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ORIGINAL ARTICLE

Non-cirrhotic Intrahepatic Portal Hypertension: Associated Gut Diseases and Prognostic Factors

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Abstract
Background/Aims Non-cirrhotic intrahepatic portal hypertension (NCIPH) is generally regarded to have a benign prognosis. We have studied a cohort followed-up at a tertiary referral center and postulate that gut-derived prothrombotic factors may contribute to the pathogenesis and prognosis of NCIPH.
Methods We retrospectively analyzed prognostic indicators in 34 NCIPH patients. We also searched for associated gut diseases.
Results Transplant-free survival in NCIPH patients from first presentation with NCIPH at 1, 5, and 10 years was 94% (SE: 4.2%), 84% (6.6%), and 69% (9.8%), respectively. Decompensated liver disease occurred in 53% of patients. Three (9%) patients had ulcerative colitis while five of 31 (16%) tested had celiac disease and on Kaplan–Meier analysis, celiac disease predicted reduced transplant-free survival ($p = 0.018$). On multivariable Cox regression analysis, independent predictors of reduced transplant-free survival were older age at first presentation with NCIPH, hepatic encephalopathy, and portal vein thrombosis. Prevalence of elevated initial serum IgA anticardiolipin antibody (CLPA) was significantly higher in NCIPH (36% of patients tested), compared to Budd–Chiari syndrome (6%) ($p = 0.032$, Fisher's exact test) and celiac disease without concomitant liver disease (0%) ($p = 0.007$).
Conclusions We have identified prognostic factors and report progression to liver failure in 53% of NCIPH

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patients followed-up at our center. Our data supports a role for intestinal disease in the pathogenesis of intrahepatic portal vein occlusion leading to NCIPH.

Keywords Non-cirrhotic portal hypertension · Celiac disease · Inflammatory bowel disease · IgA cardiolipin antibody · Portal vein thrombosis

Introduction

Though the term non-cirrhotic intrahepatic portal hypertension (NCIPH) suggests a benign prognosis, progression to liver failure is reported. The diagnosis is easily overlooked and in some patients transplanted for presumed cirrhosis the diagnosis of NCIPH is first made on the explant [1]. Though different terms, mostly describing pathological features, are used to denote NCIPH (nodular regenerative hyperplasia, idiopathic portal hypertension, non-cirrhotic portal fibrosis, incomplete septal cirrhosis, partial nodular transformation, hepatoportal sclerosis, and benign intrahepatic portal hypertension [1–3]), there is an increasing consensus that NCIPH is best viewed as a single clinical entity [1, 4]. The primary causative lesion in NCIPH has been shown to be obliteration of portal venous microcirculation on corrosion cast injection studies [5], dissection of intrahepatic vasculature [5], morphometric studies [6], and histological studies of operative wedge liver biopsy samples [7, 8] and of whole liver specimens at autopsy [8]. Selective obliteration of the portal venous microcirculation suggests that prothrombotic factors of gut origin may cause NCIPH and we have proposed serum cardiolipin (CLP) A antibody as a candidate gut-derived prothrombotic factor in NCIPH associated with celiac disease [9].

In this study, we analyzed determinants of transplant-free survival in a cohort of NCIPH patients and looked for co-existent gut diseases.

Patients and Methods

Patient Selection and Mode of Diagnosis

Diagnosis of NCIPH was made on needle biopsy of liver in 30 patients (12 had transjugular liver biopsy while 18 had percutaneous biopsy), on hepatectomy specimen (3) and on operative wedge liver biopsy (1). Those who underwent needle biopsies often had multiple biopsies (number of biopsies: 1 (1–4)) to make the diagnosis of NCIPH. Of 34 patients included in the study, 28 had definite histological features of NCIPH (three had additional pathology noted on liver histology: grade 3 siderosis in one who was homozygous for H63D mutation in HFE gene, excess copper deposits on liver biopsy in one and granulomas in liver in one). The remaining six patients were diagnosed to have 'probable NCIPH' after undergoing needle biopsies of the liver (number of biopsies: 2 (1–3)), and were included as cases, though, as biopsies were small and fragmented, macronodular cirrhosis could not be excluded definitively.

