Progress report

Non-cirrhotic portal fibrosis

Background and nomenclature

Splenomegaly with or without anaemia has drawn the attention of a number of workers since Banti of North Italy described in 1889, a disease characterised by splenomegaly and secondary liver cirrhosis.¹ Over the years it became clear that Banti's syndrome, as it used to be called, is an ill defined disorder, consisting of a variety of diseases that present with splenomegaly, hypersplenism and portal hypertension.

It was in 1956, that some physicians in India first drew attention to a clinical syndrome of portal hypertension distinct from cirrhosis. In 1962, Ramalingaswami and colleagues after a careful study of the autopsy material of some of these patients, reported an entity of splenomegaly with non-cirrhotic liver disease in North Indian patients.² Soon, many Indian workers reaffirmed the separate identity of this condition.^{3,4} In 1969, a workshop was organised by the Indian Council of Medical Research to review the available information on this condition. The study group decided to name this clinicopathological entity 'non-cirrhotic portal fibrosis' (NCPF).⁵ Boyer while working in Calcutta, saw almost identical patients and reported them under the term 'idiopathic portal hypertension'.⁶ Several workers at nearly the same time, described patients with portal hypertension with a patent portal vein and without evidence of cirrhosis.^{7,8} Mikkelsen *et al* identified 36 patients with portal hypertension without cirrhosis, who had phlebosclerosis of intra and extrahepatic portal veins and called this condition as 'hepato-portal sclerosis'.⁸ During the following years, The International Association for the Study of Liver, recognised a group of patients with 'portal and septal fibrosis associated with portal hypertension occurring predominantly in adults, mostly in males, in tropical zones' and accepted the term 'hepato-portal sclerosis'.⁹ It is, however, important to remember that Mikkelsen's patient material described under the same term, included a significant number of patients with partial or complete portal vein block,⁸ a condition which is better known as extra hepatic portal vein obstruction (EHPVO).

Whatever may be the terminology applied, it is now abundantly clear that a distinct syndrome of portal hypertension without any evidence of cirrhosis of liver and EHPVO exists and is seen in many parts of the world. There are, however, subtle differences between the patients reported from different areas. In an excellent review, Okuda recently provided a detailed account of patients with idiopathic portal hypertension (IPH) seen in Japan.¹⁰ In this review, NCPF is described as it is understood in India and is compared with IPH and similarly described entities.

Epidemiology

Non-cirrhotic portal fibrosis has been reported from almost all parts of

India.¹¹⁻¹⁴ Nearly 25–30% of all patients with portal hypertension in India who undergo surgery or sclerotherapy, have NCPF.^{13,14} In fact, the largest number of cases of NCPF (or a similar disease elsewhere) in the world have been reported from India. No large epidemiological studies are available, however, to determine the incidence of NCPF in general population. The majority of NCPF patients come from a lower or middle socio-economic background.

Non-cirrhotic portal fibrosis is usually a disease of young Indian men. Except for a single report from Chandigarh of female predisposition,¹² all series describe a male predominance (M:F, 2:1 to 4:1).^{2-6,11,13,14} This is in contrast with patients of IPH from Japan¹⁵ and USA¹⁶ where M:F ratio is about 1:3.

The mean age of NCPF patients has been reported to vary from 25 to 35 years, about two decades younger than IPH patients.^{10,15} Some workers have described a double peak of onset of NCPF, one at 21–25 and another at 36–40 years.¹² This finding has, however, not been confirmed by others.

Aetiology

Despite its common occurrence, the aetiopathogenesis of NCPF is poorly understood. A number of hypotheses have been put forward in the past, based mainly on anecdotal experiences and case reports.

EXPOSURE TO TRACE METALS AND CHEMICALS

Clinical association between ingestion of certain trace metals and hepatic fibrosis was observed long ago. Chronic ingestion of arsenic has been incriminated in the causation of NCPF because it causes predominant fibrosis of intrahepatic portal veins.¹⁷ Datta *et al* had reported significantly higher hepatic arsenic concentrations in NCPF patients compared with controls.¹⁸ Similar levels were, however, subsequently seen in patients with cirrhosis and Indian childhood cirrhosis.¹⁹ In seven of our NCPF patients studied by electron probe microanalysis, hepatic arsenic content was not different from controls.

