

Review Article

Non-cirrhotic portal hypertension: current concepts and modern management

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Abstract

Non-cirrhotic portal hypertension (NCPH) is a heterogeneous group of liver disorders of vascular origin, leading to portal hypertension (PHTN) in the absence of cirrhosis. The lesions are generally vascular, either in the portal vein, its branches or in the peri-sinusoidal area. The majority of diseases included in the category of NCPH are well-characterized disease entities where PHTN is a late manifestation. Two diseases that present only with features of PHTN and are common in developing countries are non-cirrhotic portal fibrosis (NCPF) and extrahepatic portal vein obstruction (EHPVO). Non-cirrhotic portal fibrosis is a syndrome of obscure etiology, characterized by 'obliterative-portovenopathy' leading to PHT, massive splenomegaly and well-tolerated episodes of variceal bleeding in young adults from low socioeconomic backgrounds, having near normal hepatic functions. In some parts of the world, NCPF is called idiopathic portal hypertension in Japan or 'hepatoportal sclerosis' in USA. Because 85–95% of patient with NCPF and EHPVO present with variceal bleeding, treatment involves management with endoscopic sclerotherapy (EST) or variceal ligation (EVL). These therapies are effective in approximately 90–95% of patients. Gastric varices are another common cause of upper gastrointestinal bleeding in these patients and these can be managed with cyanoacrylate glue injection or surgery. The prognosis of patients with NCPF is good and 5 years survival in patients in whom variceal bleeding can be controlled has been reported to be approximately 95–100%.

Key words : Non-cirrhotic portal hypertension, non-cirrhotic portal fibrosis, extrahepatic portal vein obstruction

Introduction

Non-cirrhotic portal hypertension (NCPH) comprises group of diseases that are characterized by an increase in portal pressure due to intrahepatic or pre-hepatic lesions, in the absence of cirrhosis of the liver. It is not merely absence of cirrhosis, but also of hepatic venous outflow obstruction, such as veno-occlusive disease and Budd–Chiari syndrome. The lesion in NCPH is generally vascular, present in the portal vein, or its branches in the peri-sinusoidal area of the liver. Wedged hepatic venous pressure (WHVP) is near normal or mildly elevated in these patients and is significantly lower than portal vein pressure.^{1,2} The majority of diseases that are grouped under this category of NCPH have portal hypertension (PTH) as a late manifestation of the disease. Two diseases, which are very common in developing countries and almost always present only with features of PTH, include non-cirrhotic portal fibrosis (NCPF) and extra-hepatic portal vein obstruction (EHPVO).

Historical perspective

Attention was drawn to a condition characterized by congestive splenomegaly, anemia, with or without gastrointestinal bleeding and ascites as early as the late 19th century.⁴ Awareness about this condition as being distinct from cirrhotic causes of PHT emerged in the Indian subcontinent in the late 1950s. In 1962, Indian scientists drew attention to splenomegaly with non-cirrhotic liver disease in North Indian patients.⁵ Soon after, Boyer et al. while working in Calcutta, reported a series of similar patients but used the term idiopathic portal hypertension (IPH).⁶ At the same time, Mikkelsen et al. described 36 patients with PHT without cirrhosis who had phleboscrosis of intra- and extrahepatic portal veins and coined the term 'hepatoportal sclerosis'.⁷ In 1969, a workshop organized by the Indian Council of Medical Research (ICMR) reviewed all available information on this condition and christened this distinct clinicopathological entity as 'non-cirrhotic portal fibrosis'.⁸ This condition was simultaneously reported from Japan, where the condition is known as IPH^{9,10} and subsequently from Iran¹¹ and Pakistan.¹²

Epidemiology

Non-cirrhotic portal fibrosis has been reported from all over the world and more in Indian sub-continent. It is

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Table-1: Common causes of NCPH