Study inclusion criteria were (1) evidence of portal hypertension—any two or more of following: varices, hypersplenism, ascites, hepatic venous pressure gradient >5 mmHg, (2) patent hepatic and portal veins on Doppler ultrasound at time of diagnosis of NCIPH, (3) absence of cirrhosis or bridging fibrosis on liver biopsy, (4) exclusion of conditions causing cirrhosis by conventional diagnostic criteria including chronic viral hepatitis, alcoholic hepatitis, non-alcoholic steatohepatitis, hemochromatosis, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis and Wilson's disease, and (5) exclusion of conditions that may cause portal venous lesions similar to NCIPH on histology such as congenital hepatic fibrosis and sarcoidosis. Patients who met all five of these criteria were enrolled in the study. Study exclusion criteria were (1) predominant histological features of another disease process in addition to portal venous insufficiency, (2) NCIPH that developed after liver transplantation, and (3) hepatic malignancy.

We retrospectively studied NCIPH patients managed in the Liver Unit, Queen Elizabeth Hospital, Birmingham, UK, from January 1999 to August 2005. Patient selection was done from two sources: from a clinical database of patients with characteristic clinical profile suggesting NCIPH and from a liver pathology database from which patients with portal hypertension were selected on the basis of compatible histology including absence of cirrhosis.

Search for Co-existent Gut Diseases

Associated gut diseases in NCIPH patients were studied. We also compared prevalence of elevated serum CLPA (a putative gut-derived prothrombotic factor associated with NCIPH) with serum CLPG and CLPM antibody levels in NCIPH patients. Serum CLP antibodies were measured using enzyme immunoassay (Bindazyme^{TM}, The Binding Site Ltd, Birmingham, UK). Normal values for serum CLPA antibody, CLPG (cardiolipin G), and CLPM (cardiolipin M) were <13 PL U/ml (phospholipid U/ml), <12 PL U/ml and <10 PL U/ml, respectively.

Factors Predicting Transplant-Free Survival

We defined baseline as first presentation with NCIPH. We analyzed the following 20 factors for an effect on

transplant-free survival: age at first presentation with NCIPH, sex and celiac disease; following parameters assessed at baseline: variceal bleed, ascites, hepatic encephalopathy; following parameters which occurred on follow-up: variceal bleed, ascites, hepatic encephalopathy, and portal vein thrombosis; first level of serum immunoglobulin A, G, and M; level of serum CLPA, CLPG, and CLPM antibodies when first tested; whether patient underwent following treatments for portal hypertension: portosystemic shunt surgery, transjugular intrahepatic portosystemic shunt (TIPS), endoscopic treatment of variceal bleed and whether patient underwent splenectomy.

Comparing Serum CLPA Antibodies in NCIPH and in Control Groups

We compared serum CLPA antibody titers in the 28 NCIPH patients in the current series who had this tested with two control groups: 18 patients with Budd–Chiari syndrome (age: 41 (20–53) years, nine males) and 16 patients with celiac disease proven on duodenal biopsy (age 49 (17–93) years, nine males) who did not have concomitant liver disease.

Statistical Analysis

Data were summarized as medians and ranges or as counts and percentages. Prevalences of elevated serum CLPA, CLPG, and CLPM antibody levels in NCIPH patients were compared using McNemar's test. Prevalence of elevated serum CLPA antibody in NCIPH and in control groups was compared using Fisher's exact test. p values for the comparisons of pairs of groups were unadjusted.

Kaplan–Meier analysis was used to produce survival curves. To study transplant-free survival, univariable analysis was done using Cox regression analysis and multivariable analysis was done using step-wise Cox regression analysis. For survival analysis, serum CLP and immunoglobulin levels were analyzed as dichotomous variables (i.e., normal or elevated) and not as actual serum levels. The following events during follow-up were represented as time-dependent covariates in both univariable and multivariable analyses—variceal bleed, ascites, hepatic encephalopathy, portal vein thrombosis, different treatments for portal hypertension, and splenectomy in transplant-free survival analysis. The level of statistical significance was set at $p < 0.05$. As increasing age at first presentation with NCIPH was an independent predictor of poor survival, this was analyzed further using stepwise Cox regression to determine the best cut-off value for predicting poor survival.

Results

Clinical Features, Details of Splenectomy/Treatment for Portal Hypertension in Study Cohort

The clinical features of the study patients are shown in Table 1. Except for one patient of Asian origin, all were Caucasians.

Splenectomy was performed for symptomatic hypersplenism (three patients) and for splenic mass lesion (peliosis) in one.

