Review Article
Open Access
CrossMark

Non cirrhotic portal fibrosis - current concepts

Abstract

Non cirrhotic portal fibrosis (NCPF) is characterized by perivenular fibrosis of the small and medium branches of the portal vein resulting in portal hypertension (PHT) while the liver structure and function remain normal. This results in an increased portal venous pressure gradient in the absence of a known cause of liver disease. It has been commonly described from India and Japan, and is being increasingly recognised in the West. The etiology of NCPF in unclear but postulated to be chronic infections, exposure to medication or toxins, thrombophilia, immunological disorders or genetic disorders. Multifactorial etiology can also be encountered. The majority of patients present with signs or complications of (PHT), mainly well controlled episodes of variceal bleeding and splenomegaly. They usually have preserved liver function. Patients can be misdiagnosed as having liver cirrhosis, but awareness of this condition (presence of portal hypertension with disproportionately large splenomegaly but preserved liver functions) along with a diligent search to rule out other causes of non cirrhotic PHT, can identify this subset of patients who have a better prognosis than cirrhotic patients with similar symptoms. The recommendations for prophylaxis and treatment of variceal bleeding are similar to cirrhotic patients. While endotherapy can successfully manage most of the varieal bleeding episodes, surgical portocaval shunts are indicated in patients with failure of endotherapy, bleeding from sites not amenable to endotherapy and symptomatic splenomegaly. Since NCPF is a benign disorder with overall good prognosis except for need for frequent endoscopic surveillance and therapy, there is deep interest in role of prophylactic surgery to prevent the first bleeding episode all together and to offer a onetime permanent solution to patients who have recovered from a bleeding episode. But shunt surgery is not entirely innocuous and technically demanding, so the debate continues.

Volume 5 Issue 1 - 2016

Supriya Sharma, VK Kapoor
Department of Surgical Gastroenterology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, India

Correspondence: Supriya Sharma, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Department of Surgical Gastroenterology, SGPGIMS, Rae Barelli Road, Lucknow, Uttar Pradesh, 226014, India, Email supriyasharmap@gmail.com

Received: March 13, 2016 | **Published:** July 18, 2016

Introduction

Non cirrhotic portal fibrosis (NCPF) is a disorder of unknown etiology, characterized by fibrosis of small and medium branches of the portal vein resulting in portal hypertension (PHT). The liver structure and function remain norma.[1] It belongs to the group of vascular conditions of liver which cause non cirrhotic portal hypertension (NCPH) wherein the pressure gradient between the portal vein and intraabdominal inferior vena cava is greater than 5mm Hg in the absence of cirrhosis.[2] The increased portal pressure and resistance to prograde splanchnic flow eventually opens up the portosystemic collateral circulation and causes congestive splenomegaly. Clinically, there are varices, moderate to massive splenomegaly with or without symptomatic hypersplenism, preserved liver function, and patent hepatic and portal veins.[2,3] It has been reported from all parts of the world, more so from the developing countries and variously labeled as NCPF (India), Idiopathic portal hypertension (Japan), Idiopathic non cirrhotic portal hypertension, hepatoportal sclerosis, incomplete septal cirrhosis, and nodular regenerative hyperplasia (West).[4–7] All display obliterative vascular lesions in the portal venous system and have similar clinical profile. Hence, it has been suggested that they all be viewed as a single entity with various pathological aspects, rather than different clinicopathological entities.[8] The consensus statement of the Asia Pacific Association for the Study of the Liver (APASL) on NCPF, states that the disease accounts for approximately 10-30% of all cases of variceal bleed in several parts of the world including India.[1] In West, a similar disease process accounts for 3-5% of cases of PHT.8 The demographic variations in clinical presentations attributable to this disease in India, Japan and the West are probably related to the differences in living conditions, ethnicity, average life span, reporting bias as well as the diagnostic criteria used (Table 1). This review aims to elucidate the natural progression of this condition and compare the clinical profile, diagnostic dilemmas and management strategies applied to this subset of patients with non cirrhotic portal hypertension across the world. Current limitations in our understanding of the natural course but the potential for therapies to possibly arrest/change the progression of this condition will be discussed. Therapeutic choices are challenging because the natural history of the disease process and its clinical manifestations are yet to be defined. Although the treatment recommendations for prophylaxis and treatment of variceal bleeding are similar to those applied for cirrhotic patients, they may not be entirely appropriate.

Etiopathogenesis

The precise etiopathogenesis of NCPF is uncertain as no single factor appears to be working in all cases. The proposed potential initiating lesions are infections, prothrombotic state, immunological disorders, toxins and medications which eventually produce the pathognomonic obliterative portal venopathy.[3] Intraabdominal infection may lead to portal pyaemia resulting in thrombosis, sclerosis and obstruction. But a definite history of umbilical vein catheterization or sepsis or intraabdominal infection is lacking in most patients. A prolonged exposure to some toxin or drugs like arsenic, vinyl chloride, vitamin A, copper sulphate, methotrexate, 6-mercaptopurine, azathioprine or irradiation can initiate a fibrogenic process affecting the small and medium sized portal vein branches resulting in PHT, but a definite cause effect relationship has not been established. Immunological factors in autoimmune diseases like systemic lupus erythematosis scleroderma, hypogammaglobulinemia can cause perivenular inflammation, cell recruitment and fibrosis. Studies from the West suggest association with prothrombotic disorders like myeloproliferative disorders, protein C and S deficiency and prothrombin gene mutation.[6,9]

Table 1 Diagnostic criteria for non cirrhotic portal fibrosis, idiopathic portal hypertension ad idiopathic noncirrhotic portal hypertension

