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Idiopathic non-cirrhotic portal hypertension

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ABSTRACT

Idiopathic non-cirrhotic portal hypertension (INCPH) is a rare disorder consisting of intrahepatic portal hypertension in the absence of other identifiable intrinsic liver diseases and/or splanchnic vein thrombosis. The exact pathophysiology of INCPH is yet to be determined. This disorder is linked with several conditions such as immunological disorders, chronic infections, prothrombotic disorders, genetic predisposition and/or toxins. There is no specific positive diagnostic test. The diagnosis of INCPH is based on a high index of suspicion, a set of clinical criteria and exclusion of other causes of portal hypertension. Liver biopsy is mandatory to firmly rule out cirrhosis or other causes of liver diseases. The patency of splanchnic venous system should be also demonstrated. Most patients present with signs or symptoms of portal hypertension (i.e. gastro-esophageal varices, variceal bleeding), which should receive the same management strategy as per the current accepted guidelines in cirrhosis. The prevalence of portal vein thrombosis in INCPH ranges from 13-46%. Although liver function is usually preserved and prognosis is generally good, some patients may develop liver-related complications that would eventually require liver transplantation and/or that would overshadow long-term prognosis.

List of abbreviations

CSPH: Clinically significant portal hypertension; EV: esophageal varices; INCPH: idiopathic non-cirrhotic portal hypertension; HE: hepatic encephalopathy; HIV: human immunodeficiency virus; HPS: hepatopulmonary syndrome; HVPG: hepatic venous pressure gradient; LT: liver transplant; OPV: obliterative portal venopathy; PVT: portal vein thrombosis; TIPSS: Trans-jugular intrahepatic portosystemic shunting.

Introduction

Idiopathic non-cirrhotic portal hypertension (INCPH) is characterized by intrahepatic portal hypertension in the absence of cirrhosis or other causes of liver disease and splanchnic venous thrombosis[1-20]. INCPH is considered a formal rare disease, as endorsed by many rare diseases networks and consortiums (Orpha number: ORPHA64743). INCPH has also been referred as non-cirrhotic portal fibrosis, hepatoportal sclerosis, incomplete septal cirrhosis, obliterative portal venopathy and partial nodular transformation. Histological findings are non-specific and comprise a wide range of features, from minor changes to sinusoidal dilatation, phlebosclerosis and portal fibrosis and nodular regenerative hyperplasia. It is still unclear whether this wide variety of histological changes reflects different stages of the disease, or a wider array of nosologic entities under the term *"INCPH"* that share the same clinical presentation. A recent retrospective study has shown how patients with obliterative portal venopathy (OPV) and absence of portal hypertension share some clinico-pathological features with INCPH patients and clear portal hypertension manifestations[1,4,5,7,12]. Authors proposed that

OPV might represent a pre-symptomatic phase of INCPH. However, this association needs further validation with prospective studies.

Epidemiology

INCPH has a worldwide distribution but it seems to be especially prevalent in Asia (India, Nepal, and Japan)[3,6,10,14,21,22]. In Western series median age at diagnosis is 30-50 years, with a predominance of male gender[6,12,17]. In India the disease has also a male predominance but tend to debut at a younger age [1,15]. Conversely, in Japan there seems to be a female predominance with an onset on the fifth decade[1,3,5,7,8]. Differences in socioeconomic status, living conditions, and ethnicity may also play a role in the different prevalence across series and countries[3,6,8,13,18,23,24].

Etiology and pathogenesis

The exact pathogenic mechanisms of INCPH remain unclear[1,5-7,18,24]. To date, five disease categories have been proposed to participate in the pathogenesis of the disease: immunological disorders, prothrombotic conditions, genetic factors, infection agents, and medications/toxins (figure 1 & table 1). Actually, a combination of more than one of these factors is frequently found in these patients.

