

NON-CIRRHOTIC PORTAL FIBROSIS

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Abstract : Non-Cirrhotic Portal Fibrosis (NCPF) characterized by splenomegaly and well tolerated episodes of variceal bleeding is very commonly seen in India. The aetiopathogenesis is not well understood but various physical, chemical, biological and immunological factors have been documented to have a role. It presents in 90% cases as variceal bleed which is massive, painless, recurrent and well tolerated. Signs of chronic liver failure are in variably absent- Endoscopy usually reveals Grade - III or IV oesophageal varices. The basis of diagnosis is exclusion of extra hepatic portal vein obstruction and, cirrhosis. NCPF is a benign disorder and has a good long term prognosis. Mean survival is 25 years from the time of diagnosis.

DEFINITION

Non Cirrhotic Portal Fibrosis (NCPF) is a distinct syndrome of portal hypertension of obscure aetiology, characterized by splenomegaly and well tolerated episodes of variceal bleeding in the absence of cirrhosis of the liver and extra hepatic portal vein obstruction (EHPVO). *SYNONYMS* Idiopathic portal hypertension (IPH), Non-Cirrhotic portal hypertension (NCPH), Hepatoportal Sclerosis (HPS). Obliterative portal venopathy (OPV) & Banti's syndrome (BS).

HISTORICAL ASPECTS

First noticed by Banti in 1883, it was Basu who coined the term NCPF in 1967. Marleau in 1975 & Futagawa in 1980 described it as NCPH & Idiopathic Portal Hypertension, respectively.

EPIDEMIOLOGY

The disease is very common in India, less common in Japan & least in Western countries. It accounts for 15-35% of all cases of PHT in India. The worldwide incidence is 3-5%. NCPF is a disease of young age. The mean age is 35 years although cases have been reported from 10-60 years. In India NCPF is more common in young males whereas in Japan it is more common in older females. The predominant patients are from the middle income group. In India it is reported more among urban dwellers, whereas in Japan most patients hail from rural areas.

ETIOLOGY OF NCPF

Despite its common occurrence, the aetiopathogenesis of NCPF is not well understood. The various aetiological factors are:

- i). **Physical agents:** NCPF has been reported following irradiation in the treatment of certain tumours e.g. Wilm's tumour.
- ii). **Chemical agents :**
 - a) *Arsenic:* Present in water, opium and some indigenous medicines, chronic exposure can lead to NCPF¹.
 - b) *Vinyl Chloride:* Chronic exposure to monomer and polyvinyl chloride leads to sclerosis of portal venules².
 - c) *Copper:* Chronic exposure to copper e.g. in vineyard sprayers².
 - d) *Vitamin A:* Chronic intoxication².
 - e) *Methotrexate* and *Azathioprine* exposure.
- iii). **Biological agents:** Infections due to parasites (malaria and schistosomiasis), bacteria (E Coli), and viruses (Hepatitis B) either as recurrent clinical or sub-clinical forms has been incriminated in NCPF.
- iv) **Immunological Factors:** NCPF has been associated with

increased incidence of HLA, DRS & DR7 and decreased incidence of HLADR2 suggesting an auto immune basis for the disease. There is decreased levels of serum IgA, C3, C4 and CD 8+ cells and an increased ratio of CD 4: CD83

CLINICAL FEATURES

(1) Age of presentation is 20-40 years (2 decades earlier than cirrhosis and one decade later than EHPVO); (2) In India. M.F :: 2: 1 to 4:1.; (3) Mode of presentation is variceal bleed (90%), splenomegaly (10%) and rarely anemia; (4) Other symptoms may be abdominal pain because of enlarged spleen and edema feet; (5) Characteristics of bleed are that it is massive, painless, recurrent and well tolerated. Overt or subclinical encephalopathy is not a feature of portal hypertension except after shunt surgery⁵. **On Examination :** 1) Signs of chronic liver failure like clubbing, spiders, palmar erythema, loss of axillary and pubic hair are invariably absent. 2) Rarely mild edema presents following a bleed; 3) Liver span may be normal or increased (not decreased), palpable in 60% cases firm nontender with a smooth surface; 4) Spleen is enlarged usually more than 9 cm; 5) Ascites is present in 20% cases after bleed (Esp, if poor dietary intake is present). It responds well to decreased sodium intake and diuretics.