Common causes of NCPH
Prehepatic
EHPVO (portal vein thrombosis)
Splenic vein thrombosis.
Splanchnic arterio-venous fistula
Hepatic
Presinusoidal
Noncirrhotic portal fibrosis (NCPF)
Idiopathic portal hypertension (IPH)
Hepatoportal sclerosis
Vinyl chloride, arsenic, or azathioprine hepatotoxicity
Sinusoidal
Alcoholic hepatitis
Hypervitaminosis A
Nodular regenerative hyperplasia
Methotrexate hepatotoxicity
Postsinusoidal
Veno-occlusive disease
Hepatic vein thrombosis (BCS)
Posthepatic
Inferior vena caval web
Constrictive pericarditis.

believed to account for nearly one-sixth to one-quarter of all causes of PTH seeking medical attention^{5,12-14} The condition has been commonly seen in people who are socioeconomically disadvantaged, not only in India, but also in Iran.¹¹ Improved hygiene and standards of living could explain the relative rarity of the disease in the West and its declining incidence in Japan. Except for an occasional report, most studies indicate a male predominance.^{13,14}

While in 1985 the reported incidence of IPH in Japan was 0.75/105 population, in 1992 only an average of 11 new patients were reported.¹⁵ This is in contrast to IPH in Japan, Europe and the USA, where the disease is more common in females. The mean age of NCPF patients varies from 25 to 35 years, which is much younger than for IPH patients.

Etiology

The etiopathogenesis of NCPF is poorly understood. A number of hypotheses have been proposed. (Table-1)

Infective hypothesis

Non-cirrhotic portal fibrosis has been commonly seen in patients from a low socioeconomic background. Abdominal infection at birth or in early childhood has been alleged to play an important role.¹⁴ Umbilical sepsis,

bacterial infections and diarrheal episodes in infancy and in early childhood are likely to lead to portal pyemia, pylephlebitis, resulting in thrombosis, sclerosis and obstruction of small and medium-sized portal vein radicals.

Experimental studies

Idiopathic portal hypertension like changes in the liver and the development of PTH, has been reported after injecting dead non-pathogenic colon bacilli into the portal vein of rabbits and dogs.^{16,17} In another model of indwelling cannulation of the gastrosplenic vein, repeated injections of *Escherichia coli* resulted in the development of splenomegaly and an increase in portal pressure at 3 months.¹⁸

Exposure to trace metals and chemicals

Prolonged ingestion of arsenic has been incriminated in the causation of NCPF.¹⁹ In a Belgian study, a previous intake of arsenic as Fowler's solution for the treatment of psoriasis was reported in eight of forty seven NCPF patients.²⁰ Interestingly, these patients had florid skin stigmata of arsenicosis, something not commonly experienced in Indian subcontinent. In patients from Iran, a history of pica was obtained in nearly half the patients.¹¹ A histological picture resembling NCPF has been observed following chronic exposure to vinyl chloridemonomers, copper sulfate (vineyard sprayers), protracted treatment with methotrexate, hypervitaminosis A and in renal allograft recipients receiving treatment with 6-mercaptopurine, azathioprine and corticosteroids.

Experimental studies

To investigate whether chronic arsenic exposure could produce NCPF, we undertook studies in albino mice with chronic oral arsenic feeding. While arsenic was found to induce a four- to 14-fold increase in hepatic hydroxyproline and hepatic collagen compared with control mice, features of NCPF or PTH did not develop in any animal.²¹ These observations suggest that although arsenic ingestion could induce hepatic fibrogenesis, it cannot be directly incriminated in the causation of NCPF.

Immunologic and immunogenetic hypotheses

Evidence supporting these hypotheses includes: (i) A reduction in the suppressor/cytotoxic T lymphocytes (T8) in NCPF patients and a decreased T4/T8 lymphocyte ratio;²²(ii) a reduction in the cell-mediated immune status in NCPF patients; and (iii) a poor autologous mixed lymphocyte reaction (MLR).²³ In Japan, IPH is frequently associated with autoimmune disorders such as systemic lupus erythematosus (SLE), progressive systemic sclerosis (PSS), thyroiditis and mixed connective tissue d

isease (MCTD).²⁴ Nearly two-thirds of Japanese female patients with IPH test positive for anti-ds DNA antibody and one-quarter test positive for antinuclear antibody.²⁵ Such a high prevalence of associated autoimmune conditions has not been the experience in the Indian subcontinent. However, familial aggregation and a high frequency of HLA-DR3 has been found in Indian patients.²⁶

