Non-cirrhotic portal fibrosis

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ABSTRACT

Portal hypertension occurs commonly in patients with cirrhosis and rarely in those without cirrhosis of liver. The two most important causes of non-cirrhotic portal hypertension are non-cirrhotic portal fibrosis (NCPF) and extrahepatic portal venous obstruction (EHPVO). Unlike EHPVO, there is no thrombosis of the extrahepatic portal vein in NCPF. In NCPF, there occurs sclerosis of medium and small branches of the portal vein. The hepatic venous pressure gradient (HVPG) is normal in NCPF, when compared with cirrhosis where it is elevated. NCPF is also known as non-cirrhotic intrahepatic portal hypertension (NCIPH), idiopathic portal hypertension, hepatoportal sclerosis, and benign intrahepatic portal hypertension. It is a disease of obscure etiology, predominantly affecting the middle-aged males and females who present with hematemesis and massive splenomegaly.

Key words: Cirrhosis, idiopathic portal hypertension, non-cirrhotic portal fibrosis

INTRODUCTION

Portal hypertension results from several diseases that increase the resistance to blood flow at the prehepatic, hepatic, and post-hepatic sites. Non-cirrhotic portal fibrosis (NCPF) and extrahepatic portal venous obstruction (EHPVO) are the two most important causes of non-cirrhotic portal hypertension.[1] In NCPF, there occurs sclerosis of medium and small branches of the portal vein, while in EHPVO there is thrombosis of the extrahepatic portal vein. The hepatic venous pressure gradient (HVPG) is normal in NCPF, when compared with cirrhosis where it is elevated.[2,3] NCPF has been described in literature by several terminologies like non-cirrhotic intrahepatic portal hypertension (NCIPH), idiopathic portal hypertension, hepatoportal sclerosis, and benign intrahepatic portal hypertension. It is a disease of obscure etiology, predominantly affecting the middle-aged males and females who present with hematemesis and massive splenomegaly.

DEFINITION

There is no universally accepted definition of NCPF as evidenced by the fact that there is difference in nomenclature for the same entity. In 1965, Mikkelsen et al. studied 36 patients who were operated for portal hypertension and whose livers were considered to be functionally and architecturally within normal limits. They found sclerosis of the portal vein and its radicals in patients with portal hypertension without cirrhosis and called it as hepatoportal sclerosis.[4] Boyer et al. described a similar condition while working in Calcutta and used the term “idiopathic portal hypertension.”[5] The term “non-cirrhotic portal fibrosis” was described as a new syndrome by Basu et al. in 1967 and was subsequently endorsed by the Indian Council of Medical Research.[6] A similar condition was reported from Japan and was called as “idiopathic portal hypertension.” Okuda et al. studied the morphological changes of the liver in the autopsy and surgical biopsy specimens of cases of non-cirrhotic portal hypertension and compared them with those
of NCPF from India. They found that liver pathology was very similar in IPH and NCPF, characterized by phlebosclerotic changes and perivascular fibrosis of the portal vein system, and parenchymal atrophy perhaps secondary to portal circulatory insufficiency.[7]

The consensus definition according to the Asian Pacific Association for the Study of Liver (APASL 2007) is that NCPF/IPH is a disease of uncertain etiology characterized by perportal fibrosis and involvement of small and medium branches of the portal vein, resulting in the development of portal hypertension. The liver functions and structure primarily remain normal.[8]

EPIDEMIOLOGY

NCPF/IPH has been reported from all parts of the world. It is more common in developing than in the developed countries.[8,9] It is more prevalent in the low socioeconomic strata. Better hygiene and standards of living have been postulated as the reason for the rarity of the disease in the West and the declining incidence in Japan. In India, there is no data registry of patients of NCPF, as compared to Japan. The exact incidence of the disease in India is not known. The earlier studies have reported that approximately 23.3% (range 7.9-46.7%) of all cases of portal hypertension is attributed to NCPF.[1] The peak age of incidence is in the third and fourth decades of life, which is one to two decades earlier than for IPH in Japan. Most of the studies in India have found the disease to be more common in males in contrast to female dominance in Japan.[10] However, in a retrospective study by Dhiman et al. involving 151 patients, 37.7% were males and 62.3% were females with the mean age at diagnosis being 30.5 years.[8]

ETIOLOGY

The exact etiology of NCPF is unknown. Three hypotheses proposed in the literature are: A) infective hypothesis, B) arsenic exposure, and C) immunological abnormalities.