asia pacific association for study of liver criteria for non-cirrhotic portal fibrosis / idiopathic portal hypertension[1]	**Japanese criteria for idiopathic portal hypertension 9**	**Idiopathic noncirrhotic portal hypertension (all five criteria must be fulfilled)[8]**
i. Presence of moderate to massive splenomegaly ii. Evidence of portal hypertension, varices, and/or collaterals iii. Patent spleno-portal axis and hepatic veins on ultrasound Doppler iv. Biochemical tests results indicating normal or near-normal liver functions v. Normal or near-normal hepatic venous pressure gradient (HVPG) vi. Liver histology-no evidence of cirrhosis or parenchymal injury vii. 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 • Unknown etiology of liver disease • Imaging with ultrasound or other imaging techniques showing dilated and thickened portal vein with peripheral pruning and periportal hyperechoic areas	i. Clinical disorder of unknown etiology with ii. Splenomegaly, anemia and portal hypertension with iii. Absence of cirrhosis, blood disease, parasites in the hepatobiliary system, and occlusion of the hepatic and portal veins. iv. Additional points • Normal to near-normal liver function tests • Varices demonstrable by endoscopy or radiography • Decrease of one or more of the formed blood elements • Liver imaging imaging, not typical of cirrhosis • Patent hepatic veins with a normal to slightly elevated wedged hepatic venous gradient (WHVP) • Grossly non-cirrhotic liver surface • Hepatic histology not indicative of cirrhosis • Patent extrahepatic portal vein with frequent collateral vessels • Elevated portal pressure (Not all these investigations are required for diagnosis)	i. Clinical signs of portal hypertension (any one of the following†) • Splenomegaly/hypersplenism • Esophageal varices • Ascites (nonmalignant) • Increased hepatic venous pressure gradient • Portovenous collaterals ii. Exclusion of cirrhosis on liver biopsy iii. Exclusion of chronic liver disease causing cirrhosis or noncirrhotic portal hypertension†† • Chronic viral hepatitis B and/or C • Nonalcoholic steatohepatitis / alcoholic steatohepatitis • Autoimmune hepatitis • Hereditary hemochromatosis\ • Wilson's disease • Primary biliary cirrhosis iv. Exclusion of conditions causing noncirrhotic portal hypertension • Congenital liver fibrosis • Sarcoidosis • Schistosomiasis v. Patent portal and hepatic veins (Doppler ultrasound or computed tomography scanning) †Splenomegaly must be accompanied by additional signs of portal hypertension to fulfil this criterion. ††Chronic liver disease must be excluded, because severe fibrosis might be under staged on liver biopsy.

Whatever be the inciting event, there has to be an underlying susceptibility to develop this disorder when exposed to the above agents. Several hypotheses have been proposed to explain the final development of obliterative portovenopathy. Sarin & Kumar [3] hypothesize that in a genetically predisposed individual, repeated microthrombotic events due to intraabdominal sepsis or prothrombotic state affect the small and medium branches of portal vein and may lead to the development of NCPF in a young adult.[3] Schoutten and collaborators propose a dual theory.[8] Diffuse strong expression of inducible nitric oxide synthetase and endothelial nitric oxide synthetase in the sinus lining cells leads to the dilatation of splenic sinuses and splenomegaly. The increased splenic blood flow secondary to splenomegaly contributes to the raised portal pressure. Sato and collaborators propose the endothelial - mesenchymal transition (EMT) theory whereby vascular endothelial cells acquire myofibroblastic features characterized by an ability to express mesenchymal cell products that are related to tissue fibrogenesis.[10] Transforming growth factor- beta1 acts as a potent inducer of EMT. After transformation, these cells synthesize type I collagen, which causes obliterative portal venopathy and presinusoidal PHT.

Pathology

Pathological changes described in NCPF/ Idiopathic non cirrhotic portal hypertension (INCPH) are based on the examination of needle

Citation: Sharma S, Kapoor VK. Non cirrhotic portal fibrosis - current concepts. *Gastroenterol Hepatol Open Access.* 2017;5(1):184–192.
DOI: 10.15406/ghoa.2016.05.00128

biopsy specimens and explant livers of patients undergoing a liver transplantation for decompensated cryptogenic cirrhosis, in which a diagnosis of NCPH is established after histologic evaluation.

Gross

Gross examination may reveal a normal, enlarged, or sometimes a shrunken liver. The surface is smooth, wrinkled, or may even show some nodularity resembling cirrhosis. Fibrous thickening of capsule of the liver with increased vascularity and some inflammation may be seen.[1]

Histology: There is heterogeneity in the lesions observed. The frequently observed changes include obliterative portal venopathy (luminal narrowing or obliteration of small portal venous branches accompanied by dense deposits of elastic fibers), increased number of portal vascular channels (portal angiomatosus), dilated portal veins herniating into the surrounding parenchyma (paraportal shunt vessels), sinusoidal dilatation (megasinusoids), thin incomplete periportal/perisinusoidal fibrosis, preserved lobular architecture and differential atrophy.[6,11,12] The most consistently noted characteristic is the dilatation of main PV trunk with thick sclerosed walls, along with thrombosis in medium and small portal vein branches, termed obliterative portal venopathy.[5] According to Wanless, this obliteration of portal venules results in disturbed intrahepatic circulation with subsequent parenchymal remodeling.[11] There is atrophy of the hepatocytes in areas with reduced portal blood supply and compensatory hyperplasia of the hepatocytes in better perfused areas. This is best appreciated in patients with the partial nodular hyperplasia and nodular regenerative hyperplasia variants of INCPH.[12]

Clinical presentation

The diagnosis of NCPF is mainly clinical - presentation with features of PHT without any evidence of liver dysfunction (rules out cirrhosis) and demonstration of patent hepatic (rules out Budd Chiari syndrome) and portal vein (rules out extra hepatic portal venous occlusion). There are some differences in the presentations of NCPF (Indian subcontinent), IPH (Japan, Far East) and INCPH (Western countries) as reflected in the different diagnostic criteria used (Table 2).

Table 2 Differentiating between NCPF, EHPVO and cirrhosis

	NCPF	Cirrhosis
Mean age	30 (NCPF), 50 (IPH/INCPH)	40
Upper GI bleed	Well tolerated	Not well tolerated
Ascites and HE	Transient and precipitated by bleed	Common
Jaundice	Uncommon	Common
Liver	Normal, rarely irregular	Small nodular
Splenomegaly	Massive	Mild
Liver function tests	Normal	Deranged
Imaging	Normal SP axis, withered tree appearance	Irregular shrunken liver, dilated portal and splenic vein
Hemodynamics		
Intrasplenic pressure	High	High
PV pressure	High	High
WHVP	Normal to raised	High
Long-term survival	Good	Worse

NCPF usually presents in young males between the third and fourth decade of life, whereas IPH and INCPH present in the fifth decade of life with a female preponderance.[13] Patients in India present well-tolerated episodes of gastrointestinal hemorrhage, a longstanding mass in the left upper quadrant (splenomegaly), anemia and thrombocytopenia.1 Of all the causes of portal hypertension, a massive and disproportionately large spleen is seen most commonly in NCPF. Left upper quadrant dragging pain due to a massive splenomegaly or acute pain in left upper abdomen due to perisplenitis and splenic infarction is not uncommon.[14] Gum bleeds, epistaxis, easy bruisability due to thrombocytopenia or repeated infections due to leucopoenia, though theoretically possible in hypersplenism, are rare clinically. It is more common to find biochemical evidence of hypersplenism on blood evaluation. There are no peripheral stigmata of hepatocellular failure. Ascites and hepatic encephalopathy are usually not seen at presentation.

