



Idiopathic Non-Cirrhotic Intrahepatic Portal Hypertension (NCIPH)—Newer Insights into Pathogenesis and Emerging Newer Treatment Options

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Chronic microangiopathy of portal venules results in idiopathic non-cirrhotic intrahepatic portal hypertension (NCIPH). Recent data suggest a role for vasoactive factors of portal venous origin in the pathogenesis of this 'pure' vasculopathy of the liver. Enteropathies (often silent), are an important 'driver' of this disease. NCIPH is under-recognized and often mis-labeled as cryptogenic cirrhosis. Liver biopsy is needed to prove the diagnosis of NCIPH. In these patients, with advancing disease and increased porto-systemic shunting, the portal venous vasoactive factors bypass the liver filter and contribute to the development of pulmonary vascular endothelial disorders—porto-pulmonary hypertension and hepato-pulmonary syndrome as well as mesangiocapillary glomerulonephritis. Prognosis in NCIPH patients is determined by presence, recognition and management of associated disorders. With better understanding of the pathogenesis of NCIPH, newer treatment options are being explored. Imbalance in ADAMTS 13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13): vWF (von-Willebrand factor) ratio is documented in NCIPH patients and may have a pathogenic role. Therapeutic interventions to correct this imbalance may prove to be important in the management of NCIPH. (J CLIN EXP HEPATOL 2014;4:247–256)

The term “portal hypertension” is used to reflect a clinical condition secondary to increased pressure in the hepatic portal circulation. Clinically, it usually presents with symptoms or signs of gastroesophageal varices, ascites, encephalopathy, splenomegaly and/or hypersplenism. Portal hypertension can be classified in terms of the anatomic location of the causal resistance to portal blood flow as pre-hepatic (e.g. portal vein thrombosis), post-hepatic (e.g. Budd–Chiari syndrome) and intrahepatic. Intrahepatic portal hypertension can be further sub-classified as pre-sinusoidal (e.g. congenital hepatic fibrosis) or sinusoidal (sinusoidal obstruction syndrome/veno-occlusive disease). This review focuses on idiopathic

non-cirrhotic intrahepatic portal hypertension (NCIPH), a cause of pre-sinusoidal intrahepatic portal hypertension.

NCIPH occurs as a consequence of increased resistance to flow within intrahepatic portal vein radicles. Based on vascular corrosion cast and morphometric studies, the site of narrowing or occlusion was localized to the 3rd/4th order portal vein radicles. Boyer¹ and Wanless² proposed that the pruning of portal vein radicles is a consequence of thrombosis, but this view is not universally accepted. Sarin et al³ have shown that there are two independent pressure gradients, one between intra-splenic and intrahepatic pressure and another between intrahepatic and wedged hepatic venous pressure indicating the likelihood of both pre-sinusoidal and peri-sinusoidal resistance to blood flow. Intra-variceal pressure is representative of portal pressure.³

Keywords: endothelial dysfunction, ADAMTS 13, von-Willebrand factor (vWF), primary haemostasis

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Abbreviations: NCIPH: non-cirrhotic intrahepatic portal hypertension; CVID: common variable immunodeficiency; tTG: Tissue transglutaminase; IBD: inflammatory bowel disease; NRH: nodular regenerative hyperplasia; SOS: sinusoidal obstruction syndrome; PVT: portal vein thrombosis; OPV: obliterative portal venopathy; HVP: hepatic venous pressure gradient; PPH: porto-pulmonary hypertension; HPS: hepato-pulmonary syndrome

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NOMENCLATURE

Various terminologies have been used in an attempt to define and characterize NCIPH—idiopathic portal hypertension,^{4–6} non-cirrhotic portal fibrosis,^{7,8} nodular regenerative hyperplasia (NRH),⁹ incomplete septal cirrhosis,¹⁰ partial nodular transformation of the liver, benign intrahepatic portal hypertension and hepatoportal sclerosis.^{11,12} Although their description differs in detail it is increasingly thought that they represent variations in appearance of a single pathological entity. For nomenclature we prefer the term

NCIPH for clinical use, as it denotes the site of block as intrahepatic thereby excluding another important cause of idiopathic non-cirrhotic portal hypertension in India, namely extra-hepatic portal vein obstruction¹³

DEFINITION

At present NCIPH remains a diagnosis of exclusion. Several lists of criteria have been proposed for establishing the diagnosis. The diagnosis is based on documentation of the combination of essential findings listed in Table 1, with inconstant supplementary elements which vary between series documented in Japan, India and South-east Asia.^{14,15}

EPIDEMIOLOGY

NCIPH has been reported from all parts of the world, though more so from developing countries where it is most commonly encountered in young males in their third to fourth decade.^{16–18} In contrast, in Japan and the West there is a female preponderance and a tendency to present around the fifth decade.¹⁹

The relative rarity of the disease in the West and an apparent decline in its incidence elsewhere as living standards and hygienic conditions improve support the notion that enteropathy plays a role in disease pathogenesis. Series of patients with NCIPH have shown a preponderance of those who belong to low socioeconomic groups.^{2,9–11,14–16}

Table 1 Criteria for Diagnosing Idiopathic Non-Cirrhotic Intrahepatic Portal Hypertension (NCIPH).