The possibility of ingestion of indigenous drugs, food adulterants, herbal and fungal toxins or parasitic infection has also been raised with little substantiation.^{6,13}

INFECTIVE AGENTS

Non-cirrhotic portal fibrosis is predominantly a disease of the poor and is common in countries like India, where the incidence of umbilical sepsis, diarrhoeal disease and bacterial infections is very high. It is speculated that thrombophlebitis and repeated embolisation into the portal circulation because of any abdominal infection initiated at birth or at a later age, could result in NCPF.^{6,13} Idiopathic portal hypertension like changes have been reported after injecting dead non-pathogenic colon bacilli into the portal vein of rabbits, previously sensitised with the same bacteria.²⁰

A higher incidence of malarial antibody positivity has been reported in NCPF patients compared with cirrhotics and controls.^{21,22} Although malaria is endemic in India and splenomegaly is common to both diseases, no direct association has so far been found between the two conditions.

IMMUNOLOGIC AND IMMUNOGENETIC HYPOTHESES

Evidences supporting these hypotheses include – (i) occurrence of non-compressive myelopathy after lienorenal shunt in a patient with NCPF,²³ (ii) a reduction in suppressor/cytotoxic lymphocytes (T8) and an alteration in the helper/suppressor (T4/T8) lymphocytes in NCPF,²⁴ (iii) a reduction in the cell mediated immune status in NCPF patients,²⁵ and (iv) some resemblance with schistosomiasis – a disease known to result from the immunological injury caused by the eggs lodged in the radicles of portal vein.²⁶ Unfortunately, whether these abnormalities are the cause or the effect of the disease is not known.

Familial aggregation has been recently reported in NCPF.²⁷ In another study of 48 NCPF patients, the frequency of HLA-DR3 was found to be significantly higher than controls. The results suggested an autoimmune basis of the disease and that susceptibility to NCPF may be HLA class II-mediated.²⁸

INCREASED BLOOD FLOW

Since the initial description of Banti, disproportionate splenomegaly in these patients has intrigued the investigators. Majority of the workers have found increased splenic and hepatic blood flow in NCPF patients^{6,13,29} but whether this is the primary event leading to portal hypertension or results from congestion caused by increased portal vascular resistance, is not clear.

Pathology

GROSS

The liver may be normal to markedly nodular.^{30,31} Although, the surface may resemble cirrhosis, the deeper portions of liver do not show any nodularity and the liver may weigh from less to more than normal.^{6,30,31} On the cut surface, hypertrophic nodules may occasionally be seen, compressing the portal vein.³¹ The portal venous system shows prominent and dilated branches with marked sclerosis of the walls. In autopsy reports, frequent thrombosis of the large and small portal vein branches with accompanying areas of ischaemic necrosis has been reported.^{30,31} Significant perivascular fibrosis along the portal vein and its branches is an important feature.

MICROSCOPY

Histological lesions in the liver were aptly summarised by Nayak *et al* as, 'obliterative portal venopathy of liver', which indicates marked subendothelial thickening of the large and medium sized intrahepatic branches of the portal vein with a patchy segmental distribution.³² In the sections obtained from autopsy livers, organised thrombi with recanalisation, scarring of the terminal portal tracts with obliteration or disappearance of the portal vein radicles and appearance of aberrant vessels are often seen. The lobular architecture and hepatic parenchyma is unaffected. In the needle biopsy specimens, the changes are often minimal or absent. Although, Okuda *et al* maintain that the pathology of NCPF and IPH is identical,³³ subtle differences are noteworthy (Table).

ULTRASTRUCTURE

A widening of the intercellular and Disse's spaces with fibrogenesis in the

Table Comparison of some features of NCPF and IPH

Feature	NCPF	IPH
Male:female	2 to 4:1	1:3
Mean age (yr)	25 to 35	43 to 56
Clinical features ^{10 13 39}		
Haematemesis/malena	94%	40%
Mass in left upper abdomen	6.0%	40%
Ascites	2.1%	10%
Anaemia and symptoms related to it	—	35%
Jaundice	2.1%	—
Bleeding tendency	—	6%
Splenomegaly	95%	88%
Hepatomegaly	61%	41%
Pathology ¹¹⁻¹³		
Irregular parenchymal nodules	53%	29%
Nodules on postero-inferior surface	25%	4%
Attempted pseudolobule	72%	30%
Bile duct proliferation	38%	4%
Haemodynamics ^{13 15 35}		
Weged hepatic vein pressure	Normal or raised	Always raised

perisinusoidal space and occasional capillarisation of the sinusoids is seen.^{13 34} The cell membrane between the hepatocytes shows development of microvilli. The intracytoplasmic components of hepatocytes are normal.

It is not clear whether the morphological changes seen in NCPF are secondary to circulatory insufficiency, as argued by Japanese workers, as they are not seen in patients with extrahepatic portal vein obstruction.