The major presenting symptoms in Japanese patients with IPH are splenomegaly (88%), hepatomegaly (44%), gastrointestinal bleeding (35%), and ascites (12%).[15] INCPH in the West usually presents with splenomegaly (26%-36%), variceal bleed (32%-55%), and ascites (34%), unlike NCPF and IPH.8 In the study by Siramlopawat and collaborators, 60% of patients were diagnosed when an imaging study was obtained during the course of evaluation for thrombocytopenia or splenomegaly.[16] In those with symptoms, variceal bleed was the most common initial manifestation.

Diagnosis

There is no single test that can be regarded as the gold standard to diagnose NCPF. Patients can be misdiagnosed as having liver cirrhosis, but awareness of this condition (presence of portal hypertension with disproportionately large splenomegaly, but preserved liver functions) along with a diligent search to rule out other causes of NCPH, can identify this subset of patients who have a better prognosis than cirrhotic patients, with similar symptoms.

Haemogram reveals reduction in cellular elements with anemia being most commonly followed by thrombocytopenia and leucopenia. Anemia may be microcytic, hypochromic (due to gastrointestinal

Citation: Sharma S, Kapoor VK. Non cirrhotic portal fibrosis - current concepts. *Gastroenterol Hepatol Open Access.* 2017;5(1):184–192.
DOI: 10.15406/ghoa.2016.05.00128

blood loss) or normocytic, normochromic (due to hypersplenism). Coagulation and platelet function abnormalities may be seen, despite procoagulant state being one of the proposed etiological factors, due to the effects of splenic sequestration and destruction. The activity of ADAMTS 13 (disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), a zinc-containing metalloprotease, which cleaves the von Willebr and factor, is significantly reduced in patients with NCPF/IPH.[17]

A pilot study in NCPH (NCPF/EHPVO) showed that a latent hypercoagulable state may be evident on thromboelastographic evaluation which is partially masked by the thrombocytopenia secondary to splenomegaly and hypersplenism.[18] Liver function tests are usually normal, but derangements in the form of prolonged prothrombin time and hypoalbuminemia may be seen in a small proportion particularly following a bleed.[19,20]

Doppler ultrasound in NCPF reveals a normal, enlarged, or shrunken liver, enlarged spleen with gamma – gandy bodies and dilated but patent splenoportal axis, and a thickened (>3mm) portal vein (PV). A withered tree appearance due to sudden narrowing of intrahepatic PV branches may also be seen. Spontaneous shunts (paraumbilical and gastroadrenorenal) are seen in 16% of the cases.[19] A contrast enhanced computed tomography scan may demonstrate intrahepatic PV abnormalities (non-visualization, reduced caliber and occlusive thrombosis), focal nodular hyperplasia like nodules and perfusion defects. These features may help in differentiating NCPF/IPH from cirrhosis.[21] Hemodynamic studies, though not routinely performed, reveal a normal wedged hepatic venous pressure, whereas intrasplenic and PV pressures are elevated.[1] These findings are consistent with the presinusoidal site of obstruction to portal flow. Nuclear imaging by technetium- 99m sulphur colloid scanning shows increased splenic size but no colloid shift to bone marrow. In contrast, cirrhotic livers show patchy uptake of colloid in liver and a significant colloid shift to bone marrow.[22]

Recently, there have been publications regarding differentiating between liver cirrhosis and INCPH with fibroscan. Mean liver stiffness in a large cohort of INCPH patients was 9.2kPa, being significantly lower compared to the observed values in patients with liver cirrhosis (>14kPa).[23] Upper GI Endoscopy reveals esophageal varices in 80%-90% of patients with a diagnosis of NCPF/IPH and in 33%-43% of patients with INCPH. Esophageal varices are larger than those seen in patients with cirrhosis. The development of spontaneous shunts probably protects these patients from variceal bleeding.[19] Gastric and anorectal varices are more common, whereas portal hypertensive gastropathy is less common than cirrhosis.[14]

Liver biopsy is sometimes obtained to differentiate NCPF from cryptogenic cirrhosis when radiological examinations are equivocal, particularly when contemplating a complete portacaval shunt procedure for prophylaxis of variceal bleed.[1] The specimen is studied after hematoxylin-eosin, Masson's trichrome and reticulin staining. Hillaire and collaborators have suggested 4 pathological findings for diagnosis of NCPF/IPH - hepatoportal sclerosis, periportal fibrosis, perisinusoidal fibrosis and nodular regenerative hyperplasia.[6] Diagnosis on liver biopsy is based on a specimen longer than 1cm with >5 complete portal tracts (CPT). In order to diagnose NCPF/IPH more than 2/3 (66%) of CPTs should have absence or reduced caliber portal venules with sclerosis or thickening of smooth muscle wall.[10]

Natural course

Worldwide since NCPF/ INCPH are rare diseases, information on the natural history, prognosis, and predictive factors of poor outcome is scarce.

NCPF is believed to be non progressive. Survival for a long time with completely asymptomatic intervals is known after adequate control of varices by either endoscopic eradication of varices or lowering of portal hypertension by a surgical shunt. Although mortality from variceal rupture is generally lower than cirrhotic patients due to better preserved liver functions, the major cause of death in NCPF/IPH is still variceal bleeding. The survival curve for patients with NCPF/IPH is between that for those with cirrhosis and for a healthy population of comparable age.[3]

It is now increasingly appreciated that in some patients with INCPH, the liver undergoes slow atrophy due to reduced blood supply to the periphery. In addition, the lack of compensatory arterial changes worsens ischemia and can contribute to liver failure.[8] It has been recently recognized that like INCPH, NCPF too can progress to clinically manifest end stage liver disease with liver failure.[20,24,25] However, criteria for diagnosis of end stage liver disease evolving from NCPF have not been defined and most cases of NCPF in explant livers have been previously diagnosed is as cryptogenic cirrhosis or some other etiologic type of cirrhosis. A study of explant livers from India showed that 9 (2.4%) out of 84 patients with cryptogenic cirrhosis had evidence of NCPF on pathological examination, emphasizing the natural course of decompensation in NCPF.[25] NCPF accounts for 5% of end-stage liver disease in patients who undergo liver transplantation.[24] Patients with intrahepatic portal hypertension and negative etiological work-up for liver disease are often labeled as having cryptogenic cirrhosis. Idiopathic NCPF should be considered as a differential diagnosis of cryptogenic cirrhosis in India.[20] Patients with NCPF who qualify for a liver transplantation have been found to be over 50years of age, have a low body mass index, disproportionately more portal hypertension, and lesser incidence of complications like recurrent encephalopathy, intractable ascites, or spontaneous bacterial peritonitis and low model for end stage liver disease scores in the face of relatively well-preserved hepatocellular function.[24]