Gastro-esophageal varices were detected in 28 patients and all were treated with propranolol. Variceal bleeding was treated by endoscopic treatment alone in nine patients and by a combination of endoscopic treatment and shunt surgery in two patients. Nine patients had TIPS inserted (details given in Table 2).

Co-existent Gut Diseases

Celiac Disease

Of 31 patients who had celiac serology (IgA tissue transglutaminase, endomysial antibodies) tested, five (16%) had positive serology and duodenal biopsy changes that confirmed celiac disease. All five had adult-onset celiac disease (Table 3). The small number of patients made it difficult to interpret the effect of a gluten-free diet on serum CLPA antibody levels or the natural history of NCIPH. One patient (patient no. 5, Table 3) had IgG kappa paraproteinemia, when tested on 1 occasion.

Ulcerative Colitis

Three patients (one male) had ulcerative colitis diagnosed 24 (5–83) months after diagnosis of NCIPH. One patient had asymptomatic celiac disease in addition (patient no. 4, Table 3) while the other two had negative celiac serology. Ulcerative colitis was treated with oral aminosalicylate in one patient and with oral prednisolone and aminosalicylates in the other two. Colitis was in remission in all three patients when serum CLPA antibody was first tested and it was found to be elevated in one patient. Serum p ANCA, tested in one patient, was elevated (one in 1,024 titers). All three patients were alive at last follow-up at 71 (62–98) months after first presentation with NCIPH.

Serum CLP Antibodies and Lupus Anticoagulant in NCIPH Cohort

Serum CLP antibodies were tested in 28 patients at 80 (1–256) months after first presentation with NCIPH.

Table 1 Clinical characteristics of the 34 patients with non-cirrhotic portal hypertension (NCIPH) studied

Sex	24 males, 10 females
Age (years) at first referral to Liver Unit*	45 (18–75)
Age (years) at first presentation with NCIPH*	38.5 (17–74)
Outcome at end of study period	
Alive	21 patients (62%)
Died	10 patients (29%)
Had liver transplant	3 patients (9%)
Follow-up (months) from first presentation with NCIPH until the end of study**	88 (2–271)
Liver failure during study period[a]	
Did not occur	16 patients (47%)
At 1st presentation with NCIPH	5 patients (15%)
During follow-up	13 patients (38%)
Blood/serum levels, Child's and MELD scores at first referral to Liver Unit are given below	
Hemoglobin (gm/dl)*	12.8 (5.7–17.2)
White cell count ($\times 10^9$/l)*	3.7 (1.1–9.3)
Platelet count ($\times 10^9$/l)*	70 (20–278)
INR*	1.2 (0.9–2.2)
Bilirubin (μmol/l)*	25 (6–170)
Albumin (gm/l)*	36 (27–51)
Aspartate aminotransferase (U/l)*	41 (12–135)
Alkaline phosphatase (U/l)*	242 (72–748)
Sodium (mmol/l)*	140 (121–145)
Creatinine (μmol/l)*	88 (47–208)
Elevated IgA (×ULN)*,[@]	2 (1–5.64) in 19 patients
Elevated IgG (×ULN)*,[@]	1.08 (1–2.18) in 17 patients
Elevated IgM (×ULN)*,[@]	1.29 (1–2.42) in 10 patients
Elevated CPLA PL U/ml*,[@]	18.5 (13–44) in 10 patients
Elevated CLPG PL U/ml[@]	14 in 1 patient
Elevated CLPM PL U/ml*,[@]	11 (10–19.7) in 3 patients
Child's score	
A	17 patients (50%)
B	13 patients (38%)
C	4 patients (12%)
MELD score*	10 (1–21)

INR international normalized ratio; *Ig* Immunoglobulin; *×ULN* times upper limit of normal; *CLP* cardiolipin antibody; *PL U/ml* phospholipid units/ml; *MELD* model for end-stage liver disease

* Median (range)

** End of study refers to last follow-up where patient was alive, had died, or underwent liver transplantation;

[a] Liver failure defined as ascites and/or hepatic encephalopathy

[@] Elevated titers at initial testing; cardiolipin antibodies tested in 28 patients only

As shown in Table 1, initial serum CLPA antibodies were elevated in ten patients (36%), while simultaneous serum CLPG and CLPM antibodies were elevated in one (4%) and three (11%) patients, respectively (p value: 0.04 comparing serum CLPA and CLPG antibody positivity, p value: 0.07 comparing serum CLPA and CLPM antibody positivity using McNemar's test). Lupus anticoagulant (dilute Russell's viper venom assay) was negative in all 17 patients tested. Anti-ß2 glycoprotein1 antibody was borderline positive on initial testing in five of 19 patients tested and negative in the rest.