Immunological disorders

INCPH has been associated with many immunological diseases (figure 1 & table 1)[1,5-7,11,12,20,24-26]. One of the proposed mechanisms involves an imbalance in several immunoglobulins or inflammatory cytokines, frequently found in autoimmune diseases, resulting in micro-thrombosis or fibrogenesis[3,5,6,9,13,17,18,20,24]. In addition, the ratio of Th1 and Th2 cells in peripheral and spleen lymphocytes was found increased in INCPH patients[4,27-30]. Serum levels of IL-6 and IFN-γ, which regulates Th1 and Th2 differentiation process, were higher in INCPH patients compared to control subjects[3,6,18,21,22,24,25,31]. The balance between Th1 and Th2 lymphocytes has a crucial role in regulating the immune system, and has been involved in the pathogenesis of many immunological disorders[1,3,5,7,8,12,32].

Prothrombotic conditions

Hypercoagulable states have been identified in 8-50% of INCPH patients[6,8,11,12,17-19,23,24]. Moreover, the high prevalence of portal vein thrombosis (PVT) in these patients supports a prothrombotic hypothesis for this disease[1,3,5-7,9,12,13,17,18]. Presumably, pre-existing hypercoagulability states lead to chronic repetitive microthrombi in portal venules, resulting in peri-portal fibrosis and obliteration[1,4-7,11,12,15,17,19,20].

Genetic factors

INCPH has been associated with several congenital disorders (e.g., Turner's syndrome, Shwachmann-Diamond syndrome, Marfan syndrome)[1,3,5,7,12,21,22]. In addition, there is familial aggregation in INCPH, and there is evidence of genetic aberrations (e.g., high prevalence of HLA-

