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Review Article

Research status of Budd-Chiari syndrome in China

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Abstract: Budd-Chiari syndrome (B-CS) is a disease with a low incidence and has obvious geographical difference in subtype and clinical characteristics. The pathogenesis of B-CS in China is significantly different from that in western countries and is a complex process involving multiple factors. However, the specific cause of this disease is not yet clear. In-depth understanding of B-CS pathogenesis will be of great importance in preventing and treating the disease and improving the quality of life of the patients.

Keywords: Budd-Chiari syndrome, pathogenesis, characteristics, China

Introduction

In China, the generalized B-CS refers to blood backflow obstruction caused by occlusion in major hepatic veins and/or retrohepatic segment of inferior vena cava and mainly manifests as the symptoms and signs of posthepatic portal hypertension and/or inferior vena caval hypertension [1, 2]. Due to the racial and geographical differences, the pathogenesis of B-CS in China is statistically different from that in western countries: B-CS in western countries is mainly hepatic vein thrombosis and occurs usually secondary to the disorders of increased blood coagulation with more specific pathogenesis. However, B-CS in China mainly refers to membranous obstruction of the inferior vena cava (MOVC), and the pathogenesis is unclear [2]. In our paper, the current research status of B-CS pathogenesis in China is summarized below according to the research experience in B-CS and by combining with the relevant literatures.

Congenital angiodysplasia

Congenital angiodysplasia was proposed firstly in 1970 by the Japanese scholar Hirooka et al [3]. The theory thought that MOVC was caused by abnormal integration of the hepatic vein and the inferior vena cava in early embryonic development; in the early stage of angiogenesis, membranous obstruction may be caused if the wall of the vein does not disappear, and if one segment missed, segmental obstruction may be caused. The early development and connection obstacle of the hepatic vein and the inferior vena cava may cause different types of B-CS. After analyzing 101 MOVC B-CS patients and performing the biopsy of the inferior vena cava in 9 patients, Simon et al [4] pointed out that failure in integration of hepatic inferior vena cava into liver-heart cavity during embryonic period was the main reason of MOVC.

However, the theory of congenital angiodysplasia has some limitations. It cannot explain many features of B-CS in China and contradicts some research results in China. The results of most studies showed that the features of local lesion in the hepatic vein and the inferior vena cava of Chinese B-CS patients are not consistent, and the lesion type, scope and extent are complex and volatile [1]. Only the obstruction end in B-CS patients with inferior vena cava obstruction has nearly 10 kinds of forms [5]. In addition, B-CS occurs in different age groups and mainly in young adults [1]. It is extremely rare in children [6] and not found in newborns based on literatures. These conditions are clearly incompatible with the features of congenital diseases. The theory thought that membrane was caused by abnormal embryonic development and located above the opening of hepatic

vein. However, studies found that the lesion membrane in some B-CS patients was located below the opening of hepatic vein [7]; a comparison of membrane tissues and normal vessels indicated that the expressions of TGFβR, PDGFR and other cytokines were different and the compositions were not obviously similar [7, 8]. In the study by Dang et al [9], it was found that there were significant differences in expression of many genes between the lesion membrane and inferior vena cava tissues. The results of the study by Bai et al [8] found that the membrane of inferior vena cava was composed of fibromuscular and elastic fibrous tissues, and this fibrous tissue was obviously different from liver parenchyma. The above-mentioned phenomena cannot be explained by the theory of congenital angiodysplasia. Moreover, the new membrane in MOVC patients can form again at the site in which the radical resection of the lesion membrane was performed (relapse) [7, 10], indicating that the inferior vena cava membrane can completely regenerate and may be acquired rather than the product of congenital angiodysplasia.

Thrombus organization

The Japanese scholar Okuda [11] had proposed the theory of thrombogenesis in order to explain why the lesion membrane in B-CS patients forms, and thought the membrane was caused by thrombus organization. Thrombus can occur at different ages and vary in form. The shorter thrombus can form the membrane after organization while the longer can form segmental fibrous tissues. Then Kage et al [12] conducted histological examination of the lesion at hepatic vein and inferior vena cava, and the results also suggested that the membrane was formed after the thrombus organization. In western countries, it may be the most common reason for hepatic vein obstruction that a variety of blood hypercoagulable states cause thrombosis and gradual organization [13-15]. The theory of thrombosis is consistent with the results from many subsequent studies, and has been supported by some scholars.