Proposed hypothesis

Based on the available information, a hypothesis was proposed for the development of NCPF and EHPVO. Both these venous inflow tract diseases could develop in a genetically predisposed individual when infection or a prothrombotic event could precipitate thrombosis in the portal vein or its radicals. If it is a major thrombotic event, occurring at an early age in life, the main portal vein becomes occluded, leading to the development of EHPVO. However, in the event of repeated microthrombotic events, the small or medium branches of the portal vein are affected, leading to the development of NCPF in a young adult.

Pathology

Liver pathology is characterized by phlebosclerosis, fibroelastosis, periportal, and perisinusoidal fibrosis, aberrant vessels in portal tract (portal angiomatosis), preserved lobular architecture, and differential atrophy.²⁷ Main PV trunk is dilated with thick sclerosed walls, along with thrombosis in medium and small PV branches – the histological hallmark termed “obliterative portalvenopathy”,²⁷ Nakanuma et al. had proposed a staging system based on gross and imaging features: stages I–IV, stage I being absence of peripheral parenchymal atrophy; stage IV showing presence of obstructive thrombosis in intrahepatic large branches or trunk of portal vein.²⁷ Spleen is disproportionately large (average weight 723 g) at portal pressures comparable to other conditions of PHT.¹¹

Hemodynamics

The intrasplenic and portal vein pressures are markedly elevated in patients with NCPF. The WHVP may be normal or slightly elevated in approximately half the patients. Two pathoanatomic sites of obstruction have been identified: a pressure gradient between the spleen (intrasplenic pressure; ISP) and the liver (intrahepatic pressure; IHP) and another between the liver (IHP) and the WHVP.²⁸ Variceal pressure has also been studied in these patients and found comparable to that in cirrhotic PHT.^{28,29} Splenic and portal vein blood flow are known to be markedly increased in IPH patients from Japan, suggestive of a hyperdynamic circulatory state. Pulmonary

hemodynamics in patients with NCPF have also been reported.³⁰ Both intrasplenic (ISP) and intravariceal pressures (IVP) are high in NCPF. There are two independent pressure gradients – one between ISP and intrahepatic pressure (IHP) (8.9 mmHg), and another between IHP and wedge hepatic venous pressure (WHVP) (6.2 mmHg), indicating 2 patho-anatomic sites of resistance in these cases – presinusoidal and perisinusoidal. As the vascular resistance is pre- and peri-sinusoidal, HVPG remains nearly normal.

Clinical presentation

NCPF/IPH is a disease of young to middle age, whereas EHPVO is primarily a childhood disorder but can present at any age from 6 weeks to adulthood.^{2,4} The commonest presentations are well tolerated episodes of variceal bleed, long standing splenomegaly and anemia, and in EHPVO, with accompanied growth retardation. In NCPF/IPH, duration of symptoms at presentation varies from 15 days to 18 years.^{9,11} Frequency of variceal bleeding episodes increase with age with a median of 1 bleeding episode (range 1–20) prior to presentation.^{11,12} History of pica may be present.⁹

In EHPVO, a bimodal age of presentation has been described – those secondary to UVC or umbilical sepsis usually manifest early (<3 years) whereas those following intra-abdominal infections or idiopathic ones manifest late (>8 years) or sometimes into early adulthood.⁴ Mean ages of first bleeding episode and initial presentation are 5.3 years and 6.3–9.3 years, respectively. Episodes of variceal bleed are recurrent, mostly related to febrile illnesses, are more frequent and severe with increasing age of onset, but recurrences tend to decrease after puberty. Splenic size and portal pressure do not correlate with the incidence or severity of bleed.⁴

Hypersplenism, mostly asymptomatic, is present in both the disorders especially in older children or young adults. Bleeding from non-gastrointestinal sites is reported in about 20%.¹³ Ascites develops in 10–34% of NCPF and 13–21% of EHPVO cases usually after a bleeding episode and is related to hypoalbuminemia, and prolonged duration of PHT with subsequent progressive deterioration of liver functions.⁴⁻¹³ Other common presentations are repeated attacks of left upper quadrant pain due to perisplenitis or splenic infarction.² Mesenteric vein thrombosis, bowel ischemia.

