GASTROENTEROLOGY IN INDIA

Non-Cirrhotic Portal Fibrosis

J B DILAWARI, S GANGULY, Y CHAWLA

Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh 160 012

Historical Background

Banti in 1889 described a disease with splenomegaly and anemia. He considered spleen to be the primary seat of the disease and anemia, cirrhosis and sclerosing endophlebitis as its consequences. In retrospect, it appears that Banti perhaps included a variety of diseases that we now recognize as cirrhosis, non-cirrhotic portal hypertension and tropical splenomegaly syndrome. Ravenna in 1940 gave the first detailed account of Banti's syndrome and called it fibrocongestive splenomegaly. Wig from Delhi observed in 1955 that a distinct group of adult patients with portal hypertension had repeated episodes of bleeding without any encephalopathy. Leather in 1961 noted many patients with splenomegaly in Uganda having portal fibrosis and sinusoidal infiltration of the liver by inflammatory cells. Pollock et al. in 1962 termed a similar syndrome as idiopathic presinusoidal portal hypertension. Ramalingaswamy, in 1966, while analyzing cases of cirrhosis in Northern India, noticed a distinct non-cirrhotic disease. He labeled these as splenomegaly type of portal hypertension without cirrhosis. Mikkelsen et al. in 1965 coined the term "hepatointestinal sclerosis" and described a concentric thickening or sclerosis of the portal vein and its radicles.

Basu in 1967 first suggested the term "non-cirrhotic portal fibrosis" (NCPF) for this disease entity. Boyer et al. in 1967 also studied such cases but called them "idiopathic portal hypertension" (IPH). They re-emphasized the presence of hepatointestinal sclerosis and of a more favorable prognosis than with cirrhosis. They also suggested that intrahepatic portal phlebitis was the causative factor of this disease. Nayak and Ramalingaswamy in 1969 characterized the histological lesion in patients with NCPF as "obliterative portal venopathy". In the same year, the title "non-cirrhotic portal fibrosis" was officially adopted at a workshop organized by the Indian Council of Medical Research.

The full spectrum of histological lesions of NCPF was described by Alkat et al. These workers studied in detail the pathological lesions of NCPF at autopsy and emphasized the presence of portal scarring, angiomatoid transformation of portal radicles and frequent nodularity of the liver surface. Excellent reviews on NCPF have recently been published.

It has now been established that NCPF is an important cause of intransapatic non-cirrhotic portal hypertension distinct from schistosomiasis, sarcoidosis, vinyl chloride poisoning, congenital hepatic fibrosis, partial nodular transformation of liver and lymphomatous deposits.

Epidemiology

NCPF has been reported from all over the world and at least 19 different names have been given to similar disease entities from different parts of the world. Its incidence over is 3%-5% of all patients with portal hypertension. In India, the frequency reported was 15% to 18% of cases. In Japan, it was 10.5% of all patients with portal hypertension.

Most of the series from different parts of India show a male predominance of 2:1 to 4:1, though other workers did not find any sex predilection. Koshy described a double peak in age incidence, one at 21-25 years and the other at 36-40 years. In Japan, IPH was more common in older females, with a male to female ratio of 3:1 and an average age of 40-60 years.

Etiology

No definite environmental factor or genetic predisposition for NCPF has yet been found. However, clustering of the disease mainly in the lower socioeconomic class suggests that malnutrition, exposure to toxins or chemicals, or recurrent intestinal infections could possibly be responsible.

Exposure to chemicals

The relationship of arsenic with NCPF was suggested by many workers in the past and was recently re-emphasized by Guha Majumder et al. These workers found high hepatic arsenic levels in patients with periportal
fibrosis. The increased hepatic arsenic was attributed to high arsenic content of drinking water, soil, vegetables and indigenous drugs.\textsuperscript{23,25} Vinyl chloride toxicity is known to induce a similar pathological lesion of the liver and portal hypertension.\textsuperscript{26} An isolated report of copper exposure producing changes similar to NCPF is also available.\textsuperscript{27}

**Infection**

Bacterial infection from the gut was suggested as a possible etiology of IPH by Boyer in 1967.\textsuperscript{9} Samii \textit{et al.}\textsuperscript{28} suggested repeated septic embolization of the portal circulation and subsequent thrombophlebitis as a more causative factor in NCPF. Portal sclerosis was experimentally produced by injecting dead non-pathogenic \textit{E. coli} into the portal circulation of rabbits previously sensitized by the same bacteria.\textsuperscript{29} Malaria was suggested as a possible cause, as levels of antimalarial antibodies were significantly higher in NCPF patients than in controls and patients with other liver disorders.\textsuperscript{30} However, no direct association between the tropical splenomegaly syndrome and NCPF has been found.\textsuperscript{31} Shikata\textsuperscript{32} postulated a viral etiology. Schistosomiasis also gives rise to non-cirrhotic portal hypertension similar to NCPF.

