NONCIRRHOTIC PORTAL FIBROSIS

Sandeep Nijhawan, Prashant Katiyar*
*Department of Gastroenterology, S.M.S. Medical College, Jaipur

INTRODUCTION

Noncirrhotic portal hypertension is a group of disorder characterized by increase in portal pressure, due to intrahepatic or prehepatic lesions, with absence of cirrhosis of the liver. Noncirrhotic portal hypertension (NCPF) is one of the important causes of noncirrhotic portal hypertension in Asian countries; it is called as Idiopathic portal hypertension (IPH). Various other terms such as hepatoportal sclerosis,1,2 noncirrhotic intrahepatic portal hypertension,3 and idiopathic Noncirrhotic intrahepatic portal hypertension4 are also used in other parts of the world to define this entity. The Asian Pacific Association for the Study of the Liver (APASL), Working Party on Portal Hypertension defined as, “NCPF/IPH is a disease of uncertain etiology characterized by periportal 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.”

EPIDEMIOLOGY

NCPF has been reported from all over the world, but its prevalence differs geographically. This condition is more common in the developing5,6,7 than in the developed countries.1-4 The reasons for the marked regional differences in prevalence are not clear. NCPF is commonly seen in people, who are from low socioeconomic strata.5-7 Initial studies done in 1980s showed incidence of about 23%,6,8,9 but more recent studies showing that the incidence of NCPF is declining in India. The patients of NCPF are commonly found among young adults in the third and fourth decade of life, while IPH commonly found in the fourth and fifth decade of life.5,8,10,11 In NCPF, there is no sex predilection. IPH is more common in females and the male-female ratio is (M: F = 1:3).12

ETIOPATHOGENESIS

Etiopathogenesis of NCPF is not clear and there is limited insight of this disease, so there are various proposed hypothesis for explaining this heterogeneous group of disease. There is varied degree of portal venous injury with predominant involvement of presinusoidal region. The factors that have been reported to be associated with NCPF are infections, xenobiotics exposure and various immunologic abnormalities.

Repeated intestinal infection may lead to formation of intra mural thrombus which may cause activation of stellate cells. Stellate cell activation leads to formation of perisinusoidal fibrosis.13

Exposure to xenobiotics seems to predispose the development of NCPF. Drinking of arsenic-contaminated water is suspected to cause NCPF.14-16 Arsenic-induced hepatic fibrosis was found to be related to hepatic oxidative stress as IL-6 and TNF-alpha levels were high in these patients.17-20 However, its role is also controversial as increased arsenic content is not always found in NCPF patients5 and moreover similar levels were seen in patients with cirrhosis.

Immunologic abnormalities are known to occur in NCPF patients.21 Abnormalities of T-lymphocytes and adhesion molecules have been found but their exact role in pathogenesis is not clear.22-24
Noncirrhotic Portal Fibrosis

Other factors that may be associated with NCPF include umbilical/portal Pyemia, autoimmune disorders, prothrombotic states; chronic exposure to vinyl chloride monomers, or copper sulfate (vineyard sprayers), prolonged treatment with methotrexate, hypervitaminosis A, and treatment of 6-mercaptopurine and azathioprine. However, the exact etiology in the majority of cases remains unknown.

**CLINICAL PRESENTATION**

NCPF patients usually present as gastrointestinal haemorrhage (app-70%), which is well tolerated due to preserved liver function. NCPF is an important cause of upper gastrointestinal bleeding, constituting 15% of the cases of variceal bleed in patients with portal hypertension. Other presentation may be awareness of a longstanding mass in the left upper quadrant (splenomegaly) or iron deficiency anemia. Jaundice, ascites/edema, and signs of liver failure are uncommon but transient ascites can develop soon after bleed. Signs of chronic liver disease like palmar erythema, parotid enlargement, spider angioma, testicular atrophy and gynecomastia are rare.

**LABORATORY STUDIES**

Liver biochemical tests are usually normal in NCPF. Semiquantitative liver function tests are also normal in these patients. Haematological tests revealed pancytopenia in the majority of patients. Anaemia may be microcytic hypochromic (due to gastrointestinal blood loss) or normocytic, normochromic (due to hypersplenism). Leucopenia and thrombocytopenia may be due to hypersplenism. The bone marrow is hypercellular.