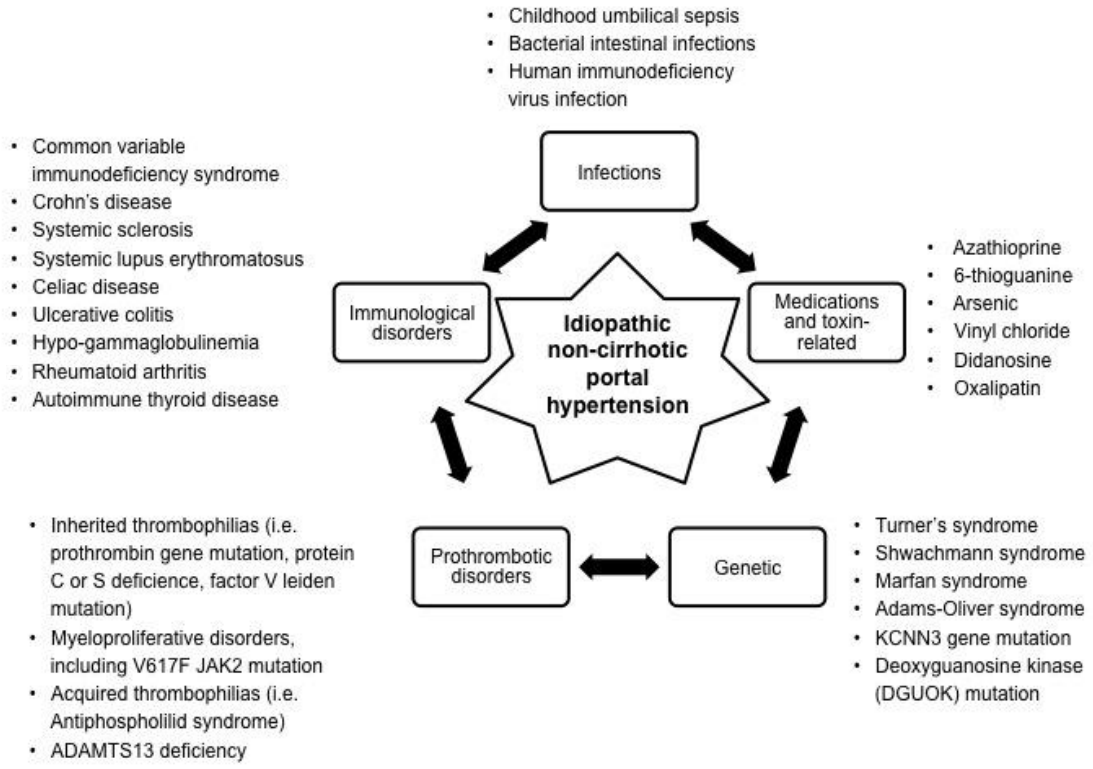

Figure 1: Conditions associated to INCPH

	Guido et al.[4] [a]	*Siramolpiwat et al.*[6]	*Schouten et al.*[12]	*Cazals-Hatem et al.*[11]	*Eapen et al.*[9]	*Hillaire et al.*[17]	*Madhu et al.*[21]	*Dhiman et al.*[38]
Country	Italy	Spain	Netherlands	France	UK	France	India	India
N	20	69	62	59[b]	34	28	30	151
Male:Female ratio	5.7:1	1.9:1	1.1:1	2:1	2.4:1	2.5:1	1.7:1	1:1.7
Age at diagnosis (mean±SD, years)	47±12	42±19	46±18	48.5±15	38.5	41.8±15	32	30.5
Follow up (mean±range, years)	ND	6 (1-18)	7.5 (2-25.8)	8.6 (1–23)	7.3 (0.2-22.6)	7.6 (1-21)	ND	ND
Presence of portal hypertension signs at diagnosis	100% All patients have esophageal varices and splenomegaly	100% • Splenomegaly & thrombocytopenia (53%) • Variceal bleeding (28%) • Ascites (10%) • Dyspnea (4%) • Abnormal blood tests (5%)	82% • Variceal bleeding (44%) • Splenomegaly (28%) • Abnormal ultrasound or endoscopy (15%) • Pancytopenia (15%)	64% • Variceal bleeding (20%) • Splenomegaly (17%) • Ascites or pleural effusion (14%) • Non-bleeding varices (12%)	100% All patients have at least 2 of the followings: varices, hypersplenism, ascites and/or HVPG>5mmHg	79% • Variceal bleeding (32%) • Splenomegaly (36%) • Non-bleeding varices (11%)	100% • Splenomegaly (60%) • Variceal bleeding (30%) • Ascites (10%)	90% • Splenomegaly (69%) • Variceal bleeding (65%) • Ascites (9%)
Associated disorders	45% • Prothrombotic disorders (25%) • Immunologic disorders (15%) • HIV infection (5%)	43% • HIV infection (22%) • Immunologic disorders (10%) • Hematologic disorders (9%) • Prothrombotic disorders (8%)	58% • Medications or toxin-related (19%) • Hematologic disorders (19%) • HIV infection (8%) • Immunologic disorders (8%) • Malignancies (6%)	47% • Prothrombotic disorders (31%) • Immunologic disorders (16%)	21% Autoimmune gastrointestinal diseases (21%)[c]	48% • Prothrombotic disorders (48%)	ND	ND
Liver transplantation and indications	ND	3% • HPS (n=2)	10% • Liver failure (n=2) • Chronic HE (n= 2) • HPS (n=1) • Liver tumour (n=1)	15% • Liver failure (n=7) • HPS (n=2)	9% • HPS (n=1) • Liver failure (n=1) • Post-TIPSS liver failure (n=1)	N/A	N/A	N/A
Mortality rate	ND	10% (n=7)	37% (n=23)	8% (n=5)	29% (n=10)	N/A	N/A	N/A
Causes of death	ND	**Liver related (n=6)** • Multiorgan failure (n=2) • Operation or procedure-related complications (n=2) • Pneumonia (n=1) • Shock post-EV bleeding (n=1) **Non-liver related (n=1)** Subarachnoid haemorrhage (n=1)	**Liver related (n=17)** • Liver failure (n=9) • Bleeding complications (n=4) • HPS (n=4) **Non-liver related (n=19)** • Malignancy (n=10) • Cardiac disorders (n=4) • Neurological disorder (n=2) • Renal insufficiency (n=2) • Infection (n=1)	**Liver related (n=4)** • Sepsis (n=2) • Hepatopulmonary syndrome (n=1) • Multiorgan failure (n=1) *3 of them 1 year after LT* **Non-liver related (n=1)** Hemorrhagic stroke (n=1)	**Liver related (n=9)** • Post-TIPSS liver failure (n=3) • Infection and liver failure (n=2) • Variceal bleeding (n=1) • Mesenteric vein thrombosis and liver failure (n=1) • Liver failure (n=1) • Procedure-related complications (n=1) **Unknown (n=1)**			