HAEMODYNAMICS

The intrasplenic and portal vein pressures are markedly elevated in patients with NCPF.^{6 11 13 35} One of the main controversies in the hemodynamic evaluation of NCPF concerns wedged hepatic vein pressure (WHVP) measurements. Wedged hepatic vein pressure has been reported from normal to moderately raised.^{6 11 13 36} Sama *et al* found increased WHVP in 91% patients.¹³ We observed it to be 8 mm or less in nearly half the patients and raised in the rest.³⁵ The differences in various studies could partly be because of the differences in the extent and site of fibrosis in the liver of patients. In patients with IPH on the other hand, WHVP is almost always raised (Table).¹⁵

The fact that WHVP is lower than portal pressure indicates a resistance to portal blood flow (portohepatic gradient). Until recently, the exact site of the resistance was not clear. It has now been shown that two independent pressure gradients exist in NCPF patients, the first between intrasplenic and intrahepatic pressure and the second, between intrahepatic and WHVP.^{35 37} While demonstration of the former gradient haemodynamically outlines the presence of presinusoidal block, the existence of the later gradient, reflects a perisinusoidal resistance to flow of portal blood. As both wedged and intrahepatic pressures underestimate the portal pressure in NCPF, intravariceal pressure should be used as a reliable indicator of portal pressure.

Two dimensional contrast echocardiography has been used to study the pulmonary arteriovenous shunts and cardiac chamber abnormalities in NCPF. While shunts were not detected in any patient, left atrial and

ventricular enlargement was seen in 64 and 57% and reduced left ventricular ejection fraction in 36% patients with NCPF.³⁸ Similar changes were also seen in cirrhotics suggesting that hyperdynamic portal hypertensive state is probably responsible for these changes. Quantitative evaluation of intra and extrahepatic portosystemic shunting has not been carried out for NCPF patients as has been done for IPH patients.^{10,15}

Although the haemodynamic investigations have helped to improve our understanding of the pathophysiology of NCPF, they have failed to provide an insight into the cause of portal hypertension and the initial events leading to development of increased blood flow, splenomegaly and pre and perisinusoidal resistance to portal blood flow.

Clinical profile

Patients with NCPF are usually young and look well. They almost always present with one or more episodes of haematemesis, which are well tolerated, and with a long standing history of a mass in the left hypochondrium. Jaundice and signs of liver failure are rare and occur transiently after haematemesis or during terminal illness.^{13,39} Except for an initial report, it is believed that ascites is uncommon in NCPF and if present, is mild and develops after a bleed.^{11,39} These features of NCPF are somewhat different from those reported in the National Study on IPH in Japan,¹⁰ where a mass in the left hypochondrium, anaemia and symptoms related to anaemia were almost as common a presentation as haematemesis. Most conspicuous physical finding in NCPF is splenomegaly which at times can fill most of the abdomen. Overt or subclinical encephalopathy is not a feature of NCPF⁴⁰ except after shunt surgery.^{13,41}

Laboratory investigations

Anaemia is seen in majority of patients. It is usually of normocytic normochromic or normocytic hypochromic type. Leucopenia ($<5000/\text{cmm}$) and thrombocytopenia ($<100\,000/\text{cmm}$) are also frequently seen.^{6,13} These changes in part could be a result of increase in plasma volume and splanchnic pooling of blood.⁶ Prothrombin time and coagulation parameters are usually within normal limits. Bone marrow is hypercellular. Although RBC survival has not been studied in detail in NCPF, the incidence of hypersplenism is not as high as that reported in IPH.¹⁵

Tests of liver function like serum bilirubin, globulin, alkaline phosphatase and transaminases (ALT and AST) are normal or mildly deranged. Bromsulphalein retention was reported to be abnormal ($>16\%$ retention) in 20% patients.¹³ An increase in arterial ammonia concentration⁴² and a reduction in pentagastrin stimulated maximum gastric acid secretion⁴³ has been shown. The biliary lipid composition is reported to be normal in NCPF patients.⁴⁴

Radiological features

Oesophageal varices were shown by barium swallow in 68% patients.³⁹ In 78 of the 81 (96%) NCPF patients studied by us with UGI endoscopy, oesophageal varices were present.

Splenoportovenography (SPV) has been the common and often the only mode of investigation used to evaluate the splenoportal axis in NCPF patients in India.^{11-13,14} Splenoportovenography usually shows dilatation of the portal and splenic veins along with various collaterals. Some workers have stressed the importance of selective dilatation of the left branch of portal vein with sudden narrowing ('cut off' sign) of major intrahepatic branches in NCPF.^{5,6,13} These features are, however, not diagnostic.

There are no published data on the sonographic findings in NCPF. In our initial experience in 36 patients, marked thickening of the portal vein walls specially of intrahepatic branches, was observed. In three patients, a thrombus was seen in the right or left main branch of the portal vein.