Chinese scholars found that the membrane was inseparable from thrombus formation and organization by the pathological examination of the lesion membrane and a comparison of thrombus and normal vessel wall tissues. They thought that the membrane may evolve from thrombus organization. Han et al [16] conducted forceps biopsy at the obstruction site of inferior vena cava in 13 B-CS patients and found 1 patient with mixed thrombus, 11 patients with fibrous connective tissue and thrombosis, of whom, newborn capillaries can also bee seen in the fibrous connective tissues of one patient. Thereby, they thought that B-CS with inferior vena cava obstruction was thrombosis originally due to a variety of causes. With the progression of the disease, the thrombus formed fibrous connective tissues after organization and fibrosis to result in membranous or segmental obstruction. The results by Zhang et al [7, 17] showed that the lesion membrane and lower extremity deep venous thrombus in B-CS patients had similar cell components and cytokine expression, which indicated that the membrane and organized thrombus may be at different pathological stages of the same tissue, and the evolution process from old thrombus at hepatic vein and inferior vena cava to membrane can be seen during the operation. Therefore, they thought that the membrane may evolve from thrombus organization.

Although many domestic studies confirmed that the thrombus organization was reasonable, the theory cannot explain some practical questions: Why B-CS tends to occur in hepatic vein and hepatic inferior vena cava? How the thrombus here forms and what is the pathologic base? Why the thrombus does not fall off to form pulmonary embolism? Although the results of some domestic studies indicated that the membrane was from organized thrombus, the reason for the initial formation of the thrombus at the predilection site of the membrane in B-CS patients was probably not blood hypercoagulable state. Because retrohepatic segment of inferior vena cava is close to atrium and has larger blood flow volume, the basic conditions forming the original thrombus is inadequate. If the thrombus forms, pulmonary embolism can be caused easily due to thrombus falling off. Therefore, only the theory that blood hypercoagulable state causes thrombus formation and organization to form the membrane is difficult to give a specific answer. Studies have pointed out that Chinese B-CS patients do not have blood hypercoagulable state [18], and abnormal clotting mechanism-induced thrombosis was not the main reason of MOVC formation in China [19].

The results of some studies thought that B-CS was not simply caused by thrombosis and organization, while it was related to vascular endothelial injury. Thrombus formation and organization was only a stage in the process of membrane formation, i.e., the formation of the membrane in B-CS patients was from endothelial damage due to a variety of causes. The progression of damage repair and aggregation of local inflammatory cells create the conditions for the thrombosis, and the thrombus gradually organized and fiberized to membrane. However, repeated continuation of this process can lead to segmental obstruction [8, 16, 20, 21].

Wang et al [22] found that there was a valve at the predilection site of membrane in inferior vena cava of normal persons, and this valve is extremely rare. They thought that particularity of the anatomy and effect of many factors caused damage to the valve and thus proliferation and growth to create conditions for formation and organization of local thrombus on basis of the original valve, finally resulting in formation of membrane.

In conclusion, the lesion membrane of B-CS patients is caused by thrombus organization. However, the initial formation of thrombus may not be from blood hypercoagulable state, while there is intimal injury and other pathological changes to create conditions for thrombosis, eventually leading to the formation of membrane tissues.

Congenital or acquired thrombosis-causing factors

Because the incidence of B-CS is inseparable from thrombosis, most scholars conducted in-depth research of the pathogenesis of thrombosis in B-CS patients. European and American scholars have found that blood hypercoagulable states due to different causes was closely related to the pathogenesis of local B-CS, and risk factors causing thrombosis can be found in many B-CS patients [13, 14]; one or more congenital/acquired procoagulant diseases existed in 84% patients, and multiple congenital/acquired procoagulant diseases in 46 % patients [14]. Although the incidences of procoagulant diseases reported by different studies are not consistent in B-CS patients, these diseases have become the more specific cause for B-CS. It is believed generally that these diseases are myeloproliferative disorders (MPD) (40%~50%), antiphospholipid syndrome (APS) (25%~35%), paroxysmal nocturnal hemoglobinuria (0%~4%), Behcet's disease (0%~33%), Factor V Leiden (FVL) mutation (6%~32%), prothrombin gene mutation (5%~7%), protein C deficiency (10%~30%), protein S deficiency (7%-20%), antithrombin deficiency (0%~23%), plasminogen deficiency (0%~4%), pregnancy (6%~12%), oral contraceptive (6%~60%), hyperhomocysteinemia (37%) and TT677 MTHFR (12%~22%) [15]. These diseases can affect blood coagulation in patients through different mechanisms to cause blood hypercoagulable state, eventually resulting in thrombosis. Due to high incidence in B-CS patients of western countries, the above-mentioned congenital or acquired factors were considered to be closely related to the pathogenesis of B-CS.

