

# The current clinical aspects of idiopathic portal hypertension

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## Summary

**Idiopathic portal hypertension (IPH) comprises disorders developing increased portal pressure in the absence of cirrhosis: the clear mechanisms to explain this disease are still not well recognized. IPH usually suggests a benign prognosis, but sometimes is complicated with severe hemorrhage due to ruptured esophageal varices, or massive splenomegaly. Conventional treatments for those complications for patients with cirrhosis usually works when diverted to patients with IPH, although some of those patients might require liver transplantation if the treatment fails. However, there are few consistent treatment strategies for IPH itself, its complications or the indications for liver transplantation. In this mini review, we summarize the clinical manifestations and several potential theories to explain the etiology, as well as the current treatment options for IPH.**

**Keywords:** Idiopathic portal hypertension (IPH), non-cirrhotic portal fibrosis, nodular regenerative hyperplasia (NRH), Idiopathic noncirrhotic portal hypertension

## 1. Introduction

Portal hypertension is a clinical manifestation which is defined as the presence of a porto-caval venous pressure gradient  $> 5$  mmHg (1). The most common cause of portal hypertension is liver cirrhosis. There are, however, a variety of disorders which develop portal hypertension without cirrhosis: Idiopathic portal hypertension (IPH) is one of the most important etiologies of portal hypertension without cirrhosis. The name IPH was first proposed by Boyer by excluding liver cirrhosis from Banti syndrome in 1967 (2).

IPH is usually regarded as a disorder with feasible prognosis, and is mainly managed by supportive treatment such as endoscopic, radiological and/or surgical management for esophageal varices and/or splenomegaly. However, it has been reported that IPH sometimes leads to poor prognosis due to gastrointestinal hemorrhage and/or liver failure (3), which would result in liver transplantation or death.

Importantly, the etiology and mechanisms to explain IPH are still uncertain. The main scope of this review is to provide an overview of IPH, including its potential etiologies, clinical manifestations and treatment options.

## 2. Terminology and Epidemiology

Japanese study groups usually use the term of "IPH", whereas Indian researchers prefer to use the term non-cirrhotic portal fibrosis for the name of this disorder. Groups in Western countries have proposed terms such as nodular regenerative hyperplasia (NRH), hepatoportal sclerosis (4), or Idiopathic noncirrhotic portal hypertension (5).

In contrast to its high prevalence in India, IPH is comparatively a rare disorder in Western countries (6). Presumably because of that reason, there are limited recent literatures published to investigate the epidemiology of IPH. Although the amount of literature quoting the epidemiology of this disease remains little, slight male predominance is reported (7).

## 3. Etiology

The definite etiology of IPH is still uncertain, although there are several theories on the potential pathogenesis of IPH. These theories include immunological

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disorders, infections, and genetic variants. There is another potential theory that IPH is associated with prothrombotic disorders ("Thrombosis theory") (8,9), but this theory is very controversial and still needs to be investigated: however, the pathogenesis of IPH seems to be multifactorial.

### 3.1. Immunological disorders

Disease in patients with IPH is sometimes complicated by progressive systemic sclerosis (PSS), systemic lupus erythematosus (SLE) and/or mixed connective tissue disease (MCTD), and hyper-gammaglobulinemia and autoantibodies are frequently seen which suggests underlying autoimmunological disorders in IPH (10-12). It has been reported that the strong expression of HLA-DR or VCMA-1 in endothelial cells of portal branches were seen in patients with IPH, which suggests the vascular endothelial cell could be the target of autoimmunity (13,14).

### 3.2. Infections

Chronic exposure to antigenemia of intestinal origin causes inflammatory reactions in portal tracts, which may trigger the histopathological changes that eventually result in IPH. This theory could be supported by the fact that IPH is frequently seen in patients from comparatively low socioeconomic areas, because abdominal infection at birth or in early childhood may play an important role to establish this potential mechanism (15). In addition, injection of *Escherichia coli* into the portal vein in an animal model was reported to contribute to the development of IPH-like symptoms (16).

### 3.3. Genetic Disorders

There are several reports mentioning that patients with IPH sometimes are observed with familial aggregation (17,18) or among a group of patients with congenital disorders such as "Adams-Oliver" syndrome (19,20) or Turner's syndrome (21). This fact suggests that IPH could be associated with a potential genetic background.

## 4. Diagnosis and clinical manifestations

The diagnosis of IPH is a challenge, as there are no guidelines or consensus on the diagnosis of this disease, so far. Difficulties also are related to the fact that this disease is rarely seen in daily practice, and physicians who first see portal hypertension usually suspect underlying liver cirrhosis (22).