Relationship between NCPF and extrahepatic portal vein obstruction (EHPVO)

Partial or complete obstruction of the extrahepatic portal vein is one of the three important causes of portal hypertension in India; the other two being cirrhosis and NCPF. Extrahepatic portal vein obstruction is usually seen in young male children who often belong to poor social class. Although the history of umbilical sepsis is not often available in EHPVO patients, it is believed that significant thrombosis of the main portal vein and its branches occurring at an early age leads to the development of this disease. Many workers^{10,12} are of the opinion that EHPVO and NCPF or IPH may be representing a spectrum of the same disease process, which has its origin in abdominal sepsis. The nature, extent, rapidity, host response and the age at the time of portal vein infection probably influences whether the infective process would result into NCPF or EHPVO. Patients with distinct EHPVO may have pyelephlebitic changes all along the portal vein and its branches. Even some hepatic histological features in EHPVO patients may resemble NCPF.⁴⁵ On the other hand, patients with NCPF may also develop intra and extrahepatic portal vein thrombi. There is, however, as yet no conclusive human or experimental evidence to support the common origin hypothesis.

Diagnosis and differential diagnosis

For the physicians and the gastroenterologists practising in India, NCPF is a distinct entity and its diagnosis generally does not pose a problem. Three conditions which, however, need to be differentiated from NCPF are compensated cirrhosis in the young, EHPVO and tropical splenomegaly syndrome (TSS). Usually the history of jaundice, the clinical profile and raised transaminases indicate the presence of chronic liver disease.⁴⁶ As the liver could be nodular and shrunken in NCPF, a liver biopsy to exclude cirrhosis is mandatory. Occasionally laparoscopy may be of great help. Usually, EHPVO can be easily differentiated from NCPF as the patients are much younger and the portal vein block can be demonstrated with a SPV or an ultrasound examination. Tropical splenomegaly syndrome (TSS), which results from an abnormal and exaggerated immune response to chronic malarial infection⁴⁷ is another common entity seen in the tropics and Africa. It can easily be excluded because of the lack of any clinical signs of portal hypertension. The intrasplenic pressure may be raised in some, but wedged hepatic pressure is within normal limits.⁴⁸

It is rarely necessary to differentiate between splenomegaly of myeloid metaplasia, Kala azar, Felty's syndrome with nodular regenerative hyperplasia or idiopathic retroperitoneal fibrosis from NCPF.

Treatment and prognosis

At present, the 'pre-NCPF' or early stage of NCPF before the development of portal hypertension, is not known. The majority of the patients present with variceal bleeding and the treatment therefore involves control of acute bleeding or prevention of rebleeding by surgical or medical means. Lienorenal shunt has been found to be quite useful. In a large series, mortality after shunt in patients with acute bleeds was reported to be 10%, but was negligible in elective shunt operations.⁴⁸ The incidence of shunt occlusion, overt chronic portosystemic encephalopathy and rebleeding was about 10%. As well as the morbidity and mortality associated with surgery, the facilities and expertise for shunt surgery are not widely available. For the past few years, many centres in India have started treating variceal bleeds in NCPF patients with endoscopic sclerotherapy. It has been found to be very effective in the management of acute variceal bleeding as well as prevention of rebleeding.^{49, 50} The incidence of variceal recurrence and rebleeding were only 22% and 3.1% respectively in a large series of patients.¹⁴ At present, sclerotherapy is recommended as the treatment of choice for NCPF patients with bleeding varices.

Although the natural history of NCPF is ill-understood, the disease seems to have a protracted benign course with a very good prognosis.^{6, 13, 14, 39} After lienorenal surgery, a five year survival of 87% has been claimed.⁴⁸ After successful eradication of oesophageal varices with sclerotherapy, 100% survival has been reported in NCPF patients.¹⁴ In fact, because the most important cause of death in NCPF is an exsanguinating haemorrhage, there seems a basis for evaluating prophylactic sclerotherapy in this group of patients.

In conclusion, NCPF should be understood as a common cause of portal hypertension in India characterised by repeated well tolerated attacks of haematemesis, long standing splenomegaly, near normal liver functions and no evidence of cirrhosis or portal vein obstruction. Although the aetiology is obscure, the pathological features of pyelephlebitis and obliterative portovenopathy and some resemblance to EHPVO indirectly suggest a role of portal vein infection. There is pathoanatomic and haemodynamic evidence of pre and perisinusoidal resistance to flow of portal blood with markedly raised intrasplenic and intravariceal pressures. The disease runs a benign course and once variceal bleeding can be successfully prevented, the prognosis is good. The fact that there are many similarities and some differences between NCPF of India and IPH of Japan indicates that though the morphological response of the liver to different aetiological agents may be similar, the clinical profile of the diseases could be quite different; young men in India and middle aged women in Japan.

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