Chinese scholars have also conducted some researches of the above-mentioned disease. However, the results were significantly different from those in western countries. In B-CS patients of western countries, MPD has an extremely high incidence, and JAK2 mutation is considered to be a reliable marker of MPD due to its important role in the mechanism [23]. A Meta analysis including 1062 B-CS patients from western countries indicated that 40.9% patients suffered from MPD and 41.1% patients had JAK2 mutation [24]. However, in a domestic study, 92 B-CS patients were examined, and the results showed that JAK2 mutation was positive in only 4 patients [25]; and the results of another study including 105 patients found that only 5 patients showed a positive JAK2 mutation [26]. The incidence of MPD in Chinese B-CS patients is less than 5%. Because JAK2 mutation is rare in Chinese B-CS patients, MPD may not be the main cause for B-CS in China [25, 27, 28].

The domestic studies also indicated that the incidence of FVL and prothrombin gene mutation is very low in B-CS patients. Qi [28] and Cheng [26] examined 136 and 95 patients, respectively, and no patient with FVL and prothrombin gene mutation was found, indicating that Chinese B-CS may be not associated with the above-mentioned mutations. Therefore, it is considered that the pathogenesis of B-CS in China is not different from that in western countries. In addition, studies had pointed out that familial B-CS was related to FVL mutation in

Han Chinese while sporadic B-CS was not associated with FVL mutation, thereby, they thought FVL mutation may be the internal cause of familial B-CS [29]. However, in the subsequent studies by other scholars, FVL mutation was not found in familial B-CS patients [30]. Therefore, the condition may be associated with geographic distribution, but the concrete mechanism remains to be further studied.

By a systematic analysis, it was found that the incidences of plasma protein C and S and antithrombin III deficiency were significantly higher in B-CS patients compared with healthy population or those without thrombus in Europeans and Americans [31]. Nonetheless, it was found by the domestic researches that the quantity of plasma protein C and S, antithrombin III and anticoagulant proteins in B-CS patients decreased significantly, but this decrease was related to secondary liver function damage and was not primary defects of the quantity, which was obviously different from the results from western countries [32]. It was considered by the researches from western countries that hyperhomocysteinemia and MTHFR C677T mutation played a role in the pathogenesis of B-CS due to their thrombosis-causing effect. Tian et al [33] also found that there was homocysteine in Chinese youth with hepatic vein B-CS, and a correlation may exist between MTHFR C677T gene homozygous mutation and plasma homocysteine level. The correlation between hyperhomocysteinemia with MTHFR C677T mutation and B-CS was similar to that in western countries, but the relationship between them and B-CS is not clear [28]. Moreover, paroxysmal nocturnal hemoglobinuria is also very rare in Chinese B-CS patients [34]; other acquired diseases including B-CS caused by oral contraceptives, pregnancy, antiphospholipid syndrome, Behcet's disease and others are only reported in some cases [35-38]. Hence, some scholars have pointed out that B-CS in China is not highly correlated to thrombosis-causing underlying diseases [39].

Mechanical injury

In the process of B-CS formation, mechanical injury of vascular wall caused by various reasons is likely to play an integral role. B-CS caused by membranous obstruction tends to occur in horizontal segment of the membrane of inferior vena cava in which the inferior vena cava exactly passes through the diaphragm and enters the chest. Both continuous movement of the diaphragm and blood flow impact produced by oversize opening angle of hepatic vein can cause inferior vena cava intimal injury. The movement of the entire liver around the horizontal axis through the bare area may result in repeated damage to hepatic vein entrance to induce intimal repair, hyperplasia and other secondary changes. Zhou et al [40] performed autopsy and study in 20 cases and found that the intimal thickness of inferior vena cava at the vena caval hiatus of the diaphragm was much greater than that at the top of the renal vein and the type I collagen had larger deposition range. They pointed out that the diaphragm movement and the blood flow impact may play an important role in MOVC course after analysis, in which, the diaphragm movement was more critical. Other domestic scholars found that von Willebrand factor (vWF), endothelin-I and vascular endothelial growth factor in inferior vena cava blood of MOVC patients had abnormally high expression, suggesting that there were continuous injury at the forming site of inferior vena cava membrane [41]. Therefore, local damage to the inner wall of the inferior vena cava in MOVC patients can be caused due to changes of blood flow shear stress at the opening of hepatic vein, and secondary repair reaction would eventually lead to the formation of the membrane tissues.