INVESTIGATIONS

- 1) **Hematological:** Anemia -hypochromic normocytic or normocytic normochromic may be present and is often due to gastro intestinal hemorrhage. In hypersplenism there is anemia leucopenia and thrombocytopenia. Bleeding time, clotting time, prothrombin time, thrombintime, are all normal. Platelet aggregation test may show hypoaggregation.
- 2) **Biochemical:** Liver function tests are normal. Serum cholesterol, serum phospholipids are normal, some patients show low serum albumin which is often due to malnutrition rather than liver dysfunction. Basal and pentagastrin stimulated gastric secretion are reduced often due to portal hypertension and collateral circulation and not due to hepatocyte dysfunction. Bromosulphthalein excretion is abnormal in 20% of cases².
- 4) **Radiology:**
 - a) *Ultrasonography :* Shows marked dilatation and thickening of portal vein walls esp. intrahepatic branches, dilatation of splenic vein & massive splenomegaly. Spleen shows marked congestion
 - b) *Spleno -porto venography (SPV) :* Dye is injected into spleen and picture of spleno -portal axis is taken. It helps in diagnosis and suitability of shunt operation. Findings are :- i) Paucity of

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middle sized portal vein branches and they assume a “weeping willow” withered tree” appearance. ii) Absent or abruptly cut off peripheral branches (4th or 5th order radicals) – Distal cut off sign
 iii) Avascular area in immediate subcapsular area. In Cirrhosis, pathology is in 2nd and 3rd order branches. In EHPVO pathology is in portal vein itself or its main branches (Proximal cut off sign)
 5) **Haemodynamic Studies**:- These are mainly used for research purpose and to demonstrate that site of PHT in NCPF is pre sinusoidal. Intrasplenic pulp pressure is increased, portal vein pressure is increased and Wedge hepatic vein pressure is normal.

6) **Liver Pathology And Liver Biopsy** :- Macroscopic appearance : Typically the liver is smooth and firm. In about 25% of the patients only the surface of the liver may show nodules (which may be restricted to only one lobe) whereas the parenchyma is bereft of such nodules. The cut surface shows irregular areas of fibrosis primarily around the portal tracts, with thickening of the capsule due to subcapsular fibrosis. The portal veins are dilated and show sclerosis of their walls and evidence of thrombosis in the large and small portal vein branches.

Microscopic Appearance:- By definition, the lobular architecture and hepatic parenchyma are unaffected. The fibrosis starts in the subcapsular region and then creeps inside the liver parenchyma to surround primarily the portal tracts. The classical changes observed in intrahepatic portal vein branches which are markedly thickened, sclerosed and studded with organised or recanalising thrombi resulting in disappearance of portal venous radicals. The entity is appropriately designated as “Obliterative portal venopathy of the liver”⁶.

Ultrastructural appearance:- The characteristic findings are deposition of collagenous material in the widened intracellular space and the perisinusoidal space (space of Disse). Capillarisation of the sinusoids and development of microvilli between the hepatocytes are also occasionally observed. There is reduction of smooth endoplasmic reticulum in the hepatocyte. The basic aim of liver biopsy is to exclude the diagnosis of cirrhosis of liver. Percutaneous needle biopsy is certainly better than a laparoscopic punch biopsy, because not only may the nodular variety of NCPF be confused with cirrhosis but a punch biopsy obtained Rt laparoscopy may reveal only the subcapsular fibrosis and hence an incorrect diagnosis of Cirrhosis may be made. The histopathological features of liver biopsy include normal liver architecture, variably increased fibrosis in portal tract with focal lymphocytic infiltration and obliteration of small portal vein radicals. There may be fibrosis of space of Disse particularly in centrilobular zone.

DIFFERENTIAL DIAGNOSIS :- This includes cirrhosis, EHPVO, tropical splenomegaly syndrome (TSS), Budd-chiari syndrome, congenital hepatic fibrosis, partial nodular transformation, nodular regenerative hyperplasia, Felty’s synd., CHF, myeloproliferative disorders.