One NCIPH patient had persistently elevated serum CLPA antibody and persistent Epstein–Barr viremia. He had steady deterioration of liver functions after TIPS insertion and died 3 months later (patient no. 1, Table 2).

Survival, Cause of Death, and Indication for Liver Transplantation

Of the 34 NCIPH patients studied, ten died while three underwent liver transplantation during the follow-up period of 88 (2–271) months from first presentation with NCIPH (Table 1). Overall transplant-free survival at 1, 5, and 10 years was 94% (SE: 4.2%), 84% (6.6%), and 69% (9.8%) (Fig. 1).

Of the ten patients who died, three died of deteriorating liver functions after TIPS insertion (patient nos. 1–3, Table 2). In the other seven patients, death was caused by esophageal variceal bleed in a Jehovah's witness (one); liver failure, suspected mesenteric venous thrombosis (one); disseminated intravascular coagulation and multi-organ system failure after bleed from capsular tear following liver biopsy (one); liver failure, septic arthritis of ankle, multi-organ system failure (one); liver failure (one); portal and mesenteric venous thromboses, liver failure, gram negative bacteremia (one); not known (one).

Three patients underwent liver transplantation: the first patient for hepatopulmonary syndrome and NCIPH, he was well with normoxemia 14 months later; the second patient for presumed cryptogenic cirrhosis with hepatic encephalopathy and ascites, but the patient died 14 days later of chest infection and adult respiratory distress syndrome while the third patient was transplanted 8 days after TIPS insertion (for uncontrolled variceal bleed and presumed alcoholic cirrhosis) as she had rapid worsening of liver functions and hepatic encephalopathy after TIPS; she was in good health after this but died 5 years later of intracerebral hemorrhage (patient no. 4, Table 2).

Predictors of Transplant-Free Survival

Significant predictors of transplant-free survival on univariable and multivariable analysis are given in Table 4.

Table 2 TIPS in patients with non-cirrhotic portal hypertension: indications for TIPS and outcome

Serial no: Age*/sex	Indication for TIPS	Liver failure prior to TIPS insertion	Hepatic encephalopathy after TIPS insertion	Patient outcome
1 30/M	Gastric variceal bleed	Mild ascites	Yes, gd III, 2 months later[a]	Died 3 months later of worsening liver functions and septicemia
2 62/M	Refractory ascites	Gross ascites	Yes, gd IV, 1 day later[a]	Died 9 days later of liver and renal failure
3 64/M	Rectal variceal bleed	Mild ascites	Yes, gd IV, 11 days later[a]	Died 52 days later of liver failure
4 62/F	Gastro-esophageal variceal bleed	Gd I hepatic encephalopathy	Yes, gd III–IV, 1 day later[a]	Liver transplantation 8 days later
5 48/M	Gastro-esophageal variceal bleed	Mild ascites	No	Alive, 9 months later
6 67/M	Portal hypertensive gastropathy bleed	No	No	Alive at discharge from hospital after TIPS (no more follow-up)
7 25/M	Gastro-esophageal variceal bleed	No	No	Alive, 9 years later
8 61/F	Gastric variceal bleed	No	Yes, gd II, 8 months later[a]	Alive, 10 months later
9 52/F	Gastro-esophageal variceal bleed	No	No	Alive, 6 years later

Liver failure defined as ascites and/or hepatic encephalopathy

* Age in years when TIPS was inserted

[a] TIPS was patent on imaging when liver functions deteriorated and hepatic encephalopathy developed

Table 3 Details of patients with non-cirrhotic portal hypertension (NCIPH) and celiac disease (celiac disease proven on duodenal biopsy in all patients)

