotoxic accumulations of δ-aminolevulinic acid and porphyrin levels. It can reduce the levels of ALA and porphyrinogen in urine to reduce further neurotoxicity. This treatment is effective and acts in a dose-dependent manner [27,28]. Heme therapy is used to reduce hepatic heme synthesis [29]. Exogenous heme can up egulate oxygenase, reduce liver and plasma triglycerides and cholesterol, reduce liver fat, and inhibit macrophage infiltration, inflammation and fibrosis to restore liver morphology. In addition, exogenous heme can reduce osteopontin and transforming growth factor beta 1 (TGF-β1). Fibronectin, collagen IV and other extracellular matrix and fibrotic proteins are associated with liver injury [30]. It has been found in animal models that heme can inhibit nuclear factor kappa B (NF-κB) P65 activity by upregulating the expression of heme oxygenase 1 (HO-1), thereby inhibiting the downstream production of inflammatory factors such as TGF-β and interleukin 6 (IL-6) and then significantly inhibiting the progression of liver fibrosis in rats [31]. However, a study in France found that frequent heme infusion can lead to chronic inflammatory liver disease, induce oxygenase and increase ALAS1 level, leading to recurrence [32]. Carbohydrate load is sometimes used in the acute attack of mild porphyria, and its basic principle is based on the inhibitory effect of glucose on ALAS1 [33]. For patients with life-threatening severe porphyrin metabolism disorder in whom preventive treatment is ineffective, liver transplantation may be needed [34]. In addition, some low-dose hydroxychloroquine is also effective for porphyrin disorder, but the mechanism needs to be further explored.

At present, there are few studies on porphyrin metabolism disorder and chronic liver disease. Domestic studies are mostly case reports, and no study has been conducted on porphyrin metabolism in patients with chronic hepatitis B (immune tolerance or inactive) and nonalcoholic fatty liver. To sum up, when the liver

enzymes of patients with chronic hepatitis B do not increased, the level of porphyrin will change. The increase or decrease of porphyrin level can directly reflect the damage of liver function. The detection of porphyrin in peripheral blood and urine can predict that the disease has entered the immune clearance period in advance, so as to signal timely antiviral treatments. This paper reviews the clinical significance of porphyrin metabolism in early liver function damage of chronic hepatitis B patients by detecting porphyrin in blood and urine, and determines whether porphyrin level can be used as a sensitive parameter for early warning and evaluation of liver function damage in patients with chronic hepatitis B. We also put together some perspectives on whether are dynamic changes of porphyrins in serum and urine of patients with the progression of liver disease, hepatitis, cirrhosis and hepatocellular carcinoma can be used as prognostic markers.

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Disclosure statement

The authors declare no conflict of interest.

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