Infective hypothesis

NCPF has been commonly seen in patients from low socioeconomic backgrounds. Abdominal infection at birth or in early childhood, umbilical sepsis, bacterial infections, and diarrheal episodes in infancy and early childhood are likely to lead to portal pyemia and pylephlebitis, which result in thrombosis, sclerosis, and obstruction of small- and medium-sized portal vein radicals.[4]

This hypothesis is supported by the development of IPH-like changes after injecting non-pathogenic colon bacilli into the portal vein of rabbits.[11] In another animal model of non-cirrhotic portal hypertension by Omanwar et al., heat-killed Escherichia coli were injected into the gastrosplenic vein of rabbits. The authors found significant splenomegaly, persistent increase in portal pressure, and mild fibrosis without hepatic parenchymal injury, similar to NCPF in humans.[12]

Exposure to trace metals and chemicals

Arsenic exposure

There are many studies which have linked chronic arsenic exposure to the development of non-cirrhotic portal hypertension.[13,14] Initial case reports suggested the use of Fowler’s solution (potassium arsenite) for the treatment of psoriasis as a possible etiological factor.[15] In a study conducted by Datta et al. in the liver biopsy specimens from nine patients, the arsenic content was found to be significantly higher in those with IPH when compared with cirrhosis and control subjects. The authors suggest that it was due to either intake of water or indigenous medicines contaminated with arsenic.

Mazumder et al. have done extensive studies on the hepatic manifestations of chronic arsenic toxicity in West Bengal.[16-18] Hepatomegaly was found in 190 out of 248 cases of arsenicosis, and NCPF was the predominant lesion in 63 out of 69 cases in whom liver biopsy was done. It has been suggested that depletion of antioxidant system of the liver followed by peroxidative damage of the lipid membranes may be reason for the liver pathology in chronic arsenic toxicity.

Chronic exposure to vinyl chloride polymers is known to produce angiosarcoma of liver and also histological changes similar to chronic arsenic poisoning and IPH.[19] Long-term treatment of psoriasis with methotrexate and hypervitaminosis A have also been associated with NCPF.[20,21]

Immunological and immunogenetic hypothesis

Many immunological abnormalities are seen in patients with NCPF/IPH. There is some evidence about the deranged immune functions and reduced cell-mediated immunity in patients with NCPF. Nayyar et al. found that the total peripheral T lymphocytes and suppressor/cytotoxic phenotype (T8) were significantly decreased and the ratio of T4 to T8 lymphocytes was significantly increased in NCPF patients in comparison with controls. However, they studied a small group of 16 NCPF patients only.[12] Increased expression and release of the soluble form of vascular cell adhesion molecule-1 (VCAM-1) from the endothelial and sinusoidal cells around the hepatic vessels has been postulated to have a role in the pathogenesis of IPH in Japan.[23]

Connective tissue growth factor (CTGF) is another molecule implicated in the pathogenesis of IPH.
CTGF functions as one of the downstream effectors of transforming growth factor-β (TGF-β) which is a potent fibrogenic cytokine. CTGF also mediates TGF-β-induced collagen synthesis.[24]

IPH in Japan has been frequently associated with autoimmune disorders like systemic lupus erythematosus (SLE), thyroiditis, and mixed connective tissue disorders.[25,26] Familial aggregation and association with human leukocyte antigen (HLA) DR3 has been reported by Sarin et al. as early as 1987.[27]

Role of gut-derived prothrombotic factors
Eapen et al. studied 34 patients with NCIPH and postulated that elevated serum cardiolipin antibodies and other prothrombotic factors from the intestine may travel upstream and obliterate small portal vein radicles, which are the first filter for splanchnic venous blood.[28]

PATHOLOGY
Grossly the liver is usually normal, but it can be nodular in 10-15% of the cases. The histopathology of biopsy specimens from patients undergoing shunt surgery for portal hypertension showed fibrosis of the portal areas along with patchy and segmental subendothelial thickening of the large and medium-sized branches of the portal vein. This has been described as “obliterative portovenopathy” by Nayak and Ramalingaswamy.[29]

The intimal thickening of the intrahepatic portal venous channels associated with obliteration of small portal venules and emergence of new aberrant portal channels is said to be characteristic of NCPF.