Serial no: Age*/sex	Symptoms of celiac disease[a]	Time interval between diagnosis of celiac disease and of NCIPH	Gluten-free diet (GFD)	Serum CLPA antibody titers** (time between start of GFD and CLPA antibody test)	Patient outcome
1 40/M	None	22 months after diagnosis of NCIPH	Irregular on GFD for 7 years	13 (73 months on GFD) 21 (83 months on GFD)	Died of liver failure
2 60/M	Yes	4 days after diagnosis of NCIPH	GFD started, but patient died 17 days after celiac disease was diagnosed	20.3 (1 month before GFD started) 21.6 (8 days on GFD)	Died of liver failure and suspected mesenteric vein thrombosis
3 31/F	Yes	27 years before diagnosis of NCIPH	Regular GFD for 27 years	44 (327 months on GFD)	Died of DIC and multi-organ failure after bleeding from capsular tear after liver biopsy
4 33/F	None	2 months after diagnosis of NCIPH	Regular GFD for 6 years	<13 on two occasions (after 5 years on GFD)	Alive
5 42/M	Yes	20 years prior to diagnosis of NCIPH	Regular GFD for 20 years	Not tested	Died after rapid worsening of liver functions 9 days after TIPS

* Age in years at diagnosis of celiac disease

[a] Symptoms of celiac disease were: Patient 2: diarrhea (10 years), weight loss (6 months), vomiting (4 weeks); Patient 3: dermatitis herpetiformis developed during pregnancy; Patient 5: diarrhea, weight loss, dermatitis herpetiformis

** Serum CLPA (cardiolipin A) antibody titers in PL U/ml; normal range: <13 PL U/ml; *DIC* disseminated intravascular coagulation

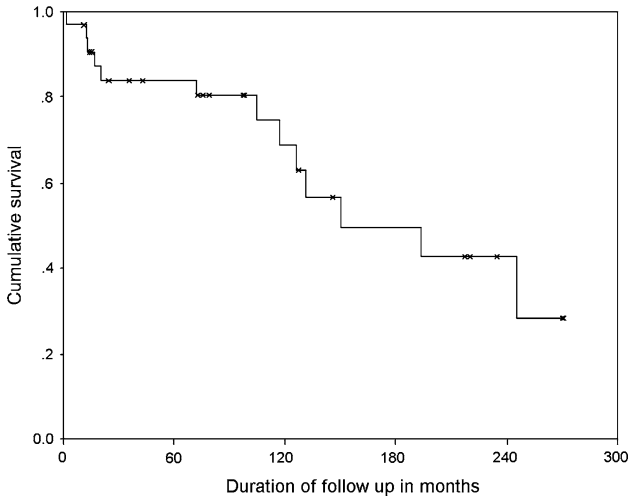

Fig. 1 Overall transplant-free survival in 34 non-cirrhotic portal hypertension patients with study baseline defined as first presentation with non-cirrhotic portal hypertension. Ten patients died while three underwent liver transplantation during the study period

The effect of celiac disease on transplant-free survival is shown in Fig. 2. In the stepwise Cox regression, the cut-off value for age at first presentation with NCIPH, which best predicted transplant-free survival, was between 50 and 57 years, with older age associated with worse outcome.

Comparing Serum CLPA Antibodies in NCIPH with Control Groups

Serum CLPA antibody was elevated in 10/28 (36%) NCIPH patients, 1/18 (6%) patients with Budd–Chiari syndrome and 0/16 (0%) patients with celiac disease without concomitant liver disease. *p* values, using Fisher's exact test, on comparing NCIPH versus Budd–Chiari syndrome was 0.032 and versus celiac disease without concomitant liver disease (*p* value: 0.007). Serum CLPA antibody titer when elevated was 18.5 (13–44) PL U/ml in NCIPH patients and 13.1 PL U/ml in one patient with Budd–Chiari syndrome.

Discussion

In the current study of 34 patients followed-up for 88 (2–271) months from first presentation with NCIPH, 18 developed liver failure and 13 either died or underwent liver transplantation, demonstrating that NCIPH is not a benign condition. An analysis of 65 autopsies of NCIPH patients from Japan reported progressive liver failure as cause of death in 16 patients [10]. These two reports contrast with the benign outcome reported in other series of NCIPH [7, 11]. As liver transplantation is performed at our center, it is likely that among NCIPH patients, those in/progressing to liver failure are selectively referred—this bias may partly explain the disparity in survival outcomes between these studies.

In our study, older age at first presentation with NCIPH, hepatic encephalopathy, and portal vein thrombosis were significant predictors of reduced transplant-free survival on multivariable analysis (Table 4).

