The Pathogenesis of Idiopathic Portal Hypertension
(so-called Banti’s Disease)

— An Experimental Study —

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Summary: The pathogenesis of idiopathic portal hypertension (IPH) was explored in animal experiments. In order to produce experimentally a condition of portal hypertension, portal vein embolization by lycopodiums and structural liver damage by intraportal injection of toxic chemicals were produced in rabbits. Obliteration of intrahepatic portal vein branches alone did not produce sustained portal hypertension due to the development of adequate intrahepatic collateral vessels. Liver damage induced by chemicals was morphologically similar to that seen in IPH and was associated with an increase of portal venous pressure for several months; however, portal venous pressure gradually declined and significant splenomegaly could not be produced. Besides hepatic vascular resistance due to obliteration of intrahepatic portal vein branches and structural liver damage, the possibility of the existence of additional factor (s) is suggested to explain portal hypertension and marked splenomegaly in IPH.

Key words: idiopathic portal hypertension—Banti’s disease—hepatoportal sclerosis—portal vein embolization—hepatotoxicity

Introduction

Portal hypertension has been generally assumed to be the result of obstruction to portal venous blood flow and classified according to the site of major vascular resistance (Whipple, 1945; Imanaga et al. 1962). However, the simplicity of this approach and the validity of the assumption have been questioned (Blendis, 1981).

The existence of non-cirrhotic portal hypertension in which no definite etiological factor can be identified (so-called Banti’s disease) has been recognized for many years (Tisdale et al. 1959; Polish et al. 1962). A large number of cases has been reported from various parts of the world under different names, such as “hepatoportal sclerosis”, “idiopathic portal hypertension (IPH)”, “noncirrhotic portal fibrosis (NCPF)” and “benign intrahepatic portal hypertension” (Mikkelsen et al. 1965; Boyer et al. 1967, 1974; Nayak and Ramalingaswami, 1969; Sama et al. 1971; Aikat et al, 1979; Levison et al. 1982). IPH is the term currently used to denote a similar disease in Japan (Okuda et al. 1982).

Many of these cases have been shown to have varying degrees of periportal fibrosis and obliteration of portal vein branches and would nowadays be classified as intrahepatic presinusoidal obstruction. However, many attempts failed to pro-
duce an experimental model of Banti’s disease, and the exact mechanism of idiopathic portal hypertension and the genesis of the associated marked splenomegaly remain elusive. The present experiments were undertaken to assess the relative importance of portal vein obstruction and parenchymal damage on portal venous pressure and the size of the spleen in rabbits.

Materials and Methods

Male adult rabbits, weighing 2.0-3.0 kg, were used. Laparotomy was performed under thiopental sodium anesthesia and a 23 gauge needle was introduced into a branch of the mesenteric vein to measure portal vein pressure (PVP) and to inject emboli or injurious agents into the portal circulation. Venous pressure measurements were taken by means of a water manometer filled with saline solution in the supine position, with adjustment of the zero level to the anatomical level of the portal vein trunk. PVP was measured at various intervals after an experimental procedure, and expressed as percent of control PVP (PVP after injection/initial PVP×100 %).

The experimental models were as follows.

1) Portal vein embolization.

Lycopodiums, which are the spores of club moss and about 25-40 μm in diameter, were used to produce portal vein embolization without accompanying parenchymal damage. Saline suspension of lycopodiums (0.04 g/kg) were injected into the radicles of the portal vein on two occasions separated by an interval of 2 weeks. PVP was measured immediately before and after the injection of emboli, 2 weeks after the first embolization, and 1 month after the second embolization.

2) Toxic damage.

One percent osmium tetroxide (OsO₄) or 100 % ethanol (0.5-1.0 cc/kg) were injected directly into portal vein system as quickly as possible in order to produce damage of vessel walls and liver parenchyma. Changes of PVP and liver histology were observed up to 12 months.

Results

1) Portal vein embolization (Fig. 1)

Immediately after the first embolization
PVP rose to an average value of 156.9 ± 25.6% (208 ± 52 mmH2O, n = 22), but it returned to the original normal level 2 weeks later (100.0 ± 12.3%, 132 ± 17 mmH2O). The PVP rose to approximately twice the control level immediately after the second embolization (203.3 ± 33.9%, n = 12) but returned to normal 1 month later (96.8 ± 17.8%).

Microscopic examination of the liver revealed the marked development of collateral vessels adjacent to the portal tracts showing obliteration of portal vein branches (Fig. 2). No parenchymal atrophy or distortion of lobular architecture was observed. Spleen weight in this group was similar to that of control group, and no remarkable change in the spleen histology was detected.

2) Toxic damage

Intraportal injection of 1% OsO4 or 100% ethanol caused submassive parenchymal necrosis and thrombosis in the portal vein branches in a few days. About 1 month later, the liver showed marked deformity due to a mixture of parenchymal scarring and regeneration of surviving cells (Fig. 3). The degree of parenchymal

Fig. 2. Experimental portal vein embolization in rabbits: Lycopodiums were injected into the portal vein as emboli. Note dilated vessels (arrows) adjacent to the fibrosed portal tract. (Elastic van Gieson stain. ×80)

Fig. 3. Inferior surface of the scarred, markedly deformed experimentally produced liver by the injection of 1% osmium tetroxide solution into the portal venous system.

Fig. 4. Changes in portal vein pressure in rabbits with scarred liver produced by injection of 1% OsO4 or 100% ethanol into the portal vein system.
damage and mortality rates tended to correlate with the amount of injected agents. Injection of 0.75–1.0 cc/kg of 1% OsO4 solution or 100% ethanol was adequate to produce marked deformity of the liver with low mortality rates.