Patients might present with episodes such as gastrointestinal bleeding (esophageal varices) and/or left upper quadrant discomfort/pain (splenomegaly). It is rare to see significant ascites at the initial presentation even

in the context of developed portal hypertension. Those patients could have abnormal liver tests, and undergo ultrasonography. The findings of ultrasonography for patients with IPH are characterized by a thick wall of the portal vein and a nodular liver surface (23-25), which is, however, frequently seen in those with liver cirrhosis as well. Differentiation between IPH and liver cirrhosis seems difficult without liver biopsy. Recent reports suggested the usefulness of transient elastography as a potential surrogate of liver biopsy by estimating liver stiffness (5).

As for the prognosis of IPH, it has been considered to be a benign disorder as long as the main complications such as esophageal varices and hypersplenism are successfully controlled, mainly because of preserved liver synthetic functions. The 5-year death rate was reported to be close to 0% (6), however, a more recent study showed an inferior survival rate (78% survival rate at 5 years) compared to the general population (26). The mortality due to acute hemorrhage in IPH is significantly lower than that observed in those with liver cirrhosis (8,27,28), however, the management of esophageal varices is one of the most important factors in following those with IPH, as variceal bleeding is the dominant cause of death in these patients (29). Once the patients with IPH develop ascitis, the prognosis is reported to be poor (26). As for the predictive factors of survival of patients with IPH, Eapen *et al.* recently has reported that older age at first presentation with IPH, hepatic encephalopathy, and portal vein thrombosis were associated with reduced transplant-free survival (30). Several reports have been published mentioning liver transplantation in patients with IPH: the indications were unsuccessful treatment for portal hypertension, hepatic encephalopathy, hepatopulmonary syndrome, and/or liver failure (22,31).

## 5. Pathological findings of IPH

The liver is often atrophic due to drop off of the peripheral liver. Those findings are usually seen in the late stage of IPH, not in the early stage. Along with liver atrophy, several stages of portal sclerosis could appear. Portal vein or its medium/large branch could be dilated or thickened. Because of the abnormal intrahepatic blood flow, hyperplastic nodules such as nodular regenerative hyperplasia (NRH) or partial nodular transformation (PNT) are often seen. At autopsy, obliterating thrombosis in medium to large portal branches is extensively detected. Based on these findings, Nakamura *et al.* proposed a staging system for IPH which is graded from 1 to 4 according to the degree of disease progression based on the histopathological findings (32).

## 6. Treatment options

As noted above, the main complications of IPH are

represented as esophageal varices and hypersplenism.

### 6.1. Esophageal varices, gastric varices and portal hypersensitive gastropathy

Most of (90%) the patients with IPH develop esophageal varices (33). The esophageal varices in IPH patients are characterized by several specific features. As the wall of the variceal vein (as well as portal vein) is thicker than the varices seen in cirrhotic patients, the varices rarely show a red-color sign. The rate of rupture should be less in IPH patients than cirrhotic patients. Firm evidence of treatment of esophageal varices in IPH patients is limited. Endoscopic sclerotherapy was reported to be effective in controlling ruptured esophageal varices (34). Endoscopic variceal ligation (EVL) is not recognized as the standard of care in this setting due to lack of scientific evidence so far, although it is widely applied in the clinical situation because of the proven superiority of EVL to sclerotherapy in controlling esophageal varices of cirrhotic patients (35).

Portal hypertension in IPH patients, again, is characterized by the preserved liver synthetic function, and the mechanisms of portal hypertension in cirrhotic patients are different because of a liver that remains functioning: hyper-dynamic mesenteric circulation and imbalance in vasoactive mediators should not be observed in IPH. This means that conventional medical treatment for cirrhotic patients such as beta-blockers (36) and angiotensin II receptor antagonists (37) should not be applied equally to patients with IPH due to this mechanism difference. There is one small study which reported the inferiority of medical therapy to endoscopic ligation for the prevention of rebleeding in those with IPH (38).

Gastric varices and portal hypertensive gastropathy are (PHG) less frequently seen in IPH patients than esophageal varices. Gastric varices was reported to be found in one fourth of the Indian IPH patients (39). In patients with liver cirrhosis, nonselective beta-blockers have been shown to suppress blood flow of gastric mucosa, and seems effective in preventing recurrent bleeding from PHG (40).

### 6.2. Hypersplenism

Pancytopenia and severe hypersplenism is now considered as one of the most important indications for splenectomy or partial splenic embolization (PSE), because those therapies have been demonstrated to decrease portal hypertension in these patients (41, 42).

## 7. Conclusion

IPH is a heterogenous disorder with varying clinical pictures, including (a)symptomatic splenomegaly and variceal bleeding. The etiology IPH still needs to

be clarified, and there is no consensus on treatment options for IPH itself or complications such as variceal bleeding or massive splenomegaly. The patients have a relatively well-preserved liver function, but further investigation of its etiology and more detailed clinical characterization is warranted, because some group of patients with IPH may develop into a critical prognosis which might require liver transplantation.

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