In addition, some scholars conducted pathological examination of the lesion tissues in patients with hepatic vein B-CS and found irregular and abnormal dysplasia of smooth muscle cells and other cells in hepatic venous intimal lesion [42, 43], which was considered to be related to the intimal injury of hepatic vein and inferior vena cava caused by pressure difference between the chest and abdominal cavities as well as the diaphragm movement. There may be an imbalance of gene regulation in the repair and proliferation process of damaged cells to result in excessive proliferation of the hepatic vein intima and secondarily induce hepatic vein stenosis or occlusion [43].

Some domestic scholars conducted a pathological examination of the membrane in B-CS patients, and pointed out that the local damage at the lesion of inferior vena cava which played a start action in the formation of the membrane and the subsequent repeated repair and prolif-

eration of vascular endothelial cells eventually result in the formation of membrane [8, 16].

Therefore, blood flow impact produced by oversize opening angle of hepatic vein, diaphragm movement, liver gravitational traction, pressure difference between the chest and abdominal cavity, deep and rapid breathing at physical labour and other factors can cause continuous damage of endangium at the forming site of the membrane. Meanwhile, they may also play an important role in vascular disease of B-CS patients, which was consistent with this phenomenon that B-CS occurs mainly in population being engaging in heavy work in China.

Infection-vascular inflammation

The inflammation or infection in the tissues around hepatic vein and hepatic inferior vena cava or vessel walls can cause adhesions around the wall, wall thickening and narrowing and other secondary changes. Some scholars conducted histological examination of the lesion membrane and found that varying degrees of inflammatory cells infiltration can be seen in the inferior vena cava and hepatic vein at the lesion segment, promoting that the local inflammatory response was closely related to the development process of vascular membrane formation and occlusion [8, 16, 21, 43].

Furthermore, it was reported in the domestic literatures that systemic vasculitis may be induced by Behcet's disease, systemic lupus erythematosus and others to cause thrombosis, thereby, B-CS may be combined in such patients [38, 44]. Hence, autoimmune disease-induced vasculitis was likely to be associated with the thrombosis in B-CS patients. Nevertheless, such cases are rare in our country.

In short, it is generally believed by the domestic researches that the inflammatory response of the vascular wall plays a role in the course of B-CS. This inflammation is mainly secondary changes after vascular intimal injury caused by various reasons. The mechanisms of vasculitis induced by other diseases in B-CS were rarely studied.

Living environmental factors

Studies showed that Chinese B-CS occurs mainly in Henan, Shandong, Jiangsu, Anhui and other the middle and lower reaches of the Yellow River and Huai River basin [1, 2]. This difference of geographical distribution prompts that the environmental factors in different areas play a role in B-CS. In some domestic epidemiological surveys, it was found that the content of iodine and fluorine of drinking water in B-CS patients increased [45], and the distribution of the patients and water iodine had a higher correlation. With increase of the content of iodine in water, the incidence of B-CS was rising [46], and elevated iodine in blood can stimulate the proliferation of fibroblast and vascular endothelial cells to promote the formation of the membrane in B-CS patients. It was considered that B-CS may be related to higher iodine content in drinking water, but the exact mechanisms remains to be studied [46, 47]. In addition, there are reports of B-CS due to Chinese herbal medicine in China [48], which may be associated with the damage of some poisonous substances to the vessels.

Furthermore, Chinese B-CS usually occurs in heavy manual workers with poor living conditions. Poor life and sanitary conditions, undernourished food and others provide an opportunity for B-CS. Combined with the difference of regional distribution; it is believed that the living environmental conditions in B-CS patients are likely to promote the occurrence of the disease by some mechanisms.

In conclusion, the results of the studies from Chinese scholars do not support congenital angiodysplasia at present, while the more common procoagulant diseases in western countries including MPD, FVL mutation, antiphospholipid syndrome and others are likely to have no obvious correlation with Chinese B-CS. On the pathogenesis and mechanism of B-CS, the Chinese scholars are more inclined to the dynamic pathological process "vascular endothelial injury-inflammatory response-endothelium repair and hyperplasia-thrombus formation and organization", and the diet, living conditions, concomitant diseases and other factors are involved. However, with in-depth study of B-CS, we also recognize that the occurrence and development of Chinese B-CS is a complex process involving multiple factors, and its mechanism cannot be explained perfectly by a single theory. Only by means of multi-disciplinary and multi-center work and deepening the basic research of B-CS, we get more understanding of the pathogenesis of B-CS.

Disclosure of conflict of interest

None.

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