On clinical examination, both the disorders have moderate to massive splenomegaly (average size-11 cm below costal margin). In NCPF/IPH, liver may be normal, enlarged or slightly shrunken, whereas in

EHPVO, it is normal or shrunken. Peripheral stigmata of chronic liver disease are absent. Jaundice and hepatic encephalopathy are rare (<2%) in NCPF/IPH and usually seen either after a major bleed or shunt surgery.¹¹

Diagnosis of NCPF and EHPVO

The diagnosis of NCPF and EHPVO is mainly clinical – presentation with features of PHT without any evidence of liver dysfunction. Patency of hepatic and portal veins is needed for the diagnosis of NCPF/IPH, whereas presence of portal cavernoma on doppler ultrasound (USG) is required for EHPVO. Various diagnostic criteria have been laid down for NCPF/IPH

Diagnostic features of NCPF (Table-2)

1. Presence of moderate to massive splenomegaly
2. Evidence of portal hypertension, varices, and/or collaterals
3. Patent spleno-portal axis and hepatic veins on ultrasound Doppler
4. Test results indicating normal or near-normal liver functions
5. Normal or near-normal hepatic venous pressure gradient
6. Liver histology-no evidence of cirrhosis or parenchymal injury
7. Absence of signs of chronic liver disease
8. No decompensation after variceal bleed except occasional transient ascites
9. Absence of serum markers of hepatitis B or C virus infection
- 10.No known etiology of liver disease
11. Imaging with ultrasound or other imaging techniques showing dilated and thickened portal vein with peripheral pruning and periportal hyperechoic areas.

Laboratory findings

Hypersplenism is seen in 27–87 % with anemia being the commonest abnormality followed by thrombocytopenia and leucopenia. Anemia is usually microcytic hypochromic and is related to multiple variceal bleeds, hypersplenism and iron deficiency.¹⁰⁻¹³ In NCPF/IPH, liver function tests are mostly normal, but derangements in liver enzymes, prothrombin time and albumin are seen in a small proportion.⁹⁻¹⁵ Similarly, in EHPVO, elevations of alkaline phosphatase and gamma glutamyl transpeptidase are seen with development of portal biliopathy, and hypoalbuminemia may be seen during bleed episodes.⁴ Hypoxemia secondary to intrapulmonary vascular dilatations may be seen.⁴ Frequencies of hepatitis B and C infections are comparable to that in the general population, but are higher in transfused patients from remote areas.^{4,12} (Table-2)

Table-2: Clinical and Lab Parameters

Symptoms	Signs	Lab Feature
Common		Pancytopenia
Hemetemesis/malena (70%)		Esophageal varices(97%)
Uncommon	Splenomegaly	Gastric varices (31%)
Awareness of lump (12%),		Increased INR
Ascites (transient) (25%)		Decreased fibrinogen
Portal gastropathy (3%)		

Endoscopic findings

Esophageal varices are seen in 80–90% of NCPF/IPH and EHPVO cases^{12,13} In comparison to cirrhotics, esophageal varices are more often large (90% vs. 70%), gastroesophageal varices (GOV1 and GOV2) more common (31–44% vs. 22%), portal hypertensive gastropathy (PHG) less common (10.9% vs. 5.4 Isolated gastric varices (IGV1) are present in around 6% of EHPVO patients and IGV2, indicative of ectopic or duodenal varices, are also common in these patients.³¹ On initial endoscopy, if esophageal varices are small, one should look for gastric varix.