In another study by Madhu et al. from Vellore, the most common histological findings in 30 patients of idiopathic NCIPH were portal fibrosis with or without formation of fibrous septa and abnormal dilatation of the portal venules.[30] These findings on liver biopsy help to differentiate it from cirrhosis where the histopathology shows a distorted liver architecture with bridging fibrosis and regenerative nodules.

HEMODYNAMICS IN NCPF
Portal vein pressures are markedly elevated in patients with NCPF. Sarin et al. studied the hemodynamics in NCPF and reported that there are two pathoanatomic sites of obstruction.[28] Firstly, a pressure gradient between the spleen and the liver [intrasplenic pressure — intrahepatic pressure (IHP)] and secondly, another gradient between the IHP and the wedge hepatic venous pressure (WHVP) (IHP — WHVP), suggestive of a presinusoidal and a perisinusoidal resistance to portal blood flow in NCPF patients. They found that the mean WHVP and IHP were significantly lower than the intrasplenic and intravariceal pressure in patients with NCPF.[2]

Variceal pressure has also been studied and is comparable with that of cirrhotics.[31] Intravariceal pressure has been found to closely reflect the portal pressure in NCPF patients and is the investigation of choice for measurement of portal pressure.

CLINICAL PRESENTATION
Patients with NCPF are usually young and present with well-tolerated episodes of upper gastrointestinal (UGI) bleed, a longstanding mass, or heaviness in the left upper quadrant suggestive of splenomegaly, and other features of hypersplenism like anemia and thrombocytopenia. Some of the features which are common in cirrhosis, such as jaundice, ascites, and hepatic encephalopathy, are very rare in these patients with normal liver functions and may be seen only after an episode of gastrointestinal hemorrhage. Large spontaneous shunts protect NCPF patients from variceal bleeding.

There are some uncommon presentations of NCPF documented in literature, such as glomerulonephritis, hypoxemia due to intrapulmonary shunting, autonomic dysfunction, and fungal brain abscess in a patient with leukopenia due to hypersplenism.[32-36] Patients with NCPF have preserved hepatic synthetic functions. Conventional tests of liver function like albumin and prothrombin time are near normal in these patients. In the study by Dhiman et al. involving 151 patients, though most of the patients had normal liver functions, elevated bilirubin was found in 8.8% patients and elevated aspartate transaminase (AST) and alanine transaminase (ALT) was found in 17.9% and 9.9% of the patients, respectively.[37]

Most patients with NCPF have pancytopenia consequent to hypersplenism. Anemia is common and can be either microcytic hypochromic due to gastrointestinal blood loss, or normocytic normochromic due to hypersplenism. Leukopenia and thrombocytopenia due to hypersplenism are not uncommon. Though most patients have hypersplenism, they are asymptomatic for the same. Some patients may present with epistaxis, gum bleeds, and skin petechiae due to thrombocytopenia. The bone marrow is hypercellular.

Coagulation and platelet function abnormalities also have been found in patients with NCPF. In a study by Bajaj et al., 78% patients with NCPF had significantly increased international normalized ratio (INR) and a decrease in fibrinogen and platelet aggregation.[38] These imbalances could be caused by chronic subclinical
endotoxemia and cytokine activation which follows the initial portal thromboembolic event.

**IMAGING STUDIES**

Ultrasonography (USG) is the initial imaging modality of choice for diagnosing NCPF. It shows a dilated and patent splenoportal axis. Increased echogenicity of the walls of the portal vein is seen in NCPF. USG is suggestive of cirrhosis, if the liver is shrunken with surface irregularities. Doppler studies can help to identify any thrombus in the portal vein. This is needed to rule out EHPVO. Spontaneous splenorenal shunts are more common in NCPF compared to cirrhosis. Portal biliopathy is also seen in patients with NCPF.