The incidence of portal vein thrombosis (PVT) is higher in patients with INCPH than in those with cirrhosis.[26] The incidence of PVT in NCPF needs to be studied.[1] Ascites is seen in patients with IPH in spite of preserved liver functions. It occurs transiently after a bleeding episode and in association with PVT. Development of PVT in patients with INCPH may be a significant poor prognostic factor. Hence in INCPH, there is a suggestion for regular screening to diagnose PVT and management of anticoagulation therapy when detected.[8] The 1-year probability of developing portal vein thrombosis (PVT) is 9%, and 53% of patients show recanalization with anticoagulation. Presence of human immunodeficiency virus (HIV) infection and variceal bleeding at diagnosis are independent predictors of PVT in INCPH.[16]

Though there are reports of liver cell atypia and pleomorphism in nodular regenerative hyperplasia liver specimens, a causal relationship between hepatocellular carcinoma and INCPH, has not been proven. Nzeako and collaborators studied the association between nodular regenerative hyperplasia (NRH) and hepatocellular carcinoma in 342 patients without cirrhosis.[27] In the majority of the patients, the concurrence of NRH and hepatocellular carcinoma could be attributed to additional factors known to be associated with the development of NRH (e.g., portal vein thrombosis, chemotherapy, and radiotherapy), and the study failed to indicate this disorder as the underlying condition of hepatocellular carcinoma. As a result, hepatocellular carcinoma surveillance in patients with INCPH is not recommended.

Citation: Sharma S, Kapoor VK. Non cirrhotic portal fibrosis - current concepts. *Gastroenterol Hepatol Open Access.* 2017;5(1):184–192.
DOI: 10.15406/ghoa.2016.05.00128

HIV and INCPH

INCPH has been reported increasingly (0.45 - 1%) in patients with HIV infection [28,29] This is due to prolonged survival of HIV infected patients following use of highly active antiretroviral therapy (HAART). The proposed mechanisms are recurrent opportunistic gut infections, usage of HAART especially didanosine and hypercoagulability (mainly protein S deficiency). HIV itself is known to infect hepatic stellate cells and cause cytokine mediated endothelial injury.[29] HIV related NCPF occurs predominantly in males (50–100%), homosexuals (50–75%), prolonged infection (median 11.5years, range 7-15years) and is associated with immune reconstitution.[28] Patients with HIV who develop INCPH are older with reduced platelets and CD4 counts, elevated liver enzymes, and have longer exposure to didanosine or concomitant exposure to stavudine or tenofovir. Presentation is with features of PHT. PVT has been observed in 25-75% of HIV patients. Liver decompensation requiring liver transplantation has been reported.[29] These patients also show evidence of pulmonary hypertension on echocardiography probably demonstrating the association between didanosine exposure and INCPH.

Management

Management in NCPH focusses primarily on managing the acute episode of variceal bleeding followed by secondary prophylaxis to prevent further bleeding episodes. Other areas which prompt therapeutic decisions are splenomegaly causing pain or interfering with the quality of life, symptomatic hypersplenism, development of PVT and ascites and the few cases progressing onto end stage liver disease (ESLD) and needing an orthotopic liver transplantation (OLT).

The risk of bleeding in NCPF/IPH is believed to be similar to the risk in patients with varices due to other causes although some believe that the development of spontaneous shunts probably protects these patients from variceal bleeding.[19] The episodes are tolerated relatively well, probably because of well-preserved hepatic functions.

Due to limited information on natural history of varices in NCPF/INCPH, current recommendations for prophylaxis and treatment of variceal hemorrhage are similar to those applied in patients with cirrhosis.[1,30]

Control and prophylaxis of variceal bleed

Medical management: General measures like airway protection, gastric aspiration and haemodynamic resuscitation are started promptly. Vasoactive drugs such as somatostatin, octreotide, or terlipressin, which reduce portal pressure, should be started early to control the bleeding episode. In presence of alarmingly low platelets (<20,000) or grossly deranged international normalized ratio (INR) or deranged thromboelastography, platelet and plasma transfusion may be used. Generally in cirrhotic patients, non selective beta blockers like propranolol, are then added for long term prevention of rebleeding. Sarin and collaborators have demonstrated equal efficacy of endoscopic variceal ligation and propranolol in preventing variceal bleeding in patients with NCPH.[31] But the authors acknowledge that it is difficult to measure the effects of these drugs objectively and titrate the dose of beta blockers as the parameter which is used in cirrhotic patients, namely HVPG is essentially normal in NCPH. Hence, beta blockers are not routinely used in NCPF.

a. Endoscopic variceal control and obliteration: Endoscopic sclerotherapy (EST) and endoscopic variceal ligation (EVL) are effective in controlling acute bleeding from esophageal varices in 80–90% of patients.[19] Combination treatment of drugs plus endoscopic therapy is more effective than endoscopic therapy or drug therapy alone, in controlling acute bleeding (88% vs. 76%, respectively) and preventing rebleeding for 5days (77% vs. 58%, respectively), while there is no difference in mortality. Endotherapy should be repeated at 2-3weekly intervals, until varices are eradicated.[1,30] EST and EVL have comparable efficacy for eradication of varices. However, EVL as compared to EST eradicates varices faster, with lesser complications and rebleed rates, but with increased rate of variceal recurrence. As there are no randomized trials regarding these events in NCPF, the therapeutic conduct used for bleeding varices in cirrhotic patients, it is applied to patients with NCPF/INCPH.1 For gastroesophageal varices and isolated gastric varices related bleed, glue injection with N-butyl-cyanoacrylate is helpful. Endoscopic therapy is effective in controlling the first bleeding episode in more than 90% of patients and can be repeated on outpatient basis, to achieve variceal eradication.

Before physicians believe that endotherapy is the most appropriate solution for long term management of patients with NCPF, they have to consider the potential of such therapy to adversely affect the natural course of the underlying disease, cause long term complications and alter the quality of life. It has been hypothesized that endoscopic obliteration of esophagogastric varices may induce formation of new gastric varices, ectopic varices and severe portal hypertensive gastropathy due to the persistence of portal pressure.[32] About 15% of patients undergoing repeated EST may develop esophageal strictures requiring endoscopic dilatation and hospital visits, which increase the overall treatment costs. Even after variceal obliteration, rebleeding can occur in the late follow up period (even beyond 10yrs) suggesting that such sequelae may continue to evolve throughout life.[33] There are no long term studies regarding natural history of varices after endotherapy in NCPF and the effects of persisting portal hypertension. Since the liver functions essentially remain normal in majority of patients, the treating clinician cannot be sure about the clinical relevance of appearance of new low grade esophageal varices or appearance of non bleeding gastric varices. In the Indian context, expertise to provide effective endoscopic variceal obliteration is more widely available compared to the surgical options. Hence, endotherapy continues to be used as an effective modality to treat active variceal bleeding in a large number of patients.

b. Surgical management: In NCPF, surgery is primarily indicated in patients with variceal bleed who fail to respond to endoscopic management (8 - 12% of cases). Other indications are bleeding from ectopic varices, symptomatic splenomegaly and or hypersplenism, lack of regular access to tertiary medical care, rare blood group and the patients' desire for a one time solution.