Essential criteria¹⁴

- Presence of portal hypertension with splenomegaly
- Patent portal vein and hepatic venous outflow tract
- Normal or near normal liver function
- Absence of parenchymal disease and cirrhosis/advanced fibrosis on liver biopsy
- No obvious etiology of chronic liver disease (e.g. alcohol, Hepatitis viruses)

Other etiologies with similar histological findings are ruled out (e.g. congenital hepatic fibrosis, primary biliary cirrhosis, sarcoidosis, schistosomiasis)

Variants–supplementary (non-essential) criteria.

Nodular regenerative hyperplasia⁹: With distinct contrast between nodular and internodular tissue in most area nodules less than 3 mm.

Hepatoportal sclerosis¹¹ (i) Thrombosis/sclerosis of small portal vein branches; and/or (ii) intrahepatic aberrant abnormal portal venules, defined as absent or clearly reduced in caliber with sclerosis of vessels.

Obliterative portal venopathy¹⁵ (i) Liver biopsy longer than 1 cm and containing more than 5 complete portal tracts; more than 2/3 (66%) of the complete portal tracts harboring thickening of the vein's smooth muscle wall.

Incomplete septal cirrhosis¹⁰ (i) Parenchymal nodularity; (ii) thin incomplete septa.

In India, Sarin et al,²⁰ based on personal communications from multiple centers, estimated that NCIPH accounted for 23% of patients with portal hypertension in 1980's but only 5.6% more recently. This reduction in incidence accords with improving standards of hygiene and healthcare and reduction of diarrheal illnesses including tropical sprue. Nevertheless NCIPH remains an ongoing problem in India. The condition is almost certainly under-diagnosed. Krasinskas AM et al,²¹ reported that in 13 (81%) of 16 patients in whom unsuspected NCIPH was first diagnosed on histological examination of hepatectomy specimens following liver transplantation, cirrhosis had been the pre-operative diagnosis. Similarly, Radomski et al,²² reported that all four patients diagnosed with NCIPH in their liver transplantation series had been diagnosed as cirrhosis and only recognized as NCIPH on examination of the removed liver.

In a prospective southern Indian study spanning 2009–2010, Goel et al,²³ diagnosed cryptogenic chronic liver disease in 203 of 583 consecutive portal hypertensive patients. Thirty nine of the 203 underwent liver biopsy which revealed NCIPH in 16 (41%).²³ Of these 16 patients (10 males; age: 31, 20–59 years; median, range), 14 belonged to middle/lower socioeconomic class. 10 of these patients were from eastern India, 2 from southern India, 3 from northern India and 1 patient from Nepal.

PATHOGENESIS

Non-Cirrhotic Intrahepatic Portal Hypertension is a Microangiopathy Affecting the Small Portal Vein Radicles

Previous studies have demonstrated that small portal vein radicles are obliterated/thrombosed in patients with NCIPH. The pathological entities of nodular regenerative hyperplasia, incomplete septal cirrhosis and hepatoportal sclerosis are probably secondary to similar pathogenic process. In NCIPH, histological changes in the liver such as portal vein sclerosis and/or portal angiomatosis, perisinusoidal fibrosis and sinusoidal dilatation (as detailed below in section on Investigation), suggests obliterative portal venopathy (OPV).

Why Does the Microangiopathy Localize to Portal Venules in Non-Cirrhotic Intrahepatic Portal Hypertension?

The Splanchnic Circulation

The pathogenesis of NCIPH is not entirely clear but various associations give clues as to the likely components which interact in its causation. The association with inflammatory diseases of the intestine and confinement, at least initially, of vascular disturbances to the portal circulation is consistent with an intestinal origin for perturbation of the afferent portal circulation to the liver.

Confluence of Portal Vein and Hepatic Artery

As the vascular occlusion is initially confined to the third and fourth radicles of the portal vein it may be surmised that a combination of mesenteric and systemic influences coincide. This would be explained if admixture of hepatic arterial and portal venous factors combine to fulfill the necessary preconditions.

