Idiopathic Noncirrhotic Portal Hypertension: What Is It?

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Portal hypertension is defined as an increase in portal pressure gradient, that is, the pressure difference between the portal vein and the inferior vena cava.

Cirrhosis is by far the most common cause of portal hypertension in Western countries. Less than 10% of cases of portal hypertension are due to causes other than cirrhosis, and these are included in a broad category designated "noncirrhotic" portal hypertension. Whereas cirrhosis is an intrahepatic cause of portal hypertension (ie, the site of increased resistance is in the liver), in noncirrhotic portal hypertension, the site of increased resistance can be intrahepatic but also extrahepatic (pre- or posthepatic). Classification and distinct recognized causes of noncirrhotic portal hypertension are listed in Table 1.

Strictly, "idiopathic" noncirrhotic portal hypertension (INCPH) is a type of noncirrhotic portal hypertension for which there is no clear cause. That is, it is established when cirrhosis and all entities listed in Table 1 are excluded.

The nomenclature of INCPH has been controversial; what is now recognized as the same entity has had different names in different countries. In India, it is known as noncirrhotic portal fibrosis; in Japan and other Asian countries, it is known as idiopathic portal hypertension.[1] In Western countries, where it is much rarer, it is also known as hepatoportal sclerosis (a histological diagnosis). Other histological entities such as incomplete septal cirrhosis and nodular regenerative hyperplasia have also been categorized as INCPH.[1]

INCPH—A Spectrum of Histological Findings

The common histological finding identified in the liver of patients with INCPH both in countries with high and low prevalence is "phlebosclerosis",[2-4] that is, intrahepatic portal venules that have a reduced or obliterated lumen in a fibrotic portal tract. Obviously, and depending on the number of portal venules affected, loss of patency of portal venules will lead to an increase in intrahepatic resistance and to presinusoidal portal hypertension.

Therefore, an evolving concept is that INCPH results from microvascular injury to small intrahepatic portal vein branches leading to their obliteration, and thus the term "obliterative portal venopathy."[5]

As the disease progresses and according to Wanless,[6] obliteration of portal venules results in an irregular distribution of blood flow resulting in atrophic areas (those that are underperfused) alternating with areas of regeneration (compensatory hyperplasia in better-perfused areas), leading to nodular regenerative hyperplasia, the second most common histological finding in patients with INCPH.[4] Eventually, and as is known to occur with extrahepatic vein occlusion (portal vein thrombosis), incomplete septal fibrosis may ensue but patients will not develop full-blown histological cirrhosis.[5]

INCPH—A Spectrum of Etiopathogenic Factors

It has also become evident that there are different types of injury that can lead to obliterative portal venopathy: autoimmune, infectious, toxic, prothrombotic, and genetic factors, which may indicate an underlying susceptibility to develop the disorder with injury, have been described underlying this entity (Table 2).[7]

The type of injury may vary by geographic location. For example, chronic exposure to antigenemia of intestinal origin causes inflammatory reactions in portal tracts, and this may explain the fact that INCPH is frequently seen in patients from low socioeconomic regions where the

Abbreviation: INCPH, idiopathic noncirrhotic portal hypertension.

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TABLE 1 Nonidiopathic Noncirrhotic Portal Hypertension

Extrahepatic	Prehepatic	Splenic vein thrombosis Portal vein thrombosis Extrinsic compression of splenic/portal vein Arteriovenous fistula
	Posthepatic	Hepatic vein thrombosis (Budd-Chiari syndrome) IVC membrane or thrombus Constrictive pericarditis
Intrahepatic	Presinusoidal	Schistosomiasis Portal granulomas (sarcoidosis, tuberculosis) Small bile duct disease (PBC, small duct PSC) Congenital hepatic fibrosis Polycystic disease
	Sinusoidal	Sinusoidal fibrosis (methotrexate, alcohol, vinyl chloride) Amyloidosis Infiltration (mastocytosis, Gaucher disease) Hepatocyte enlargement (acute fatty liver)
	Postsinusoidal	Sinusoidal obstruction syndrome

prevalence of intestinal infections at birth or in early childhood is high.[4] In Western countries, toxic injury (such as with didanosine in HIV patients) and prothrombotic disorders may play a more important role.[7] Interestingly, it is now also well recognized that patients with INCPH, mostly in Western countries, have a high incidence of extrahepatic portal vein thrombosis which would support underlying hypercoagulability.[5]