Although TIPS may at first appear to be a safe option to treat pre-sinusoidal portal hypertension in NCIPH, our series would indicate that this approach should be used with extreme caution, as four of nine patients suffered from rapid deterioration of their liver function after TIPS—three of whom died and one needed an urgent liver transplantation (patient nos. 1–4, Table 2). The presence of liver failure prior to TIPS placement appeared to be associated with a very poor outcome and we would now regard this as a contraindication to TIPS in NCIPH (Table 2).

A vascular pathogenesis of cirrhosis has been proposed in which hepatic parenchymal injury is followed by fibrous obstruction of the microcirculation (sinusoids, adjacent small portal, and hepatic veins) [12]. Microcirculatory obliteration of hepatic veins in cirrhosis was associated

Table 4 Statistically significant predictors of reduced transplant-free survival in 34 NCIPH patients

	p value	Hazard ratio (95% CI)
Univariable analysis		
Ascites	<0.001	6.7 (2.0–22.5)
Hepatic encephalopathy	<0.001	26.9 (6.2–116.6)
Portal vein thrombosis	0.011	5.3 (1.3–21.4)
Older age at first presentation with NCIPH	0.006	1.05 (1.01–1.08)
Celiac disease	0.012	4.4 (1.2–15.7)
Multivariable analysis		
Hepatic encephalopathy	<0.001	44.2 (7.6–257.1)
Older age at first presentation with NCIPH	0.002	1.06 (1.02–1.11)
Portal vein thrombosis	0.015	7.3 (1.3–40.3)

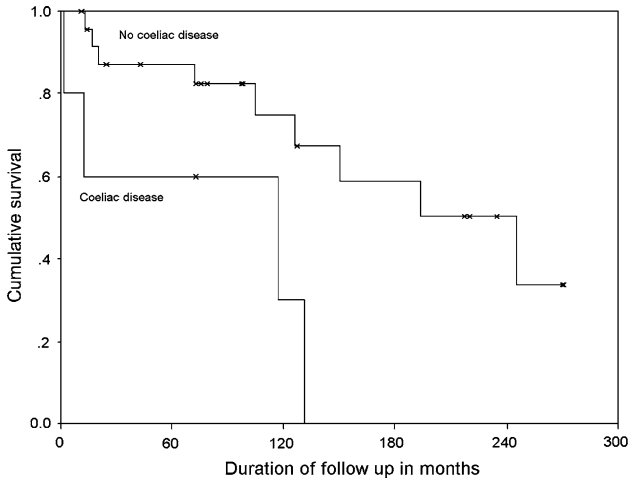

Fig. 2 Kaplan–Meier analysis demonstrating significant effect ($p = 0.018$) of celiac disease on transplant-free survival in non-cirrhotic portal hypertension (NCIPH). Five NCIPH patients with associated celiac disease and 26 NCIPH patients without associated celiac disease were studied

with focal parenchymal extinction while that of portal veins correlated with variceal bleeding [12]. One explanation for the progression to liver failure in NCIPH is extension of thrombosis from the portal venous microcirculation to sinusoids and adjacent small hepatic veins. In our study, one patient had focal small hepatic vein thrombosis on needle liver biopsy (he had liver failure at time of biopsy).

Hemodynamic studies in NCIPH patients have shown two independent pressure gradients—one between intrasplenic and intrahepatic pressures and another between intrahepatic and wedged hepatic venous pressures—indicating the likelihood of both pre- and peri-sinusoidal resistance to portal venous blood flow [13]. While thrombosis of portal venous microcirculation can explain pre-sinusoidal resistance in NCIPH [13], we postulate that extension of thrombosis into sinusoids and small hepatic veins is an explanation for peri-sinusoidal resistance. Accordingly, the interval between first presentation with NCIPH and first indication of liver failure (22 (2–126) months in 13 patients) would represent predominantly portal venous involvement while the onset of liver failure reflected progression from pre-sinusoidal to parenchymal disease.

In the splanchnic venous system of patients with NCIPH and celiac disease, we have postulated that elevated serum CLPA antibodies (produced by gluten-induced enterocyte apoptosis) arising from the gut may travel upstream and obliterate small portal vein radicles, the first filter for splanchnic venous blood [9]. It is plausible that as postulated in celiac disease [9], increased gut epithelial apoptosis in ulcerative colitis [14] can lead to elevated serum CLPA antibodies, obliteration of portal venous microcirculation, and NCIPH. In the current study cohort, celiac disease (in five of 31 NCIPH patients (16%) tested) and ulcerative colitis (in three of 34 (9%) patients) were over-represented.