Pro-Inflammatory Factors of Intestinal Origin may Drive Microvasculature Occlusion in Non-Cirrhotic Intrahepatic Portal Hypertension

We documented a 16–20% incidence of adult coeliac disease in two separate series of NCIPH patients from Britain and India respectively.^{24,25} In light of this we have postulated that the high incidence of NCIPH in India, and its predilection for lower social classes may be attributable to the high frequency of enteropathies of varying etiology encountered in this population. Dysfunction of the vascular endothelium has been documented during the development of portal hypertension.²⁶ Pro-inflammatory cytokines are elevated in the sera of patients with active coeliac disease.²⁷ Pro-inflammatory stimuli emanating from damaged gut stimulate expression of ultra-large von-Willebrand Factor (ULvWF) in portal venous endothelium. In the normal state, von-Willebrand Factor (vWF) immunostaining is usually positive in large vessels but negative in the sinusoidal endothelial cells in the liver.²⁸ On the occurrence of liver injury accompanied by a necroinflammatory process, the sinusoidal endothelial cell becomes positive for vWF, presumably in association with the capillarization of hepatic sinusoids.²⁹

In an interesting in-vitro experiment, human umbilical vein endothelial cells were treated with interleukin 6 (IL-6), IL-8, or tumor necrosis factor alpha (TNF- α), and the formation of platelet-decorated ULvWF strings were quantitated. The results suggested that the inflammatory cytokines (IL-8 and TNF- α) stimulate ULvWF release and inhibit the ULvWF cleavage (IL-6), resulting in the accumulation of hyper-reactive ULvWF in plasma and on the surface of endothelial cells to induce platelet aggregation and adhesion on the vascular endothelium.³⁰

Normal blood flow stretches the long strands of vWF, exposing sites which are cleaved by ADAMTS 13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13) thus releasing vWF into the circulation. In the absence of ADAMTS 13, there will be a tendency for ULvWF strings to remain anchored and interact with platelet glycoprotein 1b α , thereby activating intraplatelet signaling which has the potential to produce platelet thrombi.³¹

Prothrombotic Predisposition

We studied ADAMTS 13 in NCIPH which is free of various confounding variables that arise as a consequence of liver

disease *per se*. On the basis of finding severe deficiency of ADAMTS 13 in NCIPH patients with an otherwise normally functioning liver, we propose that ADAMTS 13 deficiency in NCIPH is primary and permissive of the cause in producing the pruning of intrahepatic portal vein branches which characterizes NCIPH³²⁻³⁴ (Figure 1).

Hepatic End-Organ Status

In NCIPH patients, over time, with increasing porto-systemic shunting of portal venous blood, the liver is no longer able to restrict to the portal circulation the vasoactive factors originating within mesenteric blood. It may be speculated that these vasoactive factors, some of which have culminated in portal microangiopathy in NCIPH

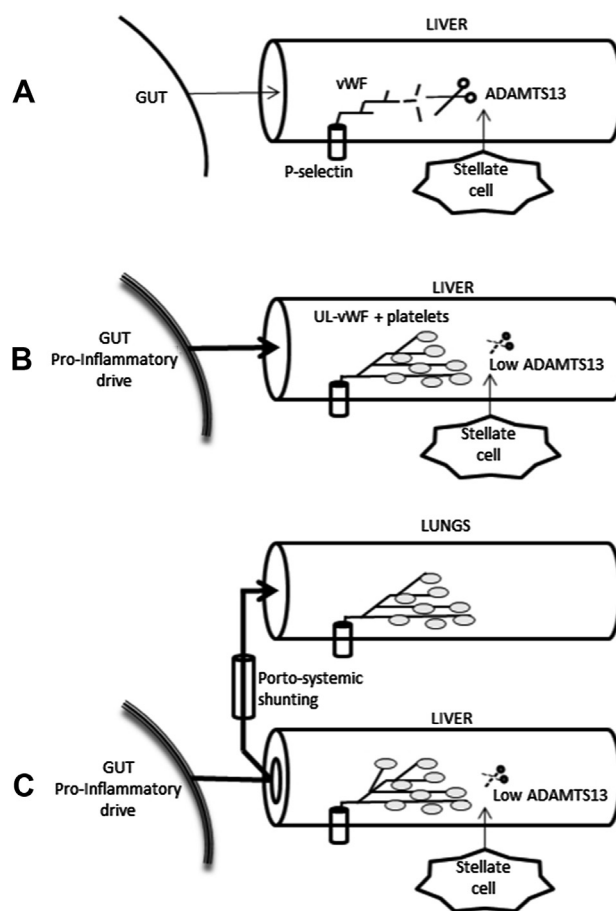


Figure 1 Proposed role of ADAMTS 13-ULvWF imbalance in pathogenesis of non-cirrhotic intrahepatic portal hypertension (NCIPH) and portopulmonary hypertension. A: Normal. Normal ADAMTS 13 production by the hepatic stellate cell leads to rapid cleavage of vWF from its p-selectin anchor; B: An increased pro-inflammatory drive of splanchnic origin leads to increased vWF production in venous endothelium which in the face of low ADAMTS 13 production results in ULvWF and platelet microthrombi; C: In the presence of low ADAMTS 13 production and increased splanchnic pro-inflammatory drive, porto-systemic shunting leads to build up of ULvWF and platelet rich thrombi in the pulmonary capillaries (Adapted from Ref 34). ADAMTS 13: A disintegrin and metalloprotease with thrombospondin type 1 motif, member 13.

contribute to the development of porto-pulmonary hypertension,³⁴ hepato-pulmonary syndrome and mesangiocapillary glomerulonephritis (see later).