Table 1: Clinical characteristics and outcomes of INCPH patients from 8 studies

[a]Guido et al study included also n=94 patients with OPV without any clinical sign of portal hypertension. It should be noted that this study lacks of follow up so it is unknown whether portal hypertension may develop in some of the OPV patients as previously described by Cazals-Hatem et al.

[b]Thirteen patients (22%) had portal vein thrombosis at diagnosis

[c]Celiac disease (12%), Ulcerative colitis (6%) and both conditions (3%)

Abbreviations: EV: esophageal varices; HE: hepatic encephalopathy; HIV: human immunodeficiency virus; HPS: hepatopulmonary syndrome; HVPG: hepatic venous pressure gradient; ND: not detailed; TIPSS: transjugular intrahepatic portosystemic shunt.

DR3, KCNN3 gene or deoxyguanosine kinase –DGUOK-mutations) in some of these patients[3,6,8,10,14,16]. This information points towards a possible genetic component in INCPH.

Infection agents

The association between umbilical sepsis or recurrent abdominal infection and the development of INCPH suggest an infectious background for this disease[1,5,7,8,18,23,24]. The high prevalence of INCPH in low socioeconomic areas with a high rate of abdominal infections in early childhood further supports this theory[1,3,5-7,13]. INCPH has been also reported in patients with human immunodeficiency virus (HIV) infection[1,5-7,11,12,18,20,24]. Although the definite

pathogenesis remains unclear, it appears that endothelial and mitochondrial injury related to specific highly active antiretroviral therapy medications could have a dominant causative role. A recent study in more than 18,000 Dutch HIV patients reported a prevalence of INCPH of 0.09%[3,5,6,9,13,17,18,20,24-26]. In this study, prolonged exposure to didanosine with or without stavudine increased the risk of developing INCPH. Of note, 2% of HIV patients who have been exposed to didanosine develop INCPH[4,6,24,29]. A predisposition to a hypercoagulable state has also been documented in HIV patients[3,21,22,27,28,30,31]. In INCPH, a higher incidence of PVT has been reported in HIV-related compared to non-HIV INCPH patients[3,6,8,18,24,25,32]. These findings support a role of underlying hypercoagulability resulting in micro-vascular thrombosis, and eventually leading to the development of full-blown INCPH.

Medications and toxins

Exposure to certain medications and toxins has been associated with INCPH. Among those, azathioprine, 6-thioguanine and arsenic as Fowler's solution are the most frequently described drugs [1-3,5-8,11,12,17-19,23,24,33].

The unifying hypothesis proposes that repeating micro-thrombotic events in small or medium branches of portal veins lead to INCPH[1,6,11,12,15]. However, the dual theory suggests that intrahepatic obstruction from obliterative portal venopathy, and an increased splenic blood flow jointly contribute to INCPH[1,5,6,12]. Proposed mechanisms for portal venules obliteration are aberrant coagulation activation or thrombosis, acquired or inherited disorders of vascular remodeling, and endothelial injury from immune cells[1,5,7,34]. Serum connective tissue growth factor, a modulator of potent fibrogenic cytokines, is significantly higher in INCPH patients than in HCV-infected patients or healthy controls[35]. Moreover, an imbalance between intrahepatic vasodilators and vasoconstrictors, a common feature in cirrhosis, has also been reported in hepatic tissue of INCPH patients[36]. A more recent pathogenic theory implicates myfibroblastic changes of portal venule endothelial cells (i.e., endothelial-mesenchymal theory)[37].