One month after injection, almost all rabbits showed varying degree of increase in portal pressure (Fig. 4). There was a general tendency for animals with more liver damage to show higher PVP values. The portal pressure gradually declined and fell to a level just above normal after 6 months. There was no case in which the spleen weighed more than 3 times normal.

Histologically, lobular architecture was distorted by a mixture of parenchymal scarring and regeneration of surviving cells (Fig. 5). Small portal vein branches were obliterated and thickening of the intima or organized mural thrombi were observed in some of the large portal vein (Fig. 6). In some animals, marked sclerosis of extrahepatic portal vein was also observed.

Discussion

The existence of a syndrome characterized by marked splenomegaly, anemia and delayed development of hepatic disease was first described by Banti (1910). This so-called Banti’s disease (or syndrome) is a poorly defined clinical entity of obscure etiology, and its existence has long been disputed. Rousselot (1936) pointed out the clinical importance of portal hypertension for the development of Banti’s syndrome. The spleen changes were found to be no different from those seen in liver cirrhosis and Banti’s syndrome became synonymous with congestive splenomegaly.

In the 1960’s, reports began to appear of portal hypertension in the absence of cirrhosis or demonstrable extrahepatic portal vein obstruction (Mikkelsen et al. 1965; Iber, 1969; Talner et al. 1969). The cause
of the obstruction appeared to be intrahepatic portal phlebosclerosis, and the syndrome became known as "hepatoportal sclerosis". These reports provided a reasonable explanation for the development of portal hypertension in patients without cirrhosis or extrahepatic portal vein obstruction. Similar clinicopathological features have been reported in India as non-cirrhotic portal fibrosis (Nayak and Ramalingaswami, 1969; Sama et al. 1971), and in Japan as idiopathic portal hypertension (Okuda et al. 1982).

The term IPH was originally used to designate those patients in whom no cause for the portal hypertension could be determined. However, many of these patients had varying degrees of non-cirrhotic portal fibrosis with occlusion of intrahepatic portal veins, and phlebosclerosis of the extrahepatic portal vein (Boyer et al. 1967; Fukuda, 1968; Iber, 1969; Nayak and Ramalingaswami, 1969; Okuda et al. 1982). In general, obliteration of intrahepatic portal vein branches is believed to be capable of leading to portal hypertension, and extrahepatic portal phlebosclerosis and splenomegaly were attributed to prolonged portal hypertension. However, this explanation does not apply to all IPH cases and doubts have been raised on whether such a marked portal phlebosclerosis and splenomegaly could develop by congestion alone. Some cases of IPH, especially of short clinical duration, show only slight portal fibrosis and phlebosclerosis. In these cases, sustained portal hypertension and marked splenomegaly cannot be explained by increased intrahepatic vascular resistance alone. It has been demonstrated also that experimental portal hypertension does not consistently produce Banti's syndrome and that the simple ligation or stenosis of the splenic vein produce in the long term splenic atrophy rather than splenomegaly (Menon, 1938; Rousselot and Thompson, 1939; Morris and Miller, 1951; Volwiler et al. 1953).

The present experiments confirm that obliteration of portal vein branches alone does not produce sustained portal hypertension which is prevented by the adequate development of intrahepatic collateral vessels. We also studied the effects of scarring and architectural distortion of the liver produced by the injection of toxic chemicals directly into the portal system. In this experiment, the changes produced were similar to those seen in IPH and were accompanied by an increase of portal venous pressure for several months. However, portal pressure gradually declined and splenomegaly could not be produced. The results of these two sets of experiments suggest that neither intrahepatic portal venous occlusion nor parenchymal scarring produce sustained portal hypertension and splenomegaly, and these alterations are unlikely to explain the pathogenesis of human IPH.

There are many reports to suggest that the splenic changes are the primary cause of IPH and that increased splenic blood flow plays an important role in producing portal hypertension (Sato et al. 1969; Kitani et al. 1983). Although the pathogenesis of splenomegaly remains elusive in IPH, the possibility of immunological abnormalities has been raised. Suzuki (1962) succeeded in producing splenomegaly by repeated injection of egg albumin in rabbits. Okabayashi (1962) reported that the histological appearances of the enlarged spleens from rabbits sensitized to egg-white was identical to that found in the spleen of Banti's syndrome. They suggested that Banti's syndrome represents a reaction to a prolonged inflammatory stimulus. Nakagawa (1983) argued that the histological features of the spleen in IPH could not be induced merely by passive congestion due to portal hypertension. Numano et al. (1969) reported on the possibility of an estrogen being a causative factor in Banti's syndrome.

Many causes, such as pylephlebitis,
Increased portal vascular resistance is mainly caused by obliteration of portal vein branches and distortion of lobular architecture. Marked splenomegaly and portal thrombo-phlebosclerosis cannot be regarded as the consequence of portal congestion alone. Unknown factor(s) which causes liver lesion may act on the spleen and portal vein branches to produce marked splenomegaly and portal sclerosis. Marked splenomegaly with increased splenic blood flow and portal sclerosis may contribute to the development and maintenance of portal hypertension in IPH.

Fig. 7. A hypothesis on the pathogenesis of IPH. Increased portal vascular resistance is mainly caused by obliteration of portal vein branches and distortion of lobular architecture. Marked splenomegaly and portal thrombo-phlebosclerosis cannot be regarded as the consequence of portal congestion alone. Unknown factor(s) which causes liver lesion may act on the spleen and portal vein branches to produce marked splenomegaly and portal sclerosis. Marked splenomegaly with increased splenic blood flow and portal sclerosis may contribute to the development and maintenance of portal hypertension in IPH.

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