ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Idiopathic Noncirrhotic Portal Hypertension

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G&H What is noncirrhotic portal hypertension, and what are the most common causes of this condition?

HJ Noncirrhotic portal hypertension is an increased pressure gradient in the portal system of more than 5 mm Hg without the presence of cirrhosis. A very wide range of diseases can cause noncirrhotic portal hypertension. Worldwide, the most common cause is schistosomiasis, which is highly prevalent in developing countries. In the Western world, the most common causes are liver diseases such as nonalcoholic steatohepatitis, alcoholic hepatitis, portal vein thrombosis, Budd-Chiari syndrome, and sinusoidal obstruction syndrome. Other causes can include congenital liver fibrosis, biliary diseases such as primary biliary cholangitis, certain neoplastic lesions such as lymphoma, and granulomatous diseases such as sarcoidosis.

G&H What are the possible etiologies of idiopathic noncirrhotic portal hypertension?

HJ As the name indicates, we often do not know the exact etiology. Idiopathic noncirrhotic portal hypertension has been associated with immunologic disorders such as systemic lupus erythematosus or primary hypogammaglobulinemia, infections such as HIV, toxins or medications such as azathioprine and didanosine, and prothrombotic disorders leading to microthrombosis in the liver. The diagnosis of idiopathic noncirrhotic portal hypertension is made by histologic exclusion of cirrhosis and the exclusion of other liver diseases that cause noncirrhotic portal hypertension, as previously mentioned.

G&H What is the pathophysiology of idiopathic noncirrhotic portal hypertension?

HJ Most importantly, there is an increased parenchymal vascular obstruction, whereas other forms of noncirrhotic portal hypertension are associated with distinct liver diseases and probably have less of a vascular etiology. In the idiopathic form, portal venous obliteration is present and caused by the aforementioned causes (immunologic disorders, infections, medications, and thrombophilia). In some instances, there may also be an increased splenic blood flow. Observed disease remission after splenectomy supports the pathogenetic significance of the often massive splenomegaly.

G&H When should idiopathic noncirrhotic portal hypertension be suspected in a patient?

HJ Roughly 70% of patients with idiopathic noncirrhotic portal hypertension present with gastrointestinal hemorrhage (ie, esophageal varices or portal hypertensive gastropathy). Many of these patients do not have symptoms until the hemorrhage occurs. Some patients present with splenomegaly and have abdominal pain or distention as a result. Rarely, patients have hepatic encephalopathy (mostly caused by massive portosystemic shunting), and ascites have been found in roughly 40% of patients. The big difference between noncirrhotic and cirrhotic portal

hypertension is that in the latter condition, the liver is damaged in such a way that its function is impaired. In contrast, patients with noncirrhotic portal hypertension have a relatively preserved functional capacity of the liver. The machinery still works, unlike with end-stage cirrhosis, but there is an obstruction causing the portal hypertension.

G&H How is idiopathic noncirrhotic portal hypertension usually diagnosed?

HJ Typically, the physician starts with an ultrasound of the liver, where sometimes there is suspicion of cirrhosis, but a good ultrasonographer may be able to distinguish between cirrhotic and noncirrhotic portal hypertension. However, that is challenging to do. What can be seen clearly on an abdominal ultrasound is features of portal hypertension and, not seldom, thickening of portal vein walls. Usually, patients go on to a liver biopsy, which is the gold standard tool for distinguishing patients with cirrhosis from patients without cirrhosis, and is also needed for the diagnosis of idiopathic noncirrhotic portal hypertension.

G&H Does liver stiffness measurement have a diagnostic role?

HJ FibroScan (Echosens), or liver stiffness measurement, can be somewhat helpful because patients with idiopathic noncirrhotic portal hypertension typically have a lower liver stiffness value than patients with cirrhosis (approximately 9 kPa on average vs over 14 kPa, respectively). A study showed that if a patient has signs of portal hypertension and has a FibroScan value of less than 12 kPa, noncirrhotic portal hypertension should be considered. However, this finding has not been validated due to the rarity of the disease and the paucity of research in this area.

G&H What is the most significant challenge in the diagnosis of idiopathic noncirrhotic portal hypertension?

HJ Idiopathic noncirrhotic portal hypertension is essentially diagnosed by exclusion. As previously mentioned, noncirrhotic portal hypertension can have a variety of causes, such as schistosomiasis or various liver diseases, and typically idiopathic noncirrhotic portal hypertension is considered only after other possible diseases have been excluded. Thus, the biggest challenge is being sure that another liver disease is not being overlooked.