Associated Disorders

Gut and Immune Disorders

An immunological aspect to the pathogenesis of NCIPH is suggested by its female preponderance in the west and its association with various immunological and autoimmune disorders. Though there has been a significant change over time in the detail of disorders associated with NCIPH there remains a consistent tendency for implicated factors to be of relevance to the immune system and gut.^{35,36} Earlier studies emphasized the importance of common variable immunodeficiency (CVID).^{37,38} Treatment with intravenous immunoglobulin replacement has largely resolved the issue, further supporting the notion that enteropathies associated with CVID were somehow promoting the vasculopathy of terminal portal venous radicles. Such a sequence points strongly to a gastrointestinal source for the initiating factors in NCIPH.

Accordingly we documented 16–20% incidence of adult coeliac disease in two separate series of NCIPH patients from Britain,²⁴ and India²⁵ respectively. In light of these findings it would appear logical to postulate that the high incidence of NCIPH reported from India in the past,¹⁶ may have been closely related to prevalent enteropathies including tropical sprue. Epidemiologically, such an association is also likely to account for the reported link with poverty.²³ On screening, deficiency of serum vitamin B12 may be an indicator of the disease.³⁹ This accords with the concept of a triad involving enteropathy (B12 malabsorption), portal hypertension and absence of hepatocyte damage (lack of leakage of B12 from the hepatocyte).

However it must not be supposed that eradication of endemic enteropathies will eradicate the disease as milder and sub-clinical enteropathies may be able to promote the same hepatic vascular reaction. In a recent Indian study consecutive patients with portal hypertension having a clinical presentation compatible with cryptogenic cirrhosis or NCIPH (cases) and controls with hepatitis B or C related cirrhosis were prospectively enrolled.²⁵ Tissue transglutaminase (tTG) antibody was positive in 66% of cases as compared to 29% in controls (P value < 0.001). Duodenal biopsy showed villous atrophy, crypt hyperplasia and lamina propria inflammation, significantly more commonly in cases as compared to controls; however most patients did not have raised intra-epithelial lymphocytes. 17 (43%) cases (including 5 NCIPH patients) as compared to 2 (18%) controls (P -value: 0.2) had this combination of tTG antibody positivity with duodenal villous atrophy. 13 of these 17 cases were followed up for >6 months (25, 11–59 months; median, range) on gluten free diet, with improvement in intestinal symptoms, tTG antibody titer and duodenal his-

tology, but no improvement in liver disease severity. A longer duration on gluten free diet may be required for improvement in liver disease.

Furthermore, although the impact of CVID has declined as a cause of enteropathy, it appears that immunodeficiency continues to be an important aetiological factor as there has been a marked rise in instances of NCIPH that are associated with HIV (Human Immunodeficiency virus) infection.^{40–45} Enteropathy is a well established feature of HIV infection. Infection of hepatic stellate cells by HIV may contribute to the pathogenesis of portal venous and sinusoidal endothelial injury via stimulation of prothrombotic cytokines such as endothelin-1, interleukins-1 and 6 and platelet derived growth factor⁴⁶ and protein S deficiency.⁴⁷ Although untested it may also be that stellate cell infection by HIV may contribute by diminishing production of ADAMTS 13 (see later). NCIPH occurring in HIV infection has been associated with prolonged exposure to Didanosine or concomitant exposure to Stavudine or Tenofovir.^{44,48}

Although typically primary biliary cirrhosis is accompanied by cholestasis which may be advanced prior to development of portal hypertension or cirrhosis, in a subgroup the illness presents with bleeding varices due to pre-sinusoidal portal hypertension in the absence of cholestasis or cirrhosis,⁴⁹ thus supporting the hypothesis that in genetically predisposed individuals, inflammation of the portal area of the liver promotes NCIPH. There are similar reports linking NCIPH with other autoimmune disorders including, systemic lupus, scleroderma,⁵⁰ Sjogren syndrome, rheumatoid arthritis⁵¹ autoimmune hepatitis^{15,52} and Felty's syndrome.^{53,54} Despite isolated case reports it is not clear that there is a significant association with the presence of anti-cardiolipin antibody.^{24,55}

Seksik et al,⁵⁶ described NCIPH in inflammatory bowel disease (IBD) patients treated with azathioprine. According to a recent review, IBD patients treated with Azathioprine have a cumulative incidence of nodular regenerative hyperplasia (NRH) of approximately 0.6% and 1.28% at 5 and 10 years respectively, whereas those treated with high-dose thioguanine (TG > 40 mg/day) have a frequency of NRH of upto 62%, which is higher in patients with elevated liver enzymes and/or thrombocytopenia than those without these abnormalities (frequency 76% vs. 33%). Conversely, low-dose TG therapy (<20 mg/day) is relatively safe, with no cases of NRH observed.⁵⁷

Devarbhavi et al,⁵⁸ described 14 patients who developed NRH, unrelated to Azathioprine in most cases, 3 months–11 years after orthotopic liver transplantation (LT). A total of 10 patients developed NRH within 4 years (early onset), and 4 other patients developed the condition beyond 4 years of LT.