**Genetic predisposition**

No definite genetic predisposition to NCPF has been reported. However, familial occurrence of NCPF is known.\textsuperscript{33} The significance of increased occurrence of HLA-DR\textsuperscript{24} in NCPF patients awaits further evaluation.

**Increased portal blood flow**

Hepatic blood flow was shown to be increased in idiopathic tropical splenomegaly with portal hypertension in Uganda, but it remains unclear whether this is a primary event or a secondary change. Donovan \textit{et al.}\textsuperscript{36} reported two cases of portal fibrosis secondary to systemic portal or arterio-venous fistulae. Datta \textit{et al.}\textsuperscript{35} showed liver blood flow to be either normal or increased in patients with NCPF. Koyama \textit{et al.}\textsuperscript{37} proposed a dual theory implicating both intrathoracic obstruction and increased splenic blood flow in the causation of portal hypertension in IPH.

**Immune alterations**

An immunological basis for NCPF is currently under active investigation. Preliminary studies showed severe granulocytopenia in NCPF.\textsuperscript{38,39} Takahashi \textit{et al.}\textsuperscript{40} noted a general T-lymphocytopenia, splenic T-cell sequestration, mild hypergammaglobulinemia and raised surface IgM on B-cells in IPH. The T4/T8 ratio was normal. Indian workers,\textsuperscript{41,42} on the other hand, reported a decrease in the T8 cells in the peripheral blood and an increase in the T4/T8 ratio. IPH has been reported to occur after renal transplan-

tation, and this has been explained, on immunological basis.\textsuperscript{43}

Portal antigenemia has been shown to cause hepatic fibrosis similar to that seen in NCPF. Porcine serum injected intraperitoneally was shown to induce extensive liver fibrosis in experimental animals.\textsuperscript{44} Ikabayashi\textsuperscript{45} provided further support to this theory by showing that prolonged antigen stimulation through the portal venous route produces extensive hepatic fibrosis and portal hypertension.

**Pathology**

**Gross**

The liver involvement may be either uniform or asymmetric, with one lobe looking atrophic.\textsuperscript{46} The liver weight is normal, or rarely increased.\textsuperscript{13} The liver surface appears normal or mildly nodular.\textsuperscript{47} Nodularity when present is limited to the subcapsular zone and does not involve the center of the liver as in cirrhosis.\textsuperscript{12,48} The portal vein is usually dilated and may show thickening and sclerosis of varying degree. A significant proportion of autopsies show dilatation, intimal thickening and thrombi in varying stages of organization in the extrahepatic portal venous system.\textsuperscript{12,48,49}

**Microscopic features**

Histological changes in NCPF show a wide variation from normal architecture to scarred areas, but there is no true cirrhosis.\textsuperscript{12} The fibrosis is mainly portal, subcapsular and rarely periportal.\textsuperscript{49} Portal-portal bridging fibrosis is also seen.\textsuperscript{12} The changes are more marked in the medium sized portal venous (3rd and 4th order) radicles. Intimal thickening and collagenization are considered to be the most significant changes.\textsuperscript{12,47} Apparent disappearance of some of the peripheral portal tracts as a result of severe portal fibrosis, termed "obliterative portal venopathy" by Nayak and Ramalingaswami, may occur.\textsuperscript{12} Presence of multiple venous collateral channels in the portal tracts is another characteristic finding.\textsuperscript{47}

Formation of microthrombi followed by sclerosis of the small and medium size portal venous branches has also been implicated in the etiopathogenesis of NCPF.

**Ultrastructure**

Electron microscopic changes in NCPF are non-specific. Though collagen deposition in the space of Disse, development of microvilli on the hepatocytic surface and reduction of smooth endoplasmic reticulum have been reported,\textsuperscript{12,50} their significance is not clear.

**Clinical features**

**Symptoms**

Gastrointestinal hemorrhage is the most important symptom.

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occurring in 53-92% of patients. In a Japanese series, the incidence was only 35%. Bleeding episodes are well tolerated. The next important symptom is awareness of a lump in the left side of the abdomen (enlarged spleen). Symptons due to anemia are more common in Japanese patients. Premonition with jaundice or ascites is rare.