The differentiating features between NCPF, EHPVO and cirrhosis are given in Table 1

A scoring system to differentiate NCPF from Cirrhosis liver is given in Table – 2

TREATMENT

Acute Bleed : Steps in management includes

Table -1 : Differentiating features between NCPF, EHPVO & CIRRHOSIS

	NCPF	EHPVO	CIRRHOSIS
Age:	20-40 Yrs	<20Yrs	>40Yrs
Presentation:	GI bleed, rarely splenomegaly	GI bleed, rarely splenomegaly	Asymptomatic hepatomegaly, ascites, jaundice encephalopathy, GI bleed.
Bleed	good	good	poor
Tolerance			
1. Signs of Ch liver Disease	--	--	+
2. Abd. Veins	+	--	prominant
3. Liver	n or increased in size, firm	N, soft	firm, shrunken nodular
4. Spleen	>9 cm	<9 cm	1-3 cm
5. Jaundice, aseites, flaps	--	--	+
INVESTIGATIONS			
1. Paneytopenia	+++	++	+
2. LFT (Includ. PTI)	N	N	Deranged
3. BSP ex. test	<10%	N(<5%)	>1%
4. SPV	Distal cut off Sign	Proximal cut off Sign	Involvement of 2 nd & 3 rd Order Branches; periphery normal
5. WHVP	N	N	Increased
6. Biopsy	subcapsular Changes, patchy Portal Fibrosis	N	diffuse changes, necrosis, regeneration

NCPF = Noncirrhotic portal fibrosis ;

EHPVO = Extrahepatic portal vein obstruction;

SPV= Splenoportovenography;

WHVP= Wedged hepatic vein pressure

Table -2 : Scoring system to differentiate NCPF from Cirrhosis Liver

Variable	Points
Age	< 30Years -2 > 30 Years +2
Ascites	Present +6 Absent -2
Liver Scan	Abnormal +2 Normal -4
Serum Albumin	< 3 +4 3 to 3.5 0 > 3.5 -3

Score : Less than 5 = NCPF
 More than 5 = Cirrhosis

- (1) Put patient in lateral position to prevent aspiration.
- (2) Ryles tube gravity drainage; nil orally, monitor vitals.
- (3) I/V fluids and blood transfusion as required; do not overload patient; keep the patient slightly hypovolemic.
- (4) No role of antacids / H2 blockers
- (5) *Balloon tamponade* with Blakemore Sengstaken tube (3 lumen) or Minnesota tube (4 lumen) with oesophageal and gastric balloons. It is quite effective in controlling bleed for 24-48 hrs. Rebleeding follows tube withdrawal in 50% cases. Complications occur in 15% or more of patients and include aspiration pneumonitis as well as oesophageal rupture. If the gastric balloon bursts or deflates, the oesophageal balloon may migrate into the oropharynx causing asphyxia. Ulceration of the lower oesophagus occurs due to prolonged or repeated use. The oesophageal tube should not be kept inflated for more than 24 hrs. and preferably for not more than 10 hrs.
- (6) Intravenous *infusion of vasopressin* at a rate of 0.1 to 0.4 μ m/c results in generalized vasoconstriction leading to diminished blood flow in the portal venous system. Control of bleeding can be achieved in upto 80% cases, but bleeding recurs in more than half after the Vasopressin is tapered and discontinued. Serious side effects include cardiac and gastro intestinal ischaemia, acute renal failure and hyponatremia. Concurrent use of venodilators such as nitroglycerine as an I/V infusion or isosorbide dinitrate S/L may enhance the effectiveness of Vasopressin and reduce complications.
- (7) *Somatostatin* and its analogue Octreotide act as direct splanchnic vasoconstrictors. Comparison of somatostatin and Octeotide and given in table 111. Somatostatin is given in dose of 250 mcg. Bolus followed by 250 mcg/hour infusion for 48-72 hrs. Maximum duration of treatment is 5 days. Side effects include transient episodes of vertigo, nausea and flushes. Orthostatic hypotension has been rarely reported; in the case, keep the patient supine during administration. Octreotide in dose of 25-30 mcg/hr is given as a continuous i.v. infusion for a maximum of five days. Side effects include local reactions like pain, a sensation of stinging, tingling 01. burning at the site of injection, with redness and swelling. (See table 3)

Table - 3 : Comparison of somatation with octreotide

PARAMETER	SOMATOSTATIN	OCTREOTIDE
Action on bleeding	well established ⁸	controversial ⁸
Spectrum of activity	broad ⁸	narrow ⁸
Half-life in normal human	1-2 min ⁷	90 min ⁷
Half-life in hepatic disease	1-2 min ⁸	240 min ⁸
Effect on portal pressure	quick reduction ⁸	no action
Hepatic blood flow		
Down regulation	no ⁹	yes ⁹
Transfusion requirement	low ⁹	high ⁹
Side effects	less ⁸	more ⁸

(8) *Emergency sclerotherapy* with absolute alcohol, ethoxysclerol, sodium tetra decyl sulfate, sodium mauruvate or ethanolamine eleate controls bleed in more than 90% cases. After acute sclerotherapy chronic injection of varices is done every 1-4 weeks till all varices are obliterated. Prophylactic sclerotherapy has no role in prevention of bleed. Side effects of sclerotherapy include transient effects like fever, dysphagia and chest pain. Mucosal ulceration may occur and result in further hemorrhage or stenosis. Endoscopic band ligation of varices is as effective as sclerotherapy

and is devoid of side effects of sclerotherapy.