In addition, it can be difficult for some liver centers to distinguish between cirrhotic and noncirrhotic portal hypertension. Very often if no liver biopsy is done, it is presumed that each patient with portal hypertension always has cirrhosis, but that is clearly not the case. Liver centers with a lot of experience know that portal hypertension can occur without cirrhosis. The next step is to distinguish idiopathic from other causes of noncirrhotic portal hypertension.

G&H What is the typical outcome of idiopathic noncirrhotic portal hypertension?

HJ Overall, the outcome is typically fairly good because liver function is still normal. For example, if a patient has a variceal hemorrhage, he or she recovers more quickly than a patient with cirrhosis, whose liver function is very poor. The function of the liver is very important for the recovery of these bleeds. If patients with cirrhotic portal hypertension bleed, they often develop infections, resulting in further liver failure and massive ascites, and they may die as a result. This does not happen often in patients with noncirrhotic portal hypertension because their remaining liver function is very good most of the time. Therefore, this condition is considered to be a relatively benign disorder.

However, there have been a few cases of idiopathic noncirrhotic portal hypertension in which patients developed hepatic encephalopathy and liver failure. In one study of patients who had obliterative portal venopathy, this happened in 7 of the 60 patients.

G&H What is the recommended therapeutic approach to idiopathic noncirrhotic portal hypertension?

HJ There have not been many studies on this disease, so physicians often adapt the guidelines for prophylaxis and management of portal hypertension in the setting of cirrhosis. Bleeding is the most significant danger in patients with idiopathic noncirrhotic portal hypertension. If a patient has a gastrointestinal hemorrhage (variceal bleeding), the patient is scoped and endoscopic banding is applied. Banding can also be done prophylactically to prevent bleeding if the varices are very large. If the bleeding cannot be treated endoscopically, typically the physician proceeds with a transjugular intrahepatic portosystemic shunt (TIPS). The TIPS procedure is done to lower pressure in the portal system, just like in the setting of cirrhotic portal hypertension. Although there has not been any proper study done in idiopathic noncirrhotic portal hypertension, nonselective beta blockers are recommended, in keeping with their good results in the setting of cirrhosis.

Some investigators advocate for anticoagulation to reduce disease progression. However, it can be difficult to

balance oral anticoagulation with the risk of bleeding and thrombosis in these patients. Anticoagulation is, thus, only recommended in cases of a clear underlying prothrombotic condition or in patients who develop portal vein thrombosis.

The last step is liver transplantation. However, this procedure is uncommon in idiopathic noncirrhotic portal hypertension, and, thus, there is very limited experience with it, because patients typically have fairly good liver function, as previously mentioned. If liver transplantation is needed, it is mostly done for unmanageable complications of the portal hypertension or liver failure, and the outcomes in these patients are generally very good.

G&H How safe are these treatment options?

HJ Overall, the treatments are relatively safe, although complications can occur with any type of treatment. TIPS and liver transplantation are very invasive procedures and, thus, have the most potential for complications. Beta blockers and endoscopic banding are quite safe.

G&H What should follow-up care consist of, and for how long?

HJ It is important to keep in mind that idiopathic noncirrhotic portal hypertension is a chronic disease, so these patients should remain under the care of a hepatologist typically for the rest of their lives. Sometimes, they are also seen by a hematologist. Regular endoscopy should be performed to monitor the extension of varices. The frequency of follow-up visits depends on whether the patient has complications, but if the patient is stable, he or she is typically seen every 3 to 6 months.

Follow-up is also important to prevent patients from developing portal vein thrombosis. Patients should be screened for this condition with ultrasound every 6 months. If there is a block in the setting of noncirrhotic portal hypertension—and it is not seldom that there is some type of prothrombotic disease—these patients can develop portal vein thrombosis, which can complicate outcomes. Several years ago, my colleagues and I published a study on portal vein thrombosis, and found that if the condition occurred in the setting of cancer, patients had the worst prognosis; if it occurred in the setting of cirrhosis, patients had an intermediate prognosis; and if it occurred in the absence of cirrhosis, patients had a fairly good prognosis.

G&H What are the next steps in research in this area?

HJ The next step is to create animal models to determine the exact pathophysiology of this disease and to clarify each etiology. This knowledge might lead to better treatment and perhaps better prevention. In addition, because idiopathic noncirrhotic portal hypertension is such a rare disease, researchers should team up to investigate it in large clinical outcome studies in scientific networks and large consortia; this has not happened much yet, owing to a lack of interest from industry. Finally, more awareness of this disease is needed. There have been times when a patient has been brought into our clinic, and the referring doctor thinks that the patient has portal hypertension because of unknown cirrhosis, but it turns out that the patient does not have cirrhosis at all. It is important that all physicians know that portal hypertension does not always occur in the setting of cirrhosis.

Dr Janssen has no relevant conflicts of interest to disclose.

Suggested Reading

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