Symposium* on
Methods for the Study of Hepatic Circulation ;
Hepatic Circulatory Disturbances in Liver Diseases

(Chairman : Prof. Dr. Kiyoo KOSAKA)

1. Etiologic Factor of Portal Hypertension in Chronic Hepatitis
2. ^{198}Au Colloid Clearance and Liver Cell Clearance in Hepatic Injuries
3. Hepatic Circulation in Liver Diseases
4. Measurement of Blood Flow in Intra- and Extra-hepatic Shunt
5. Hemodynamic Analysis on the Liver in Portal Hypertension
6. Experimental Studies on the Clearance of Indocyanine Green from the Blood
7. Discussion

1. Etiologic Factor of Portal Hypertension in Chronic Hepatitis⁺

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THERE HAVE BEEN many reports researching the etiologic factors of intra-hepatic portal hypertension, especially on the locations where intra-hepatic blood flow is obstructed. By Popper and Elias¹⁾, it has been elucidated in liver cirrhosis that intra-hepatic blood flow is obstructed at the hepatic venous radicles by compression of regenerating nodules. Some reports have been presented that various portal hypertensions were shown in viral hepa-

titis, based on splenomegaly and other clinical signs, or radiological and oesophagosopic examinations on oesophagical varices, while little work has been done in chronic hepatitis.

Some attempts are made for elucidating the etiologic factors of portal hypertensing in the cases of chronic hepatitis in this paper.

Criterion and Detailed Classification of Chronic Hepatitis

On the criterion of chronic hepatitis,

⁺(Received for Publication, August 12, 1963)

^{*}This symposium was presented on the 27th Annual Meeting of Japanese Circulation Society, 3rd April 1963, at Osaka

there are many complicated discussion and now we have not yet a coincident criterion. In this paper, criterion of chronic hepatitis is considered to have a certain wide sense; the diagnosis of chronic hepatitis have been used in the cases of viral hepatitis which do not recover clinically over 4 months from the onset. Moreover, the cases are not included in this criterion, which show the findings of the patched liver in peritoneoscopic examination or the moderate fibrosis in lobules in histological findings of biopsy tissue. They are classified into the group of precirrhotic stage of the liver.

The following detailed classifications have been done from the peritoneoscopic examination and histological findings of biopsy tissue.

Classification from the Peritoneoscopic Findings

Type I; Cases with only white wrinkle formations and without any signs of hepatomegaly, portal hypertension or small scars in the liver surface.

Type II: Cases with hepatomegaly and without any signs of portal hypertension or small scars except for white wrinkle formations.

Type III: Cases with the signs of portal hypertension and without small scars except for white wrinkle formations or hepatomegaly.

Type IV: Cases with small scars in the liver surface except for white wrinkle formations, hepatomegaly or any sign of portal hypertension.

Classification from Histological Findings of Biopsy Tissue

Type 1: Cases with liver-cell degeneration or spotty necrosis and no changes in the Glisson's capsules. (From only histological studies, these cases have the same findings of the cases of acute hepatitis)

Type 2_a: Cases with inflammatory process in the Glisson's capsules.

Type 2_b: Cases with fibrosis and without any inflammatory process in the Glisson's capsules.

MATERIALS AND METHODS

1) Peritoneoscopic and Histological Examination

In the total of 425 cases including 34 cases of acute hepatitis, 280 cases of chronic hepatitis, 29 cases of precirrhotic stage of the liver and 81 cases of liver cirrhosis, peritoneoscopic examinations were made according to Kalk's²⁾ report, and histological studies were also made on those biopsy materials.

On the peritoneoscopic findings, splenomegaly, portal venous dilatation and the collateral vessels were observed to be the main signs of portal hypertension.

2) Measurements of Hepatic Blood Flow and Intra-sinusoidal Pressure in Liver and Spleen

In the total of 105 cases including 6 cases of acute hepatitis, 71 cases of chronic hepatitis, 8 cases of precirrhotic stage of the liver and 19 cases of liver cirrhosis, wedged hepatic venous pressure were measured by means of hepatic venous catheterization. And in the same cases, effective hepatic blood flow and intra-hepatic shunt flow were measured by means of Nakamura's³⁾ method with constant intra-venous infusion of galactose. In the total of 36 cases including 2 cases of acute hepatitis, 23 cases of chronic hepatitis, 3 cases of precirrhotic stage of the liver and 9 cases of liver cirrhosis, intra-splenic pressure were measured by means of modified method of the Atkinson's⁴⁾ report under the direct vision of peritoneoscopy. Under the control of peritoneoscopy, intra-splenic pressure can be estimated without any dangerous bleeding in consequence of spleen puncture.