Although a dual theory, implicating both increased intrahepatic obstruction and increased splenic blood flow, has been hypothesized regarding the development of INCPH,[2] the pathogenesis of portal hypertension in this entity could be explained solely on the basis of portal venule obliteration with secondary portal hypertension that would in turn lead to a hyperdynamic circulatory state with increased splenic blood flow (among others) as amply described by Groszmann in experimental models of prehepatic portal hypertension.[8]

INCPH—A Spectrum of Clinical Findings

INCPH is considered a benign entity in which, at least initially, portal hypertension is presinusoidal. In fact, obliterative portal venopathy is not always associated with portal hypertension.[5,6] One can surmise that portal hypertension would develop once a "critical mass" of portal venules is obliterated.

Once portal hypertension develops, it can be entirely asymptomatic, and initially, may be only associated with laboratory abnormalities such as thrombocytopenia or imaging abnormalities such as portal vein enlargement, splenomegaly, and/or collaterals (without varices). This will evolve to the development of gastroesophageal varices and then variceal hemorrhage, which is the typical clinical presentation.

As in any presinusoidal entity, liver synthetic function is normal and there is no ascites because hepatic sinusoids are normotensive. The predominantly presinusoidal nature of the entity has been confirmed in a study measuring hepatic venous pressure gradient, which is a measure of sinusoidal pressure, that showed normal pressure in 22% and mild in 60% of the cases.[9] However, in 8% of the cases, there was clinically significant portal hypertension.[9] In fact, it is now recognized that these patients may develop ascites, encephalopathy, and hepatopulmonary syndrome with some of them requiring liver transplantation.[5,10] A recent study showed that INCPH is not as seemingly "benign", with 10-year overall survival of only 56%.[11]

What Is Idiopathic Noncirrhotic Portal Hypertension?

What we have learned over the years, and as I have described above, INCPH is not generally idiopathic, it can end up behaving like cirrhosis and require liver transplant, and in its initial stages, it may not even be associated with portal hypertension.

Although histological, for now the most adequate term to describe the entity would be "obliterative portal venopathy."[3,5] The entity is characterized by damage to portal venules that results in their obliteration, which could progress

TABLE 2 Conditions That Have Been Associated With INCPH

Type	Specific Condition	Purported Mechanism
Autoimmune	Autoimmune hepatitis Primary biliary cirrhosis Systemic lupus erythematosus Scleroderma Rheumatoid arthritis Common variable immune deficiency Celiac disease	Immune-mediated venulitis and/or thrombophilia leading to obliteration and then fibrosis
Infectious	Repeated gastrointestinal infections HIV	Septic emboli to portal venules Hypercoagulability, didanosine
Drug-induced	Didanosine Azathioprine 6-Thioguanine Oxaliplatin	Toxic injury
Prothrombotic	Myeloproliferative disorder Protein C/S deficiency Factor II deficiency ADAMTS13 deficiency	Chronic microthrombi in portal venules leading to fibrosis and obliteration
Genetic	Turner's syndrome Adams-Oliver syndrome Familial cases	Abnormal development or vascular malformations Confers susceptibility in face of other conditions?

to an intrahepatic presinusoidal type of portal hypertension and later on to postsinusoidal disease that may mimic cirrhosis. Therefore, it has a wide spectrum of clinical features, from lack of portal hypertension, to varices that have not bled, to variceal hemorrhage, and finally to complications suggestive of cirrhosis (eg, ascites, encephalopathy, hepatopulmonary syndrome).

The issue of an erroneous nomenclature is not only semantic but has clinical implications. The term "idiopathic" may lead to lack of appropriate workup for conditions that are potentially treatable (such as immune and prothrombotic disorders). The term "noncirrhotic" suggests that these patients will never need liver transplantation and will not die from the disease, leading to a false sense of security. Finally, although its main clinical manifestations are related to portal hypertension, obliterative portal venopathy can be present before portal hypertension even develops (in which case the term "portal hypertension" would also be inaccurate), but these patients would need to be worked up and monitored for the development of portal hypertension. ■

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