Radiological features

Doppler USG is the first line radiological investigation in both disorders. In NCPF/IPH, liver is normal in size and echotexture. Spleen is enlarged with presence of gamma-gandy bodies; splenoportal axis is dilated and patent in NCPF/IPH. PV is thickened (>3 mm) with echogenic walls and its intrahepatic radicles are smooth and regular. There is sudden narrowing or cut-off of intrahepatic second and third degree PV branches – “withered tree” appearance along with approximation of vascular channels. Splenic index and PV inflow are high.^{32,33} Spontaneous shunts (paraumbilical and gastroadrenorenal) are seen in 16%.³³ Intrahepatic PV abnormalities (non-visualization, reduced caliber, occlusive thrombosis), focal nodular hyperplasia like nodules and perfusion defects are certain features on contrast-enhanced computed tomography (CT), which help in differentiating NCPF/IPH from cirrhosis.³⁴ For the diagnosis of EHPVO, Doppler USG of SPA has a sensitivity and specificity above 95%.³ There is cavernomatous transformation of PV. Splenoportography or arterial portography have been replaced by non-invasive methods – CT and magnetic resonance

(MR) angiography and portography, which besides providing diagnosis also give anatomical road-map prior to shunt surgery³⁵

Liver biopsy

Liver biopsy is not essential for the diagnosis of EHPVO unless the underlying chronic liver disease is suspected, but it is indicated in NCPF/IPH to exclude cirrhosis and other etiologies of PHT^{36,37} Hillaireet al. have considered 4 pathological findings for diagnosis of NCPF/IPH – hepatoportal sclerosis, periportal fibrosis, perisinusoidal fibrosis and nodular regenerative hyperplasia

Management

Management of NCPF patients include prevention of active bleeding along with primary and secondary prophylaxis.

Management of acute bleeding

Acute variceal bleeding is a life-threatening condition and requires ICU care. General management include monitoring signs vital, blood transfusion and intravenous fluids.^{38,39,40} Nasogastric tube is optional, especially if the bleeding has taken place more than 12 hours ago.⁴¹ Endoscopic therapy is preferred for control of acute bleed and is effective in 80-90%.^{42,43} Band ligation is preferred over sclerotherapy. Vasoactive drugs which decrease portal pressure can be used while endoscopic therapy is being arranged. Combination treatment with drugs plus endoscopic therapy is more effective.^{42,43} Failure of endoscopic therapy is defined, as further variceal bleeding after two endoscopic treatments during a single hospital admission for acute bleeding. Failure occur in 8–12% of patients⁴² and these patients should be treated by alternative modes of treatment like surgery or transjugular intrahepatic portosystemic shunt (TIPS).

Primary prophylaxis

Endoscopic variceal ligation (EVL) and beta blockers are commonly used for the primary prophylaxis of large esophageal varices in cirrhosis⁴³ but there is paucity of data regarding their use in NCPF. Drug and endoscopic therapy are equally effective.⁴⁴

Role of shunt surgery for primary prophylaxis is controversial but can be done in patient of NCPF who has large esophageal varices with

1. Symptomatic large splenomegaly
2. Very low platelet count (<20,000)
3. Stays far away from a good medical center where an upper GI bleed can be tackled
4. Rare blood group

Secondary prophylaxis

Both endoscopic therapy and elective decompressive surgery are effective and safe. EVL has been shown to be better than EST in almost all the studies, hence, it could be recommended in NCPF.⁴⁵

Newer therapies

Image-guided interventions (IGI) are recent means of treating and preventing variceal bleed. These include

1. Partial splenic embolization
2. Balloon-occluded retrograde transvenous obliteration
3. Percutaneous transhepatic obliteration (PTO)
4. Transjugular intrahepatic

Natural history and prognosis

The prognosis for patients with NCPF is excellent. The mortality from an acute bleed in NCPH is significantly lower than that observed in cirrhotic patients.⁴⁶ After successful eradication of esophagogastric varices, a 2 and 5 year survival of nearly 100%.

Non-cirrhotic portal hypertension continues to be a common cause of PHT in selected geographic areas of the world, especially in socially disadvantaged people. The etio-pathogenesis of this condition is possibly multifactorial. The clinical presentation of patients is with splenomegaly and/or complications of PTH. The patients have a relatively well-preserved liver function. The diagnosis is based on clinical and endoscopic evidence of PHT, as well as radiological and histological features. If managed suitably, these patients have a life expectancy similar to that of the population at large. Future research should aim to elucidate pathogenetic mechanisms so that the condition can be effectively prevented.

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