3) Measurement of Diameters of the Intra-hepatic Branches of Portal and Hepatic Veins by Venographs

In the total of 24 cases including 20 cases of chronic hepatitis and 4 cases of liver cirrhosis, hepatic venous radiographs were taken using hepatic venous catheterization and urografin 76% (Schering) as the contrast media. By taking venograph, it is necessary that urografin is infused rapidly into a main branch of hepatic vein from the catheter against the blood stream.

Radiographs of intra-hepatic portal branches were taken in the total of 10 cases including 9 cases of chronic hepatitis and 1 cases of liver cirrhosis. By taking these portographs, two different methods were used. One was splenoportography under the control of peritoneoscopy, and the other was taken using a back-flowing infusible technique of contrast media, from the catheter which was wedged into a branch of hepatic vein

through the sinusoid to intra-hepatic portal branches. In comparison between these two methods, back-flowing method is better than splenoportography in the investigation of localized portal branches or measurements of their diameters.

From these venographs, the diameter of each division of both intra-hepatic venous branches can be estimated in comparison with the shade of the catheter.

4) Observation by Stereogram Reconstructed on Serial Sections of Liver Biopsy Tissue

Using the large size of Silverman-Boecker's biopsy needle, a considerably big liver biopsy tissue (diameter is about 2 mm, length is about 20 mm) can be obtained under the control of peritoneoscopy. And the stereogram has been made up by means of reconstruction on serial sections of this biopsy materials with the aid of Abbe's instrument and vinyl plates. In this stereogram, abnormal changes of peripheral branches of portal vein, hepatic vein, hepatic artery and bile ducts can be observed. The total of 30 cases of chronic hepatitis including 18 cases with portal hypertension and 12 cases without portal hypertension were studied by these stereograms.

RESULTS

1) Comparison of Morphological Findings and Hemodynamic Changes in Chronic Hepatitis

a) Relationship between Peritoneoscopic and Histological Findings of Needle Biopsy Tissue

As indicated in figure 1, it was noticed that type III having signs of portal hypertension in peritoneoscopic classification exhibited a high percentage of type 2_b, having the fibrosis in Glisson's capsules, and type IV having small scars on liver surface in peritoneoscopic findings showed a high rate of type 2_a having inflammatory process in histological findings.

b) Relationship between Peritoneoscopic Findings and Hepatic Hemodynamic Changes

In almost all cases of type I and II normal hepatic hemodynamics were present and abnormal hepatic hemodynamics were shown in the cases of type III and IV. (figure 1).

In the cases of type III, the characteristic findings of portal hypertension were present in peritoneoscopic examination, while normal

Fig. 1. Correlation between Hepatic Hemodynamics, Peritoneoscopic and Histological Findings

wedged hepatic venous pressure was measured. This was clearly seen in figure 2 in which markedly high level of intra-splenic pressure (236 ± 53 mm H₂O) was noted, while normal wedged hepatic venous pressure (111.6 ± 25.9 mm H₂O) was measured. Effective hepatic blood flow was measured as normal level or lower than normal, and little or no intra-hepatic shunt flow was measured.

In the cases of type IV, wedge hepatic venous pressure was measured to be higher than normal level (195 ± 16.1 mm H₂O), while the signs of portal hypertension could not be seen in peritoneoscopic examination. Effective hepatic blood flow (592 ± 231 cc/min/m²) was measured to be lower than normal level. And marked degree of intra-hepatic shunt flow (268 ± 158 cc/min/m²) was noted.

2) Radiographic Studies of Intra-hepatic Branches of Portal and Hepatic Veins

Fig. 5. Stereogram Reconstructed by Serial Sections of Liver Biopsy Tissue

The case on the left is classified to type II with normal hemodynamics. The normal pattern of portal vein has been shown in its stereogram. The case on the right is classified to type III with elevated intra-splenic pressure and normal wedged hepatic venous pressure. One out of three Xth divisions of portal branches is almost completely obstructed with marked fibrosis in Glisson's capsules. Two out of three XIth divisions of another branch are also obstructed. The last branch is remained without any obstruction and is moderately dilated.