Association of elevated serum CLPA antibody, celiac disease, and NCIPH is being increasingly recognized [9, 15]. Of five NCIPH patients with celiac disease in the current series, celiac disease was recognized after diagnosis of NCIPH in three (Table 3). Delayed diagnosis of celiac disease causing prolonged exposure to gut-derived prothrombotic factors may explain why celiac disease was a negative determinant of transplant-free survival in our study (Fig. 2). We did not find elevated serum CLPA antibody in 16 patients with celiac disease without concomitant liver disease.

We chose Budd–Chiari syndrome as a control group to analyze the prevalence of elevated serum CLPA, a candidate prothrombotic factor of gut origin associated with NCIPH [9]. We postulated that despite being a thrombotic disorder, a gut-derived prothrombotic factor would not be expected to be present in Budd–Chiari syndrome. It is of interest that only one among the 18 Budd–Chiari patients (6%) we studied had a minimal elevation of serum CLPA; while significantly higher prevalence of elevated serum CLPA antibody (36%) and higher titers of serum CLPA antibodies, when elevated, was seen in NCIPH patients.

Schistosomiasis [16], toxins/drugs (arsenic [17, 18], vitamin A [19], azathioprine [20], 6-thioguanine [21, 22]), immune disorders (Felty's syndrome [23], common variable immunodeficiency disorder [24, 25]) and myeloproliferative syndromes [26] are associated with NCIPH. The current study suggests that gut disorders are yet another association to be looked for in patients with NCIPH. We did not analyze the details of drugs ingested by the study patients—this is a limitation of the current study.

NCIPH is an under-recognized entity that closely mimics cirrhosis and needs a strong index of suspicion to make this diagnosis [27]. How can the diagnosis of NCIPH be confirmed? [27, 28]. In patients with cryptogenic intrahepatic portal hypertension, a liver biopsy showing preservation of normal vascular relationships with the absence of advanced fibrosis or cirrhosis is required to make a diagnosis of NCIPH. Additional findings supporting the diagnosis of NCIPH are the presence of sclerotic portal tracts lacking appropriately sized portal vein branches and features of nodular regenerative hyperplasia in the liver parenchyma. Nodular regenerative hyperplasia may be difficult to recognize in routinely stained sections and reticulin staining is therefore recommended to demonstrate this often-subtle lesion. The vascular and architectural changes that characterize NCIPH are typically patchy in distribution, and are

therefore prone to sampling variability, particular if small liver biopsy samples are obtained. Hepatic vein pressure studies provide support to the diagnosis: hepatic vein pressure gradient <5 mmHg is noted in the pre-sinusoidal phase of NCIPH and ≥ 5 mmHg can be seen in the later stages of NCIPH [27].

In a recent report from South India, 30 of 62 patients (48%) thought to have 'cryptogenic cirrhosis' were actually found to have NCIPH after detailed evaluation [29]. The current study suggests that the diagnosis of NCIPH should be considered in the following scenarios: patients labeled as having 'cryptogenic cirrhosis' with near-normal liver functions as well as in those in liver failure; patients with chronic liver disease along with gut disorders (celiac disease or ulcerative colitis) or with any condition associated with NCIPH (as mentioned above) and patients with chronic liver disease and elevated serum IgA cardiolipin antibody levels.

What are the future research questions to study intrahepatic portal vein occlusion leading to NCIPH? Systematic analysis of patient cohorts with disorders known to be associated with NCIPH needs to be done to better delineate the incidence of NCIPH. Detailed study of the intrahepatic portal vein branches (as shown in NCIPH associated with myeloproliferative disorders [26]) needs to be done in NCIPH associated with different predisposing conditions. The mechanisms of disease linking intrahepatic portal vein occlusion with gut disease need to be elucidated. Whether treating these gut disorders (e.g., gluten-free diet to treat celiac disease) will improve the natural history of NCIPH needs to be studied.

In conclusion, we document progression to decompensated liver disease in 53% of NCIPH patients studied (38% either died or underwent liver transplantation during the study period) and have identified factors predicting transplant-free survival. The association with celiac disease and ulcerative colitis and the prevalence of elevated serum IgA anticardiolipin antibodies in this predominantly Caucasian study cohort supports the hypothesis that factors of an enteric origin contribute to intrahepatic portal vein obliteration in NCIPH.

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