Radionuclide scintigraphy with Tc99m sulfur colloid scan has also been used to differentiate NCPF from cirrhosis. High marrow uptake on scintigraphy is considered to be pathognomonic of cirrhosis. Normally about 85% of the colloid is trapped in the Kupffer cells of the liver. In cirrhosis, the colloid is not readily extracted by the liver due to fibrosis, but is taken up by the reticuloendothelial cells of the spleen and the bone marrow. In contrast, in NCPF, there is no bone marrow shift as the liver parenchyma is normal. The liver uptake is homogenous in NCPF, compared to patchy uptake in cirrhosis. The spleen uptake and the spleen size are significantly more in NCPF than in cirrhosis.

**Portovenography**

The classical portographic findings in NCPF include selective dilatation of the left branch of the portal vein with a sudden narrowing of major intrahepatic branches (cut-off sign), paucity of medium-sized (third and fourth order) portal branches, obtuse-angled division of peripheral branches, avascular area beneath the liver surface, and intrahepatic collaterals. However, duplex Doppler ultrasound has now become the preferred investigation method for the evaluation of splenoportal axis and spontaneous shunts.

**Endoscopy**

Approximately 70% of patients present with the initial history of major variceal bleed. Esophagogastric varices have been reported in 85-95% of patients with NCPF. Gastric varices also are more common in NCPF compared to cirrhosis. Antral varices are uncommon and may develop in up to 3.8% of patients after eradication of esophageal varices. Anorectal varices are also reported to be more common in NCPF. Patients with NCPF tolerate GI bleed well probably because of the preserved hepatic synthetic function. Though patients with NCPF tolerate GI bleed well, it is the most important cause of mortality in these patients.

**DIAGNOSIS OF NCPF**

The diagnosis of NCPF should be suspected when a young male/female presents with history of variceal bleeding, moderate to massive splenomegaly without any features of chronic liver disease. The following are the consensus statements regarding the diagnostic features of NCPF according to the APASL recommendations (2007). All of the following are needed to make a diagnosis of NCPF:

- Diagnostic features of NCPF/IPH:
  - Presence of moderate to massive splenomegaly
  - Evidence of portal hypertension, varices, and/or collaterals
  - Patent splenoportal axis and hepatic veins on ultrasound Doppler
  - Test results indicating normal or near-normal liver functions
  - Normal or near-normal HVPG
  - Liver histology- no evidence of cirrhosis or parenchymal injury

- Other features:
  - Absence of signs of chronic liver disease
  - No decompensation after variceal bleed, except occasional transient ascites
  - Absence of serum markers of hepatitis B or C virus infection
  - No known etiology of liver disease
  - Imaging with ultrasound or other imaging techniques showing dilated and thickened portal vein with peripheral pruning and periportal hypechoic areas

**DIFFERENTIAL DIAGNOSIS**

- Child A cirrhosis — Can be differentiated by abnormal liver function tests, viral serology, and histology
- EHPVO — USG shows cavernoma (bunch of collaterals) and Doppler may show the portal vein thrombus
- Tropical splenomegaly syndrome — Portal hypertension is uncommon; elevated serum IgM and antimalarial antibody titers

**MANAGEMENT**

**Management of acute bleeding in NCPF**

Variceal bleeding due to portal hypertension may be the initial presentation in patients with NCPF and can be a life-threatening complication. The management of acute bleeding is similar to that of cirrhosis. There is no sufficient data on the efficacy of vasoactive
drugs like octreotide and terlipressin in NCPF patients with acute variceal bleed. The preferred modality of treatment for acute variceal bleed is endoscopic therapy with either sclerotherapy or band ligation, both of which are effective in controlling acute bleeding in NCPF patients.[1] Endoscopic band ligation is preferred because of the low complication rates.

**Primary and secondary prophylaxis for variceal bleeding**

**Beta-blockers and endoscopic variceal ligation (EVL)** Both beta-blockers and EVL are commonly used for primary prophylaxis of large esophageal varices in cirrhosis. In a study by Sarin et al. comparing EVL and propranolol with EVL alone for primary prophylaxis of variceal bleeding in cirrhotic and non-cirrhotic portal hypertension, both were found to be effective in primary prophylaxis and addition of beta-blocker did not decrease the risk of first bleed or death in patients on EVL.[47] The response to beta-blockers in patients with NCPF is difficult to assess because HVPG is near normal. Studies have shown that prophylactic antibiotics reduce the variceal rebleeding and improve survival in patients with cirrhosis, but similar studies are lacking in patients with NCPF.