Fig. 6. Morphological Changes in Stricture of Peripheral Branches of Portal Veins

12 cases of type I or II, normal pattern of portal vein were observed. In 3 cases out of them, both normal and slightly dilated portal veins were shown. And in only 2 cases out of them, normal, dilated and narrowed portal veins were mixed (Figure 5).

While observations of the cases of type III revealed both normal and dilated portal veins in only 2 cases out of 18 cases. In 4 cases out of them, normal, dilated and narrowed portal veins were mixed. In 7 cases out of them, both normal and narrowed portal veins were observed. And in 5 cases out of them, only moderately or markedly narrowed portal veins were revealed.

On observations of hepatic venous system, significant abnormal changes could not be found, in cases of type I, II and III.

b) Various Histological Changes in the area of the Narrowed Portal Vein

In the area of the narrowed portal vein, fibrosis and inflammatory process could be found. And as figure 6, the degree of fibrosis was well correlated with the degree of these strictures.

Moreover, narrowed changes of hepatic arteries were simultaneously found to be more than 70%, and narrowed changes of bile ducts were exhibited in about 50%, in observation of the area showing markedly narrowed changes of portal veins (Figure 6).

DISCUSSION

From the above-stated examinations various portal hypertension are seen in the cases of chronic hepatitis. Moreover they are able to be classified into two groups as based on above morphologic and hemodynamic studies. One is type III showing portal hypertension and normal wedged hepatic venous pressure, and the other is type IV with elevated wedged hepatic venous pressure, and without splenomegaly or any signs of blood stagnations in portal area. Following discussion is presented upon the etiologic factors of these 2 groups.

a) Portal Hypertension Caused by Strictures of Terminal Branches of Portal Veins

About the etiologic factors of portal hypertension, a few reports have supposed a location of a resistance of blood flow in intra-hepatic portal area. Imanaga⁵⁾ reported that these cases showed normal wedged hepatic venous pressure, contrary to markedly elevated portal venous pressure, and portograph show-

ed the findings without any obstructions of extra-hepatic and intra-hepatic portal veins.

Now, in chronic hepatitis, the findings of blood stagnation in portal area, markedly elevated intra-splenic pressure and normal wedged hepatic venous pressure were shown in the cases of type III, by means of peritoneoscopic and hemodynamic observations. These results supported Imanaga's opinion. Furthermore, more detailed examinations were attempted upon each divisions of both portal and hepatic veins of the cases of type III. Namely, each diameter from their 5th division to the proximal was measured by both venographs, and stereograms of their 10th division to distal were reconstructed by serial sections. On these two examinations in almost all cases of type III, strictures or obstructions were observed at the terminal branches of portal veins, and its macroscopic branches were moderately dilated, while in hepatic venous system, significant abnormal changes could not be found. Moreover, in histological examination of the area of narrowed portal vein, these strictures were well correlated with the degree of fibrosis in Glisson's capsules, and at the same time stricture of hepatic artery or bile ducts were found in the same area in most of these cases.

It is clear from the above data that one type of portal hypertension in chronic hepatitis originated in strictures or obstructions of terminal branches of portal veins. Simultaneously, inferences are drawn that strictures or obstructions of hepatic artery in the same area concerns these portal hypertension. And it is quite possible that these strictures or obstructions are caused by fibrosis of Glisson's capsules.

b) Influences of Strictures of Peripheral Branches of Hepatic Veins and Intra-Hepatic Blood Flow on Portal Hypertension

By Nakamura's galactose method, intra-hepatic shunt flow could be estimated, using Fick's principle and extraction rate based on the fact that the galactose which is infused within the limits of its hepatic extraction value is completely extracted.

In the cases of acute hepatitis, intra-

hepatic shunt flow are absent. In the cases of type I, II and III of chronic hepatitis, absent or a little value of intra-hepatic shunt flow was measured, while in almost all cases of type IV moderate degree of intra-hepatic shunt flow was present. In all cases of liver cirrhosis, various degrees of intra-hepatic shunt flow are observed. Concerning intra-hepatic shunt flow and these scars on liver surface, following two facts have already been reported⁶⁾. Namely, intra-hepatic shunt flow is directly proportional to the degree of these small scars. On observation of a stereogram which was reconstructed by serial sections of surgical biopsy tissue of this scar, many peripheral branches of both portal and hepatic veins were mixed with each other and the anastomosis of both venous systems was presumed.