Various types of surgical procedures are:

1. Shunt/bypass procedures: surgically created shunts between a tributary of portal vein and systemic vein bypass the portal blood either totally (end to side portacaval shunt) or partially into systemic circulation and thus, decrease the portal pressure. Partial shunts permit some amount of prograde flow into the liver while still diverting a significant proportion of splanchnic circulation directly into the systemic circulation bypassing the liver, e.g side to side portacaval shunt, mesocaval shunt, central splenorenal shunt. Though theoretically designed to permit prograde flow into the liver, over a period of time, these shunt become totally diverting shunts and may lead to encephalopathy. Partial shunts

which selectively decompress only the gastrosplenic territory like distal splenorenal shunt (DSRS) and Inokuchi shunt (left coronary vein to vena cava) have been described. Data on DSRS in Indian patients with NCPF is absent, despite its purported superiority by Western groups in cirrhotic recipients.[34,35] One of the main concerns in patients with NCPF is the disproportionately large and symptomatic splenomegaly and the concern itself about the efficacy of DSRS to effectively decompress the dysplasic spleen, often reaching till the umbilicus. The most commonly reported partial shunt performed in NCPF patients with variceal bleed is the proximal splenorenal shunt (PSRS). The group from All India Institute of Medical Sciences have reported their experience with 272 elective PSRS for NCPF with an operative mortality <1%, low variceal rebleeding rate (8%) and low post shunt encephalopathy rate (13%). The study by Sharma and collaborators involving 30 patients with NCPF, had reported a significant decrease in splenic pulp pressure (44.3 ± 13.5 vs. 33.8 ± 7.6 cm of saline solution) and splenic size from 9.1 ± 3.3 to 6.8 ± 4.6cm in 28 patients after successful patent shunt surgery.[36] Shunt occlusion, overt chronic portosystemic encephalopathy, and rebleeding after elective shunt surgery were seen in approximately 10% of patients. Thus following shunt surgery, esophageal varices, splenic size and splenic pulp pressure does decrease, but there is a risk of minimal hepatic encephalopathy, glomerulonephritis, pulmonary arteriovenous fistula and ascites. Nonetheless, shunt surgery is a one-time treatment procedure with durable, long term efficacy in preventing variceal rebleeding and has to be considered in patients who continue to bleed despite endotherapy. It is also particularly relevant in the Indian context where several patients that come from rural areas, have no access to safe blood bank facilities or tertiary medical care in the event of a massive bleed.[33]

Ablative procedures

Esophagogastric devascularization in combination with splenectomy is done in patients with failed shunts and life threatening bleed or in emergency situations, as with refractory variceal bleed, when the shunt surgeon is not available. Mathur and collaborators have described transabdominal extensive esophagogastric devascularization with esophageal or gastric stapled transection (modified Sugiura procedure) for long term control of variceal bleeding.[37] The early postoperative mortality was 4% and esophageal strictures developed in 15% of the survivors. The surgeon may also have to consider devascularisation when the shunt surgeon is not available and when there is a suspicion of underlying cirrhosis, to avoid hepatic decompensation, following a shunt surgery.

Failure of endoscopic therapy

In 8-12% of cases, endotherapy may fail to control acute variceal bleed. Failure is defined as further variceal bleeding after two endoscopic treatments during a single hospital admission for acute bleeding.[38] In emergency situations, the alternative options are balloon tamponade of varices at esophagogastic junction using Sengstaken Blakemore tube for temporary control of bleeding, surgical devascularisation with a splenectomy, transjugular intrahepatic portosystemic shunt (TIPS), or balloon occluded retrograde transvenous obliteration.

In the Indian context, most clinicians resort to emergency PSRS or a devascularisation with splenectomy. In the West, despite the alleged safety and efficacy of shunt surgery,[35,39] INCPH patients with uncontrollable hemorrhage are currently preferentially treated with transjugular intrahepatic portosystemic shunt (TIPS), because of its lower invasiveness.[40] Due to the preserved liver functions, complications of this procedure observed in patients with cirrhosis (e.g., hepatic encephalopathy) are expected to be rare. However, no long term data are available. The clinician has to accept that the long term patency of TIPS is not equivalent to a surgically created shunt, and frequent endovascular reinterventions are needed to ensure stent patency. There may be no need for OLT since the liver function is maintained. Thus, the long term complications of TIPS, like shunt thrombosis, and the associated need for frequent endovascular interventions to maintain patency, assume greater implications in INCPH. In India, expertise for TIPS is even more scarce compared to surgical expertise for an effective PSRS.

Prevention of variceal bleeding in NCPF/IPH (primary prophylaxis)

The natural history of esophageal varices in NCPF is not clearly understood. In cirrhotic patients, progression of variceal size occurs at a rate of 10-15% per year, mostly dependent on liver dysfunction. Such a progression of varices in NCPF is less likely to occur, as the liver function remains normal.[1] Similarly, a decrease in the size of esophageal varices, as seen in patients with cirrhosis with an improvement in liver functions, is unlikely in NCPF, unless interventions like endoscopic sclerotherapy are applied, which obliterate Esophagogastric varices. Recently, some data was published suggesting that, at least in IPH, there is one year rate of variceal development and growth (of 10% and 13%, respectively), which is similar to those seen in cirrhotic patients. So, Siramolpivat and collaborators suggest that applying a surveillance strategy for esophageal varices as is being currently applied to cirrhotics is appropriate and safe.[16]