**Shunt surgery**

In cirrhotic patients with portal hypertension, prophylactic portosystemic shunts have been found to be ineffective as deaths from post-shunt liver failure exceed those from bleeding. Shunt surgery for primary prophylaxis in NCPF can be considered only in those patients who have large varices with massive splenomegaly, severe thrombocytopenia (<20,000), and in those for whom access to health care facility is limited in case of a major variceal bleed.[1] In a study by Pal et al., proximal splenorenal shunt surgery was considered safe for secondary prophylaxis in NCPF patients.[48]

**NEWER CONCEPTS — IS NCPF REALLY BENIGN?**

NCPF is generally considered to be a disease with benign prognosis. But recent studies have shown that progressive liver failure can occur in NCPF also and some patients require liver transplantation. Eapen et al. proposed that extension of thrombosis from the portal venous microcirculation to sinusoids and adjacent small hepatic veins may be the cause of progressive liver failure.[28] Krishnan et al. suggest that NCPF is associated with slowly progressive cirrhosis with the progression occurring over decades.[29] Saigal et al. have reported NCPF-related end-stage liver disease requiring transplant.[50] Long-term follow-up over several decades is advisable to detect deterioration of NCPF patients.

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51. Mukta, et al: Non cirrhotic portal fibrosis

How to cite this article: Mukta V, Sivamani K, Panicker LC. Non-cirrhotic portal fibrosis. Int J Adv Med Health Res 2013;1:145-51.

Source of Support: Nil, Conflict of Interest: None declared.
Multiple Choice Questions

1. Non-cirrhotic portal fibrosis (NCPF) closely resembles all of the following except
   a. Idiopathic portal hypertension
   b. Benign hepatoportal sclerosis
   c. Non-alcoholic fatty liver disease
   d. Idiopathic portal hypertension

2. Toxicity with which of the following heavy metals is etiologically related to NCPF?
   a. Mercury
   b. Copper
   c. Iron
   d. Arsenic

3. Which of the following about NCPF is true?
   a. Wedge hepatic venous pressure is elevated
   b. Intravariceal pressure is normal
   c. Portal vein thrombosis is a characteristic finding
   d. Portal phlebosclerosis is commonly seen

4. All of the following are true about NCPF except
   a. Upper gastrointestinal bleed is a presenting feature
   b. It is common in tropics
   c. Can be cured by splenectomy
   d. Associated with hypersplenism

5. Radionuclide scintigraphy with Tc99m sulfur colloid scan in an NCPF patient shows which of the following findings?
   a. Uptake of colloid by bone marrow
   b. Patchy colloid uptake by liver
   c. Patchy colloid uptake by spleen
   d. No colloid shift to bone marrow

6. All of the following statements about NCPF are true except
   a. Portal pyemia can lead to portal hypertension in NCPF
   b. Hypervitaminosis A is associated with portal hypertension in NCPF
   c. Methotrexate is associated with portal hypertension in NCPF
   d. Hepatitis C infection leads to portal hypertension in NCPF

7. Shunt surgery is indicated in NCPF in which of the following conditions?
   a. Severe hypersplenism
   b. Portal gastropathy
   c. Appearance of ascites
   d. Portal vein thrombosis

8. All of the following are differential diagnosis for NCPF except
   a. Tropical splenomegaly syndrome
   b. Child A cirrhosis
   c. Extrahepatic portal vein obstruction
   d. Megaloblastic anemia

9. USG in NCPF can have all the following findings except
   a. Increased periportal echogenicity
   b. Multiple periportal collaterals
   c. Hypoechoic areas in liver
   d. Portal biliopathy

10. All of the following about management of acute variceal bleed in a patient of NCPF are true except
    a. Emergency shunt surgery is the first line of treatment
    b. Endoscopic banding of varices is preferred
    c. Transfusion of blood products is necessary
    d. Management is similar to that of cirrhosis with hematemesis

Key to multiple choice questions:
1. c, 2. d, 3. d, 4. c, 5. d, 6. d, 7. a, 8. a, 9. c, 10. a