Although both the sinusoidal obstruction syndrome (SOS) and NCIPH may present as nodular regenerative hyperplasia it is important to differentiate between them. In a

setting of carcinoma colon with liver metastases, NRH occurred in 22 of 146 treated patients (15%; 20 of these patients received Oxaliplatin). Patients treated by Oxaliplatin more often had NRH compared with Oxaliplatin-naïve patients (22 vs. 4%). Although operative mortality was nil, the presence of NRH was associated with increased postoperative hepatic morbidity (50 vs. 29%). Careful histological review suggested that the causative injury was to the endothelium lining hepatic sinusoids (SOS) rather than to portal venules (NCIPH).^{59,60}

Toxins

Prolonged exposure to several toxins especially arsenic has also been incriminated as a cause of NCIPH.⁶¹ Clinical and laboratory investigations were carried out on 248 patients with chronic arsenic toxicity due to drinking of arsenic contaminated water (0.05–3.2 mg/l) in 6 districts of West Bengal. Portal hypertension was found in 33.3% patients. Liver biopsy in 69 patients showed non-cirrhotic portal fibrosis in 63.⁶²

Pro-Thrombotic Factors

A role of prothrombotic disorders in the pathogenesis of NCIPH is supported by autopsy studies showing high prevalence of portal vein thrombosis (PVT) and studies from the West indicating association with prothrombotic states in 30–50% of the patients.^{15,63}

Hematologic Disorders

Potentially prothrombotic myeloproliferative disorders have been reported by Wanless et al in patients with NCIPH.⁶⁴

Genetic Disorders

Finally, support for the notion of genetic predisposition to development of NCIPH has come from reports on the familial occurrence as reported by Sarin et al⁶⁵ and a family we documented in which several members developed porto-pulmonary hypertension in association with NCIPH.⁶⁶

CLINICAL PRESENTATION

History

The typical patient with NCIPH presents in early adulthood with a complication of portal hypertension, usually bleeding varices.^{14–16} Ascites is uncommon except transiently after gastrointestinal bleeding. Not infrequently the patient will have presented to a hematology clinic following detection of thrombocytopenia or anemia with splenomegaly, in the absence of any other symptoms or signs to implicate liver disease.

Clinical Examination

Examination Reveals moderate splenomegaly but no hepatomegaly, indeed the liver may appear reduced in size. A se-

ries of 16 liver explants, of which 15 had NRH and 9 had incomplete septal cirrhosis, weighed a mean of 1,100 g.²¹ In a more recent survey involving 55 patients, ultrasonography showed a shrunken liver in fifty-eight percent.⁶⁷

Excluding cirrhosis is difficult in the absence of liver histology. Blood tests most frequently reveal thrombocytopenia but otherwise are unremarkable with normal or near normal liver function tests. Laboratory testing for diagnosis of other known causes of liver disease is unyielding. Both, hepato-pulmonary syndrome²¹ and porto-pulmonary hypertension,^{34,68} may arise as complications of NCIPH.

INVESTIGATION

Imaging

NCIPH is defined by the combination of pre-sinusoidal portal hypertension with a patent extra-hepatic portal vein and the absence of cirrhosis. At present, available conventional imaging tests i.e. ultrasonography, computerized tomogram and magnetic resonance imaging are limited in their ability to visualize small intrahepatic portal vein radicles. Subjective assessment of the size of liver on ultrasonography may reveal a shrunken liver in majority of these patients. In a recent study, Goel et al reported that 30 of the 45 patients with NCIPH had shrunken liver.³⁹ Few studies have explored the role of Role of Tc99m sulfur colloid scintigraphy⁶⁹ and fibroscan⁷⁰ in NCIPH, but their role in differentiating NCIPH from cirrhosis remains uncertain.

Pathology of the Liver

Grossly, the liver may be normal, enlarged or atrophic and/or nodular. The surface may appear normal or may show wrinkling or nodularity, depending on the stage of the disease.