In almost all cases of type IV, diameters of peripheral branches of hepatic veins changes to slender than normal, and moderately elevated wedged hepatic venous pressure was presented. It is reasonable to presume that such elevation of hepatic-sinusoidal pressure is based on strictures of peripheral branches of hepatic veins.

While in these cases, splenomegaly and any signs of blood stagnation of portal area could not be found. This inconsistency of hepatic hemodynamic changes can be explained from the fact that the blood stagnation in portal area is removed through the intra-hepatic shunt.

CONCLUSION

1) For the studies of abnormal hepatic hemodynamics, hepatic venous catheterization, venographs of both portal and hepatic venous systems and stereogram of liver biopsy material were examined in the cases of chronic hepatitis which were classified into 4 groups from peritoneoscopic examinations and histological findings of liver biopsy tissue.

2) One type of portal hypertension in chronic hepatitis is caused by strictures and obstructions of terminal branches of portal veins, and it is presumed that these changes are based on fibrosis of Glisson's capsules.

3) In the other type of portal hypertension in chronic hepatitis, it is presumed that the location of resistance of blood flow is peripheral branch of hepatic veins. While in this type, splenomegaly and blood stagnation in portal area can not be found, due to the existence of intra-hepatic shunt flow.

REFERENCES

1) Popper, H., Elias, H. & Petty, D.: *Am. J. Clin.*

Pathol., **22**: 717, 1952.

2) Kalk, H. & Brühl, W.: *Leitfaden der Laparoskopie u. Gastroskopie*: G. Thieme, Stuttgart, 1959.

3) Nakamura, T. et al.: *Igaku No Ayumi* (Japanese), **29**: 741, 1959.

4) Atkinson, M. & Sherlock, S.: *Lancet*. **1**: 1325, 1954.

5) Imanaga, H.: *Acta Hepatologica Japonica*, **2**: 137, 1960.

6) Shimada, Y. et al.: *J. Jap. Soc. Internal Med.*, **50**: 552, 1961.

2. ¹⁹⁸Au Colloid Clearance and Liver Cell Clearance in Hepatic Injuries⁺

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IT HAS BEEN reported by Fauvert and Watanabe, that simultaneous measurements of ¹⁹⁸Au clearance and BSP clearance are very useful for the observation of hepatic blood flow and hepatic injuries in various liver diseases. In the present study simultaneous measurements of ¹⁹⁸Au clearance and rose bengal, ¹³¹I-rose bengal (¹³¹I-RB) or azorubin S clearance were performed and the results were compared with those obtained by measurements of ¹⁹⁸Au clearance and BSP clearance.

MATERIALS AND EXPERIMENTAL METHODS

The number of cases examined was 43. They consisted of 32 cases of various liver diseases and 11 normal controls: On these patients and normal controls, simultaneous measurement of ¹⁹⁸Au clearance and one of the dye clearance (BSP, rose bengal, ¹³¹I-rose bengal or azorubin S clearance) was performed early in the morning at fasting state, and one week thereafter the measurement of the other dye clearance was performed. For the measurement of ¹⁹⁸Au clearance, 20–40 μ c of ¹⁹⁸Au colloid was injected rapidly into the cubital vein and the radioactivity in the blood as well

as the surface count over the liver and thigh were measured at 5 minute intervals for 30 to 60 minutes using well-type scintillation counter and collimated scintillation counter, respectively. However, in order to avoid experimental errors, only the values obtained by the measurement of blood radioactivity was employed for the determination of ¹⁹⁸Au clearance. For the measurement of BSP, rose bengal and azorubin S clearance, 5 mg per Kg body weight of BSP, 2 mg per Kg body weight of rose bengal or 1.5 mg per Kg body weight of azorubin S was injected rapidly into the cubital vein, and the concentration of the dye in the blood was determined at 5 minute intervals for 30 minutes using the Beckman-type spectrometer according to the method described by Gaebler or at the wave length of 550 m μ or 510 m μ , respectively. For the measurement of ¹³¹I-rose bengal clearance, 10–15 μ c of ¹³¹I-rose bengal was used.

RESULTS AND DISCUSSION

1) ¹⁹⁸Au Colloid Clearance

In normal controls the ¹⁹⁸Au clearance was 1.40 % min⁻¹ on an average. In acute hepatitis it was usually within the normal range, being 13.7 % min⁻¹ on an average, although there were some cases showing de-

⁺ (Received for Publication, October 7, 1963)