Clinical manifestations

Patients with INCPH usually present with unequivocal signs of portal hypertension (table 1)[4,6,9,11,12,17,21,38]. In a recent series, 60% of patients were asymptomatic at diagnosis; INCPH was diagnosed during the investigation of thrombocytopenia and splenomegaly[6]. In symptomatic cases, variceal hemorrhage was the most frequent initial clinical manifestation. Notably, liver function tests are generally preserved in INCPH patients. This makes variceal bleeding usually well tolerated; with a 6-week mortality rate less than 4%[6,12]. In those patients without variceal bleeding at diagnosis, varices are found in almost 75% at initial endoscopy, mostly of them large, requiring primary prophylaxis[6]. In those without varices or with small varices at diagnosis, the annual incidence of developing varices or varices growth is similar to that reported in compensated cirrhotic patients. In this study, the 1-year probability of developing variceal bleeding despite primary prophylaxis was 9%, and variceal re-bleeding despite secondary prophylaxis was 22%[6].

Ascites is present in around 30-50% of patients[6,12]. It usually develops in association with other concurrent events (e.g., infection, variceal bleeding). It is mainly transient and easily-controlled by correcting the trigger, and low-dose of diuretics[6,12]. Hepatic encephalopathy is rare. Most reported cases were as a results of trans-jugular intrahepatic portosystemic shunting (TIPSS) placement or triggered by infection[6,12]. Hepatopulmonary syndrome, portopulmonary hypertension and hepatocellular carcinoma have been sporadically reported in INCPH[1,5,7].

Portal vein thrombosis was reported in up to 40% of cases[6,12,17,19]. HIV patients seem to have a higher risk of developing PVT than those without HIV[6]. Ultrasonographic surveillance for PVT in INCPH, particularly in high-risk patients, is recommended. Whether development of PVT affects the prognosis of INCPH requires further investigation, but it may preclude TIPSS implantation or liver transplantation[5,6,19].

Diagnosis

The diagnosis requires the exclusion of other causes of liver diseases and/or portal hypertension. The absence of a specific positive diagnostic test probably favors INCPH underdiagnosis since a significant proportion of patients are erroneously diagnosed as cirrhotics[6,27,39]. The diagnosis criteria are[5]: 1) presence of unequivocal signs of portal hypertension (e.g., gastroesophageal varices, ascites, and/or splenomegaly); 2) absence of cirrhosis, advanced fibrosis or other causes of chronic liver diseases that can cause portal hypertension and; 3) absence of thrombosis of the hepatic veins or of the portal vein. The current diagnostic tests for INCPH are detailed in table 2.

Histology findings in the liver biopsy are non-specific and very heterogeneous, ranging from minor changes to sinusoidal dilatation, phlebosclerosis, portal fibrosis and nodular regenerative hyperplasia. An adequate histological evaluation by an expert liver pathologist is crucial. Table 3 summarizes the morphological findings in the liver biopsy of patients with INCPH.

Treatment

There is no specific therapy for patients with INCPH; treatment is based on managing its complications, mainly portal hypertension and PVT. Data on specific management and prophylaxis of variceal bleeding in INCPH patients are scarce. Expert's opinion recommends following the guidelines of prophylaxis and management of portal

Mandatory diagnostic tests [5,7,25]	
Medical history	• Investigate presence of concomitant diseases • Investigate exposure to drugs, toxins • Investigate familial association
Blood test	• Rule out other causes of liver diseases (i.e. autoimmune hepatitis, cholestatic diseases, viral hepatitis) • Assess the presence of hypersplenism (i.e. thrombocytopenia, leukopenia, anemia)
Abdominal imaging [a]	• Determine the presence of radiological signs of portal hypertension such as splenomegaly, collaterals or ascites • Asses the patency of splanchnic venous axis • Assess liver morphology, parenchyma, and biliary tree. Most patients present radiological signs of chronic liver disease (i.e. liver surface nodularity) despite the lack of histologic cirrhosis [27].
Liver biopsy	• Rule out cirrhosis and/or other causes of liver diseases or portal hypertension (i.e. NAFLD, congenital fibrosis, sarcoidosis, schistosomiasis…)
Optional diagnostic tests	
HVPG[b]	HVPG is normal (≤5mmHg) or slightly increased (5-10mmHg) but below the previously described cut-off for CSPH in cirrhosis (HVPG>10 mmHg) [40,41]
Transient elastography (Fibroscan®)[b]	• Liver stiffness value is lower than the described cut-off values for diagnosis cirrhosis, varices and CSPH in cirrhosis [18,40]
ARFI	• The spleen/liver stiffness ratio is higher in INCPH compared to cirrhosis and chronic hepatitis [42]