A variety of morphological patterns can be seen on histological examination of the liver, which include NRH characterized by diffuse parenchymal nodularity due to alternating hyperplastic and atrophic hepatocytes without fibrosis (Figure 2a and b); incomplete septal cirrhosis in which there is slender septal fibrosis (Figure 3) demarcating the liver parenchyma into inconspicuous nodules and approximation of portal tracts with each other and with central veins; partial nodular transformation in which there are grossly visible nodules of hyperplastic hepatocytes located in the perihilar region of the liver; and obliterative portal venopathy (OPV) characterized by portal vein sclerosis and/or aberrant portal vein branches/angiomatosis (Figures 4 and 2b), sinusoidal dilatation and perisinusoidal fibrosis.^{21,71–73}

The whole liver can show heterogenous morphology and the findings can be focal and vary in severity. This should be kept in mind while evaluating liver biopsy

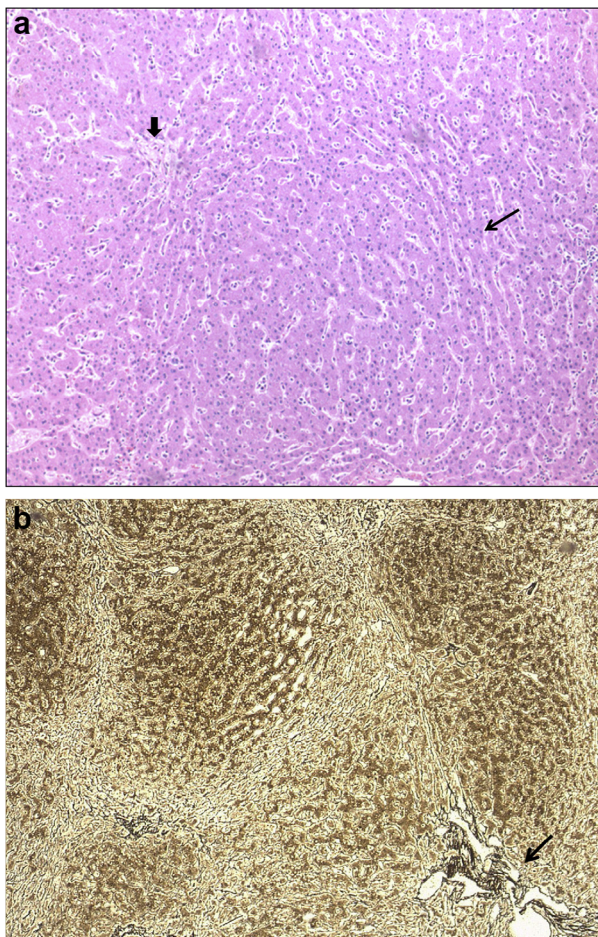


Figure 2 a. Nodular regenerative hyperplasia (NRH) showing hyperplastic hepatocytes surrounded by atrophic hepatocytes (long arrow) and hypoplastic portal tract (short arrow), H&E 100x. b. Nodular regenerative hyperplasia (NRH) showing parenchymal nodularity without fibrosis and portal angiomas (arrow), reticulin stain 50x.

samples or explant livers. Liver biopsy is essential to exclude cirrhosis. Histological changes of OPV, perisinusoidal and portal/periportal fibrosis and NRH have been reported in liver biopsies which are of adequate length (>1 cm) or multiple cores with adequate number of portal tracts (>5).^{15,18} In per operative cases both wedge and needle biopsies are advisable, since subcapsular nodularity can be mistaken for cirrhosis.¹⁵ In advanced stages of the disease, thrombosis of the medium and large portal vein branches has been reported.⁷³

These morphological patterns could represent a histological spectrum of different stages of a single clinical entity, resulting in non-cirrhotic intrahepatic portal hypertension.^{21,72}

Hepatic Venous Pressure Studies

NCIPH being a pre-sinusoidal portal hypertension, is expected to have normal hepatic venous pressure gradient (HVPG :difference between wedged hepatic and free hepat-

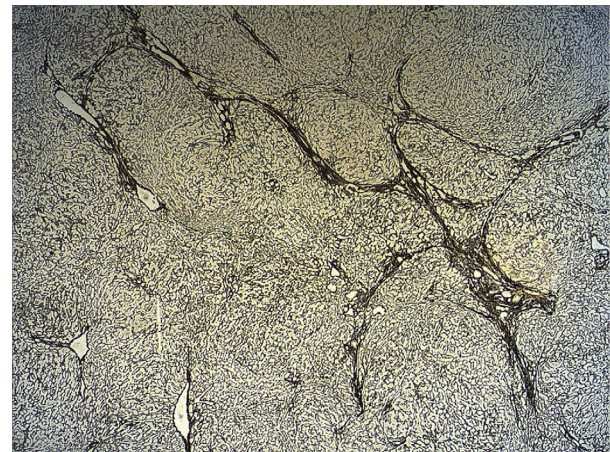


Figure 3 Thin septa extending from the portal tracts, reticulin stain 25x.

ic pressure). Sarin et al,³ showed two pressure gradients in these patients, one being between intrahepatic and wedged hepatic, thus suggesting a peri-sinusoidal component to portal hypertension. In our center, we found that up to 1/3rd of patients with NCIPH have normal HVPG.^{67,74} This suggests that in a majority, may be with advancing disease, there is a peri-sinusoidal component contributing to portal hypertension in these patients.