**Signs**

Splenomegaly is universal. The spleen size (below the costal margin) ranges from 4 to 15 cm, the average being 8 cm. Liver enlargement is not striking. However, the liver is palpable 2 cm below the costal margin in 35% of cases. Ascites is present in 2.5% to 13.3% of patients and usually follows an attack of gastrointestinal bleeding especially in those with poor dietary protein intake. Due to relatively well preserved hepatic function overt encephalopathy is uncommon even during episodes of bleeding.

**Hematological tests**

Anemia is common and is mainly due to an increase in plasma volume. It may also be related to recent blood loss or hypersplenism. The degree of hypersplenism is related to splenic size and duration of illness. Red cell survival is however reported to be normal. In contrast to patients with cirrhosis, there is no significant alteration in coagulation pathway and fibrinolysis.

**Liver function tests**

Serum concentrations of bilirubin, transaminases and alkaline phosphatase are normal. Mild hypoalbuminemia is occasionally present. Serum globulin levels were normal except in one study which showed raised levels. Bromsulphthalein excretion is abnormal in 20% of cases and cytoplasmic BSP conjugating enzyme level is reduced. Indocyanin green extraction measurement also confirms mild hepatocellular dysfunction.

**Biochemical changes**

Serum angiotensin II activity is mildly elevated in patients with NCPF. Role of other vasospastic factors in its pathogenesis needs to be studied. An increase in arterial ammonia concentration resulting from extensive encephalitis and minimally damaged liver has been reported.

**Radiology**

Spleenporteovenography shows a patent splenoporal axis, with dilated portal and splenic veins in patients with NCPF (Figs 1, 2).

Futagawa et al demonstrated changes in medium sized (3rd and 4th order) portal venous radicles including reduction in number, gross tortuosity, winding, irregularity, bending and crossing over of the neighboring vessels. Perirenal pruning produces a relatively avascular area under the liver capsule. Branching angles were obtuse instead of being acute. Hepatic venography showed similar irregularities in small and medium size veins, producing a typical "weeping willow" pattern.

Intrahepatic anastomoses between portal vein and hepatic vein radicles on hepatic venography have been suggested to be characteristic of IPH. Relative narrowing of the right branch of the portal vein is occasionally seen. Thickening of the hepatic artery has also been noted.

Large natural or spontaneous splenorenal shunts are redemonstrable in 10% of NCPF patients. In addition, umbilical venous hum as described in the Cruveilhier-

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**Fig 1** Slices of block in NCPF (3rd and 4th order interhepatic portal vein radicles) and EHVO (nasal/lost order branches).

**Fig 2** Transhepatic portography in a patient with NCPF showing irregularity of interhepatic portal venous radicles. PV=portal vein.
Baumgarten syndrome in association with cirrhosis has also been described in NCPF patients. Esophageal varices can be detected in 90% and 81% of NCPF patients on endoscopy and barium swallow respectively. Rectal varices, distinct from hemorrhoids, are present in 70% of NCPF patients.

There are no published data on ultrasonographic findings in NCPF. However, portal and splenic veins are dilated and multiple collaterals present at the splenic hilum. The echogenicity of the portal vein wall is invariably increased.

**Hemodynamics**

Detailed hemodynamic studies have not been carried out in NCPF. Splenic pulp pressure is increased but bears no relationship to the presence of varices, splenic size and duration of disease. Wedged hepatic venous pressure (WHVP) was shown to be elevated by Japanese workers while Indian studies found it to be normal or mildly raised. In contrast, it is always raised in cirrhosis while in extra-hepatic portal venous obstruction (EHPO) it is usually low. Based on pressure measurements, Datta identified two subgroups: Type I with very high liver blood flow, high splenic pulp pressure and minor elevation in corrected sinusoidal pressure (WHVP minus free hepatic venous pressure), and Type II with normal to moderately elevated liver blood flow, high splenic pulp pressure, and moderate elevation in corrected sinusoidal pressure. Type I patients had minimal collaterals on barium swallow and splenorenorenography and no history of gastrointestinal bleeding, whereas these were present in Type II patients. This observation, however, has not been confirmed by others. Sarin and Singh demonstrated two pressure gradients in NCPF patients, the first between intrasplenic and intrahepatic pressures and the second between intrahepatic pressure and WHVP indicating the presence of both pre sinusoidal and per sinusoidal resistance to the portal blood flow.