(9) *Surgery* has a limited role in the management of patients with NCPF. The present day **indications** for surgery include:-

- i) Failure of sclerotherapy to control bleeding.
- ii) Bleeding from large gastroesophageal varices or isolated gastric varices which cannot be controlled by sclerotherapy.
- iii) Symptomatic hypersplenism spontaneous bleeding episodes requiring transfusion.

Non selective shunt surgery: The procedure decompresses the entire portal system and includes *end to side* and *side-to-side* portocaval and proximal splenorenal shunt.

Selective shunt surgery: This is done to decompress only the varices while maintaining blood flow to liver. This includes distal splenorenal shunt.

Non selective shunts are more likely to be complicated by *encephalopathy* than selective shunts. Emergency portal systemic non selective shunts may control acute hemorrhage but such surgery is usually used only as a last resort because early operative mortality is greater than 30%. Surgically created shunts effectively reduce the risk of recurrent hemorrhage, but the overall mortality of patients undergoing such surgery is comparable to medical therapy for control of bleed.

(10) *TIPS:- Transjugular intrahepatic portasystemic shunt* offers an alternative to shunt surgery. The main drawback is stenosis and occlusion of shunt over a period of months.

PREVENTION OF RECURRENCE OF BLEED

- 1) *β -blocker* propranolol in a dose sufficient to decrease the resting pulse rate by 25%.
- 2) *Chronic sclerotherapy:-* One absolute indication for sclerotherapy is no availability of vein for shunt surgery as revealed by SPV.
- 3) *Shunt Surgery :-* One absolute indication for shunt surgery is hypersplenism.

PROGNOSIS

The disease is benign and has a good long - term prognosis. Mean survival is 25 yrs. from time of diagnosis (5 yrs. for cirrhosis).

After successful eradication of varices a 2 yr. And 5 yr. survival of 100%) has been observed. After splenorenal shunt surgery, a 5 yr. survival rate of 87% has been reported.

REFERENCES

1. Morris J.S Schmid M., Newman S., et al., Arsenic and non-cirrhotic portal hypertension: Gastroenterology, 1974;66:86-94.
2. Sama S.K., Bhargawa S., Gopinath N., et al., Non-cirrhotic portal fibrosis. Am. J. Med., 1971;51:160-9.
3. Nayyar A.K., Sharma B.K., Sarin, S.K., Broor S.L., Characterization of peripheral blood lymphocytes in patients with non-cirrhotic portal fibrosis- a comparison with cirrhosis and healthy controls. J. Gastroenterol hepatol, 1990.
4. Koshy A., Relationship between NCPF and EHO. In: Okuda K., Omata M., eds Idiopathic portal hypertension, Tokyo: University of Tokyo press, 1983:13-17.
5. Sarin S. K Nundy S., Subclinical encephalopathy after portasystemic shunts in patients with non-cirrhotic portal fibrosis. Liver, 1985;5, 142-6
6. Nayak N.C., Ramalingaswamy B., Obliterative portovenopathy of the liver. Arch. Pathol., 1969; 87:359-69.
7. Burroughs A.K. et al, Scand J Gastroenterol 1998;33 suppl 26:14-24.
- 8) Bosch J et al. Scand J Gastroenterol 1998 ; 33 suppl 226:14-24.
- 9) Avgerinous A. Digestion, 1998;59(Suppl 1): 1-22.
- 10) Sarin S.K., Nanda R., Gaur S.K., et al., Repeated endoscopic sclerotherapy for active variceal bleeding. Ann. Surg., 1985; 202: 708- 711.
11. Nundy S., Tandon B.N., The proximal lieno-renal shunt in the management of varices. In: Okuda K., Omata M., eds. Idiopathic portal hypertension, Tokyo: Univ. of Tokyo Press, 1983: 535-44.