Endoscopic variceal ligation (EVL) and beta blockers are used for the primary prophylaxis of large esophageal varices in cirrhosis. Since patients with NCPF are all in Child-Pugh class A, it is suggested that the results of EVL and beta blockers could be extrapolated to NCPF. But it is difficult to assess the response to beta blockers in patients with NCPF as HVPG is normal, so EVL is the preferred mode of therapy. Moreover, since the lifespan of patients with NCPF is normal, compliance to lifelong drug therapy is unlikely. Additionally, the natural history of varices in NCPF has not been well delineated, so it is difficult to predict the clinical value and cost effectiveness of such treatment in preventing deaths from variceal bleeding. Shunt surgery for primary prophylaxis was evaluated for high risk varices, with or without hypersplenism for patients which reside in rural areas.[41] Despite the efficacy of surgery in preventing variceal bleeding, the high incidence of post shunt morbidity seen in 48% of patients in form of portasystemic encephalopathy, glomerulonephritis, pulmonary arteriovenous fistulae, ascites requiring diuretics, probably does not justify its use in the prophylactic setting in patients with NCPF and cannot be recommended. Patients with gastric varices of more than 2cm which cannot be managed by endotherapy, can be taken up for surgical shunt or balloon-occluded retrograde transvenous obliteration, if a splenorenal shunt is present, although studies are scarce.[1]

Secondary prophylaxis

Randomized control trials on secondary prophylaxis of bleeding varices in NCPH are scanty. Small studies have demonstrated a reduction in bleeding rate by endotherapy. Since EVL has been shown to be better than EST, it is the preferred endoscopic approach for variceal eradication. Though widely practiced, it is hypothesized that obliteration of varices by endoscopic procedure may adversely affect the natural course of the underlying disease by inducing formation of new gastric varices, ectopic varices and severe portal hypertensive

Citation: Sharma S, Kapoor VK. Non cirrhotic portal fibrosis - current concepts. *Gastroenterol Hepatol Open Access.* 2017;5(1):184–192.
DOI: 10.15406/ghoa.2016.05.00128

gastropathy. In addition, clinicians one haves to consider the potential for endoscopic therapy to cause long term complications (esophageal strictures) and alter the quality of life of patients with NCPF, who are in the prime of their life. A rigorous schedule of endoscopic variceal obliteration, and then follow up surveillance for 10-20years, needs repeated hospital visits, which are likely to adversely impact a young patient and his/her family in many ways.[33]

Shunt surgery has been shown to have durable long term efficacy in NCPF. The AIIMS group has reported their experience with 285 elective proximal lienorenal shunts with low mortality (0.8%), low variceal rebleeding rate (8%) and low post shunt encephalopathy rate (13%). Shunt occlusion, overt chronic portosystemic encephalopathy, and rebleeding after elective shunt surgery were seen in approximately 10% of patients. But, despite the purported superiority of surgical shunts in preventing rebleeds, it has to be remembered that some patients with NCPF/INCPH do have an underlying liver parenchymal pathology, which can progress even necessitating transplantation. This progression may be accelerated by an ill timed shunt surgery. NCPF was found to account for 5% of all cases of ESLD who underwent OLT.[24] Factors which could help identify the subset of patients with NCPF at risk of progression to liver failure have not been defined, but the understanding that NCPF can progress to end stage liver diseases is gaining ground.

As opposed to a surgical shunt, the technical expertise to perform endotherapy is more widespread. Since the natural history of each of the disease components is still not clear and the factors which have ominous connotations due to esophagogastric varices and splenomegaly are still elusive, and the long term consequences of esophagogastric variceal eradication by endotherapy unknown, these patients continue to be managed endoscopically. Shunt surgery is reserved for associated symptomatic splenomegaly with or without hypersplenism or if the patient is desirous of a onetime solution.

Treatment of splenomegaly and hypersplenism

Patients with NCPF have a massive splenomegaly which can be asymptomatic or can produce dragging discomfort in left upper abdomen. Hypersplenism is defined as defect in one or more cell lines in the peripheral blood smear, in the presence of enlarged spleen and normal or a hypercellular bone marrow which resolves with splenectomy.[42] The incidence of hypersplenism varies from 22% to 80%. In the study by Rajalingam and collaborators, it was shown that the size of spleen was not associated with severity of hypersplenism suggesting that, apart from sequestration and destruction of blood in the spleen, other factors may be involved in depletion of cell counts and its clinical consequences.[43] Patients with clinically relevant hypersplenism were found to be older, had three times more cell line defects and had higher portal pressures (inferred by the higher grade of varices on endoscopy). In their series, hypersplenism was effectively relieved by both surgical shunt and splenectomy. They concluded that PSRS is preferable, as it not only relieves hypersplenism, but also decompresses the portal hypertension. Orloff and collaborators inferred that a DSRS reduces hypersplenism as well,[44] but there is no published data about the efficacy of DSRS in regressing symptomatic splenomegaly in Indian patients, where NCPF is associated with moderate to massive splenomegaly.

Oral anticoagulation

There is a high incidence of thrombophilia and portal vein thrombosis in INCPH patients.[6] Additionally, a trend toward poor prognosis has been reported in patients with INCPH who develop portal vein thrombosis. As a result, anticoagulation therapy has been proposed by several investigators to prevent disease progression and to maintain portal vein patency.[45] However, considering the fact that gastrointestinal bleeding is the main complication of INCPH and the uncertain role of thrombophilia in the pathogenesis, this treatment is still a matter of debate and cannot be generally implicated until more solid data are present. Nonetheless, Schoutten and collaborators believe that anticoagulation therapy must be considered in patients with INCPH with an underlying prothrombotic condition and in patients who develop portal vein thrombosis on follow up.[8]

Orthotopic liver transplantation

Generally, patients with decompensated end stage liver disease need orthotopic liver transplantation (OLT). Although we are still far from identifying precise factors which will identify the minority of patients with NCPF or INCPH in whom the liver functions can be expected to deteriorate over a period of time. Several reports describing liver transplantation in NCPF have been published emphasizing the new idea that NCPF can progress to end stage liver disease and this factor must probably be considered when planning therapeutic and prophylactic strategies.

Madhu and collaborators in a 2year study from South India, evaluated causes of liver disease in patients with unexplained intrahepatic portal hypertension and concluded that 48% of it is due to NCPF on liver biopsy.[20] Majority of these patients were classified in Child-Pugh class A score. They suggest that since the clinical presentation and investigations of NCPF closely mimic cryptogenic cirrhosis, NCPF should be considered as a differential diagnosis of cryptogenic cirrhosis in India. Saigal and collaborators in their study to determine the frequency of NCPF among adults transplanted for end stage chronic liver disease concluded that NCPF constitutes about 5% of the subset of ESLD considered eligible for transplantation, presenting mostly as cryptogenic cirrhosis.[24] A diagnosis of NCPF should be considered when patients, presumed to have cryptogenic or other cirrhosis, become eligible for OLT even in the presence of relatively well-preserved liver function and low MELD scores. Nayak and collaboratots also conclude that a proportion of cryptogenic cirrhosis cases that require OLT are constituted by NCPF.[25]