Hemodynamic studies after shunt surgery revealed significant reduction in total hepatic blood flow, corrected sinusoidal pressure and splenic pulp pressure. However, though intrasplenic pressure falls after surgery it still remains above normal limits. The reason for this is not clear.

**Treatment**

Variceal hemorrhage is the most important presentation of NCPF. These patients tolerate the bleed better as compared to cirrhotic patients. Apart from supportive measures like blood transfusion, vasopressin infusion and Sengstaken-Blakemore tube balloon tamponade, endoscopic sclerotherapy is the treatment of choice for acute variceal hemorrhage in NCPF.

Rebleeding can be prevented either by shunt surgery or by sclerotherapy. Various techniques of shunt surgery have been described. Mitra et al. reported side to side ileo-renal shunt to be effective. This procedure avoids technically difficult splenectomy and its consequences like pneumocele and *Helicobacter pylori* infection. Recurrence of bleeding was seen in 2.1% to 8.8% of their cases. Hepatic encapsulating after biliary shunt surgery was seen in 8% of patients and 5 year survival rate was 87%.

Repeated sclerotherapy is very effective in obliterating esophageal varices, obviating the need for shunt surgery. Recurrent major bleeds and residence in a remote area have been suggested as indicators for surgery. Variceal recurrence and rebleeding after complete obliteration by sclerotherapy were seen in 22% and 3.1% of patients respectively. Lifelong followup is essential after obliteration of varices. There are no controlled studies comparing sclerotherapy and shunt surgery. However, both the methods of treatment are very effective. Long term therapy with pharmacological agents like beta-blockers is being tried.

Management of patients with varices who have not yet bled is controversial. If splenogram shows large natural shunts, no therapy may be required. Since the most important cause of death in NCPF is exsanguinating hemorrhage, the role of prophylactic sclerotherapy in this disease needs to be evaluated in greater detail.

The disease runs a benign course and if variceal bleeding can be controlled, long term prognosis is very good.

**Comparison between NCPF and EHPO**

A number of features are common to NCPF and EHPO; these include splenomegaly, esophageal varices, episodes of bleeding and liver histology showing mild to moderate fibrosis and absence of cirrhosis. Major difference between the two conditions is in the site of thrombosis along the portal venous system (Fig 1). In EHPO large (to main and 1st order) branches of the portal vein are thrombosed while in NCPF smaller (3rd and 4th order) branches are involved (Fig 2). Collateral formation is around the site of block in both conditions in around the major vessels in EHPO (portal cavernoma) and around the smaller vessels in NCPF (intrahepatic). While EHPO is common in males and is mostly seen in the first and second decades, NCPF is commoner in females in the third and fourth decades. Spleen usually extends >7 cm below the costal margin in NCPF and <7 cm in EHPO.

Grossly, the liver surface looks normal in EHPO.
ever, it may be normal to grossly nodular in NCPF. Varying degrees of portal fibrosis, pseudolobulation and angiomatoid malformation of intrahepatic portal venous radicles are present in NCPF. Sometimes, however, it is difficult to differentiate between the two histologically.

Comparison of NCPF of India with IPI of Japan

While the peak incidence of NCPF in India is in the 3rd and 4th decades of life, IPI in Japan is commoner in the fifth and sixth decades. The commonest mode of presentation of NCPF is hematoma (70-94%) while that of IPI is awareness of a mass in the left hypochondrium and anemia (60%). WHVP is normal or mildly raised in NCPF but is always raised in IPI. Attempted pseudolobule formation and bile duct proliferation are seen less frequently on histology in IPI than in NCPF.52

Comparison between NCPF and Tropical Splenomegaly Syndrome (TSS)

The only similarity in the two conditions is the presence of massive splenomegaly. TSS however differs from NCPF in presence of raised antinuclear antibodies, therapeutic response to antimalarial drugs, presence of lymphocytes in the sinusoids on liver biopsy, and absence of portal hypertension.

Future prospects

NCPF is an important cause of variceal bleeding in India. A well controlled multicenter study on its epidemiology and clinical features is needed. The role of immune responses in the pathogenesis of this common yet enigmatic disease needs to be explored in greater detail. Ultrasonography should be used more frequently to delineate the splenorenal axis, collaterals and thickening of the portal vein wall in NCPF. Long term results of randomized controlled trials of shunt surgery versus sclerotherapy currently underway are keenly awaited.

REFERENCES

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