PROGNOSIS/NATURAL HISTORY

Although many published series report that overall survival of NCIPH patients is excellent,²⁰ there are caveats to that assertion as with longer follow up there is evidence of significant morbidity impacting survival.²¹ The studies with highest number of patients consist largely of patients who have presented at a relatively early age with bleeding varices. Given that many of the patients are relatively young, largely Child's class A status and that their follow up was relatively short it is not surprising that no excess

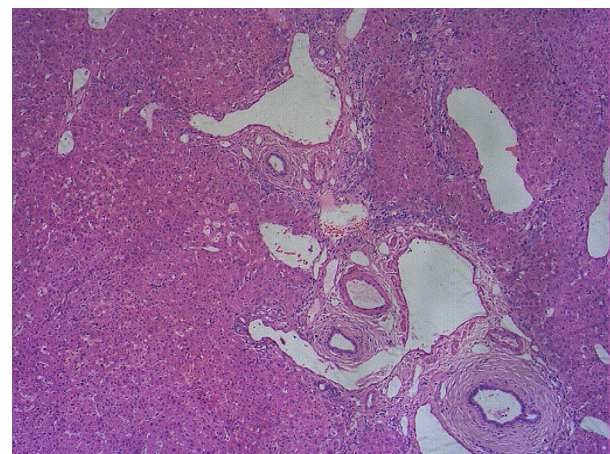


Figure 4 Aberrant and dilated portal venules herniating into the parenchyma, H&E 50x.

deaths are recorded for several years. In a more recent series, active celiac disease diagnosed late in the natural history contributed significantly to an excess of early deaths.²⁴ Schouten et al,⁴⁴ reported in a cohort of 62 patients followed up for a median of 90 months (range 24–310) overall survival were 100% (95% CI 95–100%), 78% (95% CI 67–89%) and 56% (95% CI 40–72%) at 1, 5 and 10 years respectively which was significantly decreased as compared to general population ($P < 0.001$). It is mandatory therefore that patients are monitored for extra-hepatic factors that may not be directly associated with their liver disease including disorders affecting the splanchnic circulation. Although by definition NCIPH occurs in the absence of PVT it is well documented that as the disease progresses that there is a high incidence of PVT. From this it is tempting to postulate that the factors which have contributed to NCIPH may have also contributed to PVT. Indications for liver transplantation include decompensated liver disease, porto-pulmonary hypertension (PPH) and hepatopulmonary syndrome.⁷⁵

COMPLICATIONS

Hepato-pulmonary Syndrome (HPS)

Orthostatic hypoxemia due to dilatation of intrapulmonary capillaries may occur late in many liver diseases including NCIPH. In a series of 15 NCIPH patients undergoing liver transplantation, the indication for transplantation was hepatopulmonary syndrome in 3 patients.²¹

Porto-Pulmonary Hypertension (PPH)

In a patient with NCIPH and severe PPH, we documented significant reduction in pulmonary artery pressures following a period of weekly transfusions of fresh frozen plasma as a source of replacement ADAMTS 13.³⁴ Subsequent infusion of platelet concentrate resulted in an immediate and almost fatal exacerbation of pulmonary hypertension. We postulated that increasing porto-systemic shunting complicating NCIPH in this patient transferred the pathological events of portal venous occlusion to the pulmonary vessels and as a consequence of severe ADAMTS 13 deficiency involved occlusion of pulmonary arterioles by platelets.

Cryptogenic Cirrhosis

It is uncertain whether the evolution of NCIPH may in some cases progress to cirrhosis.⁷⁶ In many areas of the world a majority of cases of cryptogenic cirrhosis is believed to be a consequence of non alcoholic steatohepatitis. However there is not the same prevalence of obesity in areas of India where NCIPH is most common suggesting an alternative pathogenesis. It is possible that continuation of the vascular injury that has led to NCIPH could culminate in cryptogenic cirrhosis. Clinically, NCIPH can mimic cirrhosis in every

aspect, and these patients are clumped together as 'cryptogenic' cirrhosis prior to liver biopsy. Only when the liver biopsy shows absence of fibrosis encircling hepatocyte nodules is the diagnosis of NCIPH confirmed. Thus clinico-epidemiological studies tend to under-estimate the prevalence of NCIPH. In a prospective study of etiology of portal hypertension conducted, only 20% patients with cryptogenic chronic liver disease underwent biopsy.²³ In a retrospective analysis (during 2005–2007), of the 62 patients with cryptogenic chronic liver disease who underwent liver biopsy at our centre, 30 (48%) had NCIPH.¹⁸ Finding of a tendency for Indian patients with cryptogenic cirrhosis of Child's class A to have low plasma ADAMTS 13 levels raises the intriguing possibility that NCIPH and cryptogenic cirrhosis in India are pathogenetically related.³³

Nephropathy

Of NCIPH patients who were treated by meso-caval shunt surgery for bleeding varices a high proportion developed glomerulonephritis (mesangiocapillary glomerulonephritis–MCGN),⁷⁷ and similar findings occurred in those in whom shunt surgery had been performed prophylactically to prevent variceal bleeding.⁷⁸ In contrast, patients who underwent meso-caval shunting for variceal bleeding caused by extra-hepatic portal vein thrombosis did not develop nephropathy. The implications again point to the presence in mesenteric blood, emerging from the intestine, of pro-inflammatory factors which when confined to the mesenteric circulation result in NCIPH but which on spill-over into the systemic circulation may result in PPH, HPS or MCGN.