In the West, reported indications for liver transplantation in INCPH were medically unmanageable portal hypertension, hepatopulmonary syndrome, hepatic encephalopathy, and progressive hepatic failure.[10,46] Recently, Karsinskas and collaborators described a small cohort of INCPH patients treated with liver transplantation.[47] The main indication for liver transplantation was medically unmanageable severe portal hypertension; few were listed because of hepatic encephalopathy. Notwithstanding the fact that resistant bleeding in INCPH patients can be treated with portosystemic shunting before considering the option of liver transplantation, only two patients underwent pretransplant portosystemic shunting procedures (TIPS or mesocaval shunt). Presumably, the high frequency of cirrhosis misdiagnoses in these patients led to early referral for liver transplantation. To prevent unnecessary liver transplantation in these patients, early discrimination between cirrhosis and INCPH is extremely important. Based on small-sized cohorts (with limited follow-up), post-transplantation outcome in these patients is good and INCPH tends not to recur.[48,49]

Follow-up

It is recommended that NCPF/INCPH cases should be followed-up for evidence of decompensation and development of PVT and hepatopulmonary syndrome. Endoscopic surveillance is needed following variceal eradication, as varices can recur even 15years later.

Citation: Sharma S, Kapoor VK. Non cirrhotic portal fibrosis - current concepts. *Gastroenterol Hepatol Open Access.* 2017;5(1):184–192.
DOI: 10.15406/ghoa.2016.05.00128

The outlook is generally good following therapy for portal hypertension patients with INCPH/NCPF. But long term follow-up is needed to detect long term complications of the chosen therapy and identify patients progressing onto end stage liver disease.

Conclusion

In India NCPF accounts for upto 30% of variceal bleeds in non cirrhotic portal hypertension. Thus it constitute a considerable disease burden and affects young adults in the prime of their lives. A similar disease process is being increasingly reported in Western series of NCPH due to increasing awareness of this condition and its reported higher incidence in patients with HIV infection or treatment. Though the bleeding episodes are well tolerated, there is an increasing emphasis on finding the best strategy (endotherapy v/s surgical shunt) to arrest/reverse the disease process. At the same time, it is being reported that unlike as believed previously, this disease does progress in a few patients, therefore those have to be salvaged with OLT. There is a strong need for larger series, from South East Asia and West, to illustrate and compare the natural history and effects of therapeutic strategies to be able to offer evidence backed solutions to these patients with an otherwise benign disorder.

Acknowledgments

None.

Conflicts of interest

Author declares there are no conflicts of interest.

Funding

None.

References

1. Sarin SK, Kumar A, Chawla YK, et al. Noncirrhotic portal fibrosis/ idiopathic portal hypertension: APASL recommendations for diagnosis and treatment. *Hepatol Int*. 2007;1(3):398–413.
2. Sanyal AJ, Bosch J, Blei A, et al. Portal hypertension and its complications. *Gastroenterology*. 2008;134(6):1715–1728.
3. Sarin SK, Kumar A. Noncirrhotic portal hypertension. *Clin Liver Dis.* 2006;10(3):627–651.
4. Okudaira M, Ohbu M, Okuda K. Idiopathic portal hypertension and its pathology. *Semin Liver Dis*. 2002;22(1):59–72.
5. Nayak NC, Ramalingaswami V. Obliterative portal venopathy of the liver. Associated with so-called idiopathic portal hypertension or tropical splenomegaly. *Arch Pathol*. 1969;87(4):359–369.
6. Hillaire S, Bonte E, Denninger MH, et al. Idiopathic non-cirrhotic intrahepatic portal hypertension in the West: *a re-evaluation in 28 patients. Gut*. 2002;51(2):275–280.
7. Schouten JN, Nevens F, Hansen B, et al. Idiopathic noncirrhotic portal hypertension is associated with poor survival: results of a long-term cohort study. *Aliment Pharmacol Ther*. 2012;35(12):1424–1433.
8. Schouten JN, Garcia-Pagan JC, Valla DC, et al. Idiopathic noncirrhotic portal hypertension. *Hepatology*. 2011; 54(3):1071–1081.
9. Cazals-Hatem D, Hillaire S, Rudler M, et al. Obliterative portal venopathy: portal hypertension is not always present at diagnosis. *J Hepatol*. 2011;54(3):455–461.
10. Sato Y, Nakanuma Y. Role of endothelial-mesenchymal transition in idiopathic portal hypertension. *Histol Histopathol*. 2013;28(2):145–154.
11. Wanless IR. Micronodular transformation (nodular regenerative hyperplasia) of the liver: a report of 64 cases among 2,500 autopsies and a new classification of benign hepatocellular nodules. *Hepatology*. 1990;11(5):787–797.
12. Ludwig J, Hashimoto E, Obata H, et al. Idiopathic portal hypertension; a histopathological study of 26 Japanese cases. *Histopathology*. 1993;22(3):227–234.
13. Khanna R, Sarin SK. Non-cirrhotic portal hypertension - diagnosis and management. *J Hepatol.* 2014;60(2):421–441.
14. Vassia M, Curciarello JO, Corrons F, et al. [Idiopathic portal hypertension with splenic infarct. An unreported complication]. Acta *Gastroenterol Latinoam*. 2001;31(1):27–30.
15. Aoki H, Hasumi A, Yoshida K, et al.A questionnaire study on treatment of idiopathic portal hypertension and extrahepatic portal obstruction, in Annual report on portal portal-hemodynamics abnormalities Editor. 1988;179–189.
16. Siramolpiwat S, Seijo S, Miquel R, et al. Idiopathic portal hypertension: natural history and long-term outcome. *Hepatology.* 2014;59(6):2276–2285.
17. Mackie I, Eapen CE, Neil D, et al. Idiopathic noncirrhotic intrahepatic portal hypertension is associated with sustained ADAMTS13 Deficiency. *Dig Dis Sci*. 2011;56(8):2456–2465.
18. Kapoor S, Pal S, Sahni P, et al. Thromboelastographic evaluation of coagulation in patients with extrahepatic portal vein thrombosis and non-cirrhotic portal fibrosis: a pilot study. *J Gastroenterol Hepatol*. 2009;24(6):992–997.
19. Dhiman RK, Chawla Y, Vasishta RK, et al. Non-cirrhotic portal fibrosis (idiopathic portal hypertension): experience with 151 patients and a review of the literature. *J Gastroenterol Hepatol*. 2002;17(1):6–16.
20. Madhu K, Avinash B, Ramakrishna B, et al. Idiopathic non-cirrhotic intrahepatic portal hypertension: common cause of cryptogenic intrahepatic portal hypertension in a Southern Indian tertiary hospital. *Indian J Gastroenterol.* 2009;28(3):83–87.
21. Glatard AS, Hillaire S, d'Assignies G, et al. Obliterative portal venopathy: findings at CT imaging. *Radiology.* 2012;263(3):741–750.
22. Chakraborty D, Sunil HV, Mittal BR, et al. Role of Tc99m sulfur colloid scintigraphy in differentiating non-cirrhotic portal fibrosis from cirrhosis liver. *Indian J Nucl Med.* 2010;25(4):139–142.
23. Seijo S, Reverter E, Miquel R, et al. Role of hepatic vein catheterisation and transient elastography in the diagnosis of idiopathic portal hypertension. *Dig Liver Dis.* 2012;44(10):855–860.
24. Saigal S, Nayak NC, Jain D, et al. Non-cirrhotic portal fibrosis related end stage liver disease in adults: evaluation from a study on living donor liver transplant recipients. *Hepatol Int*. 2011;5(4):882–889.
25. Nayak NC, Jain D, Vasdev N, et al. Etiologic types of end-stage chronic liver disease in adults: analysis of prevalence and their temporal changes from a study on native liver explants. *Eur J Gastroenterol Hepatol*. 2012;24(10):1199–1208.
26. Matsutani S, Maruyama H, Akiike T, et al. Study of portal vein thrombosis in patients with idiopathic portal hypertension in Japan. *Liver Int*. 2005;25(5):978–983.
27. Nzeako UC, Goodman ZD, Ishak KG. Hepatocellular carcinoma and nodular regenerative hyperplasia: possible pathogenetic relationship. *Am J Gastroenterol*. 1996;91(5):879–884.
28. Maida I, Garcia-Gasco P, Sotgiu G, et al. Antiretroviral-associated portal hypertension: a new clinical condition? Prevalence, predictors and outcome. *Antivir Ther*. 2008;13(1):103–107.