Table 2: Diagnostic tests for INCPH
[a]Doppler ultrasound in addition to CT angiography or MRI angiography is recommended
[b]Values for HVPG and liver stiffness than those described for cirrhosis and CSPH can be helpful by ruling out cirrhosis in a patient with signs of PH.
Abbreviations: ARFI: Acoustic radiation force impulse; CSPH: clinically significant portal hypertension; HVPG: hepatic venous pressure gradient; NALFD: non-alcoholic fatty liver disease.

Portal tracts & periportal area	• Hypoplastic portal tracts • Dilated portal veins • Portal sclerosis (fibrous thickening of the portal vein wall leading to lumen obliteration) • Periportal fibrosis • Abnormal spacing between portal tracts and veins • Increased number of vascular structures in the portal tracts • Arterialization of the wall of portal veins • Paraportal shunting vessels
Parenchyma	• Sinusoidal dilatation • Congestion and pericellular fibrosis • Aberrant hepatic vessels • Dilatation of the central vein with or without perivenular fibrosis • Incomplete septa • Nodular regenerative hyperplasia

Table 3: Histological features associated with INCPH
References: [43-45]

hypertension in cirrhotic patients[5,25,26]. A recent cohort study reported good long-term outcome of INCPH by applying a management strategy based on current guidelines for cirrhotic variceal bleeding [6]. TIPSS is an effective alternative in patients who fail to respond to medical and endoscopic therapy. Although portal hypertension related complications are successfully controlled and liver function is usually well preserved, some patients may require a liver transplant (LT). The indications for LT include unmanageable portal hypertension complications, progressive liver failure, chronic hepatic encephalopathy, hepatopulmonary syndrome and hepatocellular carcinoma (table 1). Post-LT outcomes of INCPH patients are good and the disease tends not to recur[27]. However, data on this issue are still limited and mostly based on small cohorts.

Anticoagulation has been proposed to prevent disease progression regardless of PVT. However, there is not enough evidence to recommend this treatment. The potentially added risk of anticoagulation over the portal hypertension bleeding risk needs to be factored in the decision to initiate anticoagulation. It may, however, have a role in patients with underlying prothrombotic diseases or to treat PVT[6,25]. Many questions remain open such as which patients may benefit from anticoagulation, which is the best drug or what is the optimal duration for anticoagulation.

Prognosis

INCPH patients have a benign long-term outcome, with a 5-year survival of nearly 100%[3,7,12], which is probably by virtue of preserved liver synthetic function. However,

over the past few years, studies have shown that some INCPH patients (3-15%) may develop severe liver-related complications that lead to death or liver transplantation[6,11,12]. The 10-year mortality rate of INCPH is between 18 and 44% (table 1). Two recent studies have shown that ascites is a poor predictor of survival[6,12]. Development of ascites may indicate advance hepatic sinusoidal injury, what suggests severe liver-related complications. A study from Japan that compared the prognosis of patients with ascites in INCPH and cirrhosis and showed how patients with INCPH have a higher rate of variceal bleeding and PVT[34]. Conversely, ascites did not have any impact on INCPH survival as compared with cirrhosis (1- and 5-year survival was 100% in INCPH *vs.* 69.1% and 34.4% in cirrhosis)[34].

Two studies have concordantly shown that immunologic disorders or malignancy have a deleterious impact on INCPH long-term prognosis[6,11]. The study[12] that reported a mortality rate of 37% in INCPH included a significantly higher number of patients with immunologic disorder or malignancy compared to the other studies[6,11]. Whether INCPH patients with these associated disorders should be managed differently, other than correcting complications related to portal hypertension, merits further investigation.

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