Despite normal liver function NCPF patients may have coagulation abnormalities. These patients may have significantly increased international normalized ratio (INR) and a decrease in fibrinogen and platelet aggregation secondary to endotoxemia or portosystemic collaterals. Coagulation abnormalities in these patients need to be investigated further.

Esophageal varices are seen in 85-90% of patients and these varices are usually of high grade at the time of diagnosis. Gastric varices are seen in about 25% of patients with NCPF. Portal hypertensive gastropathy is uncommon in these patients than in cirrhotic patients. Anorectal varices are common in NCPF.

Site of resistance is predominantly presinusoidal in NCPF so, hepatic venous pressure gradient (HVPG) is normal or near normal.

**HISTOPATHOLOGY**

Gross examination of NCPF liver is variable and it may be normal, enlarged, or even shrunken. Surface may be smooth or may be nodular like in cirrhosis with fibrous thickening of capsule. Deeper parenchyma is grossly normal. Sclerosis of large to small intrahepatic portal vein branches has been documented. There is increased portal collagenous connective tissue and sclerosis and obliteration of small branches of portal veins in most cases. This histological hallmark of NCPF was termed obliterative portal venopathy by Nayak and Ramalingaswami. Recanalized thrombi are sometimes seen. Needle biopsy material may show only mild and subtle changes. These changes include small portal vein obliteration, aberrant vasculature, portal tract fibrosis and absence of significant hepatocellular injury. There must be absence of regenerative nodules or any features of cirrhosis in an adequate-sized liver biopsy.

**DIAGNOSIS**

Diagnosis is relatively easy but must be differentiated from child ‘A’ cirrhosis and extra hepatic portal vein obstruction.

Diagnostic features of NCPF
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 hypechoic areas.

**Table 1: Clinical and Lab Parameters**

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<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
<th>Lab Feature</th>
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<tbody>
<tr>
<td>Hematemesis/malena</td>
<td>Splenomegaly</td>
<td>Pancytopenia</td>
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<tr>
<td>(70%)</td>
<td></td>
<td>Esophageal varices</td>
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<td></td>
<td></td>
<td>(97%)</td>
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<tr>
<td></td>
<td></td>
<td>Gastric varices</td>
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<tr>
<td></td>
<td></td>
<td>(31%)</td>
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<td></td>
<td></td>
<td>Increased INR</td>
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<td></td>
<td></td>
<td>Decreased fibrinogen</td>
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</tbody>
</table>

**Uncommon**

Awareness of lump Ascites (transient) (25%) Portal gastropathy (3%) (12%)
NATURAL HISTORY
NCPF unlike cirrhosis is non-progressive and has a good prognosis, particularly if the raised portal pressure is reduced by shunt surgery or other procedures. Recently however, wide use of orthotopic liver transplantation (LT) has brought to light the fact that NCPF can progress to end stage liver disease needing LT, as shown by morphological study of native explant livers from cases mostly labelled clinically as cryptogenic cirrhosis (CC).35-41

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 vital monitoring Blood transfusion and intravenous fluids.42-44 Placement of nasogastric tube is optional, especially if the bleeding has taken place more than 12 hours ago.45 In NCPF, there is no study on the use of prophylactic antibiotics in bleeds but can be given.

Endoscopic therapy is preferred for control of acute bleed and is effective in 80-90%.46-47 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.46-47 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 patients46 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 cirrhosis48 but there is paucity of data regarding their use in NCPF. Drug and endoscopic therapy are equally effective46 but EVL is preferred mode of therapy since patient has to take these drugs lifelong so compliance is an issue, moreover it is difficult to monitor the efficacy of beta blockers because HVPG is normal in these patients.

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.50

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 (BRTO)
3. Percutaneous transhepatic obliteration (PTO)
4. Transjugular intrahepatic portosystemic shunt (TIPS)

PROGNOSIS
The prognosis for patients with NCPF is excellent. The mortality from an acute bleed in NCPF is significantly lower than that observed in cirrhotic patients. After successful eradication of esophagogastroduodenal varices survival is excellent. These patients can be managed with selective shunt surgery but shunt occlusion and post-shunt encephalopathy may cause some morbidity.

REFERENCES
8. Bhargava DK, Dasarathy S, Sundaram KR, Ahuja RK. Efficacy of endoscopic sclerotherapy on long-term management of esophageal varices: a comparative study of results in patients with cirrhosis of the liver, non-cirrhotic portal fibrosis (NCPF) and extra