29. Chang PE, Miquel R, Blanco JL, et al. Idiopathic portal hypertension in patients with HIV infection treated with highly active antiretroviral therapy. *Am J Gastroenterol*. 2009;104(7):1707–1714.

30. de Franchis R. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol*. 2010;53(4):762–768.

31. Sarin SK, Gupta N, Jha SK, et al. Equal efficacy of endoscopic variceal ligation and propranolol in preventing variceal bleeding in patients with noncirrhotic portal hypertension. *Gastroenterology*. 2010; 39(4):1238–1245.

32. Sarin SK, Govil A, Jain AK, et al. Prospective randomized trial of endoscopic sclerotherapy versus variceal band ligation for esophageal varices: influence on gastropathy, gastric varices and variceal recurrence. *J Hepatol.* 1997;26(4):826–832.

33. Pal S, Sahni P. Extrahepatic portal venous obstruction: is the knife irrelevant? *Indian J Gastroenterol*. 2009;28(6):198–200.

34. Livingstone AS, Koniaris LG, Perez EA, et al. 507 Warren-Zeppa distal splenorenal shunts: a 34-year experience. *Ann Surg*. 2006;243(6):884–892.

35. Henderson JM, Boyer TD, Kutner MH, et al. Distal splenorenal shunt versus transjugular intrahepatic portal systematic shunt for variceal bleeding: a randomized trial. *Gastroenterology*. 2006;130(6):1643–1651.

36. Sharma BC, Singh RP, Chawla YK, et al. Effect of shunt surgery on spleen size, portal pressure and oesophageal varices in patients with non-cirrhotic portal hypertension. *J Gastroenterol Hepatol.* 1997;12(8):582–584.

37. Mathur SK, Shah SR, Nagral SS, et al.Transabdominal extensive esophagogastric devascularization with gastroesophageal stapling for management of noncirrhotic portal hypertension: long-term results. *World J Surg.* 1999;3(11):1168–1174. discussion 1174–1175.

38. de Franchis R, Dell'Era A, Iannuzzi F. Diagnosis and treatment of portal hypertension. *Dig Liver Dis*. 2004;36(12):787–798.

39. Santambrogio R, Opocher E, Costa M, et al. Natural history of a randomized trial comparing distal spleno-renal shunt with endoscopic sclerotherapy in the prevention of variceal rebleeding: a lesson from the past. *World J Gastroenterol*. 2006;12(39):6331–6338.

40. Jacobi D, de Muret A, Arbeille B, et al.Transjugular intrahepatic portosystemic shunt for the treatment of portal hypertension secondary to non-cirrhotic perisinusoidal hepatic fibrosis. *Eur J Gastroenterol Hepatol.* 2006;18(5):549–551.

41. Pal S, Radhakrishna P, Sahni P, et al.Prophylactic surgery in non-cirrhotic portal fibrosis:is it worthwhile? *Indian J Gastroenterol*. 2005;24(6):239–242.

42. Liangpunsakul S, Ulmer BJ, Chalasani N. Predictors and implications of severe hypersplenism in patients with cirrhosis. *Am J Med Sci*. 2003;326(3):111–116.

43. Rajalingam R, Javed A, Sharma D, et al. Management of hypersplenism in non-cirrhotic portal hypertension: a surgical series. *Hepatobiliary Pancreat Dis Int*. 2012;11(2):165–171.

44. Orloff MJ, Orloff MS, Girard B, et al.Bleeding esophagogastric varices from extrahepatic portal hypertension: 40 years' experience with portal-systemic shunt. *J Am Coll Surg.* 2002;194(6):717–728.

45. Valla DC. Thrombosis and anticoagulation in liver disease. *Hepatology*. 2008;47(4):1384–1393.

46. Bernard PH, Le Bail B, Cransac M, et al. Progression from idiopathic portal hypertension to incomplete septal cirrhosis with liver failure requiring liver transplantation. *J Hepatol*. 1995;22(4):495–499.

47. Krasinskas AM, Eghtesad B, Kamath PS, et al.Liver transplantation for severe intrahepatic noncirrhotic portal hypertension. *Liver Transpl*. 2005;11(6):627–634.

48. Dumortier J, Bizollon T, Scoazec JY, et al. Orthotopic liver transplantation for idiopathic portal hypertension: indications and outcome. *Scand J Gastroenterol.* 2001;36(4):417–422.

49. Loinaz C, Colina F, Musella M, et al. Orthotopic liver transplantation in 4 patients with portal hypertension and non-cirrhotic nodular liver. *Hepatogastroenterology*. 1998;45(23):1787–1794.

Citation: Sharma S, Kapoor VK. Non cirrhotic portal fibrosis - current concepts. *Gastroenterol Hepatol Open Access.* 2017;5(1):184–192.
DOI: 10.15406/ghoa.2016.05.00128