Hepatocellular Carcinoma

Hepatocellular carcinoma has been rarely associated with NRH.⁷⁹ The possibilities of NRH being primary or secondary to the HCC need further studies.

TREATMENT

It is very likely that progression of NCIPH is to some extent dependent on the strength of the intestinal pro-inflammatory drive. It can be surmised that the widely reported reduction of incidence of NCIPH in India in recent years,⁸⁰ is to some extent related to the reduction seen in the incidence of chronic enteropathies such as tropical sprue. In a Caucasian population, Eapen et al reported a significantly worse prognosis of NCIPH in those with untreated adult coeliac disease.²⁴ A major facet in patient management must therefore be detection and treatment of any identifiable source of a pro-inflammatory drive within the mesenteric circulation.

The commonest complication is of bleeding oesophageal varices. A single controlled trial involving a 2 year follow up of 101 patients showed no significant difference

in the rate of rebleeding between patients treated with propranolol or sclerotherapy.⁸¹ Pal et al,⁷⁸ reported on 41 patients with NCIPH in whom prophylactic proximal lienorenal shunt was performed and concluded that the morbidity was sufficient for them to advise against the practice. Though there were no operative deaths and no one died of bleeding there was an excess of delayed morbidity in 47% including a death from chronic renal failure, porto-systemic encephalopathy (7 patients), glomerulonephritis (4), HPS (2) and ascites (5). Thus only 20 (53%) patients were symptom-free on follow up.⁷⁸ Although successful in reducing portal pressure and risk of rebleeding, we therefore believe that porto-systemic shunt surgery should be avoided unless totally necessary as it may have systemic complications.

Prevention and management of variceal bleeding can probably be performed according to the same guidelines as for cirrhosis: beta-blockers and/or endoscopic therapy for the prevention of bleeding⁸²; endoscopic therapy associated with vasoactive drugs for the treatment of acute variceal bleeding. In NCIPH patients, transjugular intrahepatic portosystemic shunt should be held in reserve as it has been reported to be associated with liver failure and excess mortality.²⁴

Although not reported in the literature we are aware of cases in which unanticipated fatal cardiopulmonary collapse has complicated treatment by portosystemic shunting in patients with NCIPH. We postulate that these cases have arisen as a consequence of transfusion of platelets or colloid in patients with pre-existing but unidentified porto-pulmonary hypertension.³⁴ We envisage a scenario in which if on pre-operative assessment of a patient with any liver disease, porto-pulmonary hypertension is found, attention to their ADAMTS 13: ULvWF ratio becomes a necessary step in preparing for surgery. Platelet transfusion in such patients should either be deferred until ADAMTS 13 deficiency has been excluded or reversed by infusion of fresh frozen plasma. Should urgency preclude such management, platelet transfusion should be monitored with sensitive measures to detect early signs of rapidly increasing acute pulmonary vascular resistance.

LIVER TRANSPLANTATION

Various studies have documented excellent prognosis in patients with NCIPH, but transplant units, especially from this part of the world, would encounter patients with NCIPH. In a series from N. India, of the 402 transplanted patients; 87 had a pre-transplant diagnosis of cryptogenic cirrhosis and 10 of these patients were diagnosed as NCIPH after explant biopsy.⁸³ At our center 20 of the 54 (39%) patients, who underwent liver transplant during 1999–2013, were labeled as cryptogenic liver disease at the time of liver transplant. On histopathological examination of the explanted liver, 3 patients had NCIPH.

During liver transplantation, pre-existing deficiency due to end-stage liver disease is compounded by the interval during which restoration of normal levels of ADAMTS 13 by the implanted liver lags behind the recovery to normal of vWF function. During this window period, a hyper-coagulable state may pertain. ADAMTS 13 deficiency is not only associated with NCIPH but is also a significant complication of advanced liver disease of any cause and may contribute to the risks of surgery including liver transplantation.⁸⁴ In a recent analysis, platelet transfusion was the only statistically significant factor that could be identified which was associated with excess mortality following liver transplantation.⁷⁶ On autopsy evidence, the excess was accounted for by pulmonary ‘hepatisation’ and right heart failure indicative of platelet driven occlusion of the pulmonary microvasculature.⁸⁵ We have proposed that this scenario is a consequence of ADAMTS 13 deficiency, and if so, may be prevented by adequate correction of ADAMTS 13 blood levels prior to any platelet transfusion in such patients.³⁴

CONFLICTS OF INTEREST

All authors have none to declare.

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