Portal hypertension in children

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Abstract

Portal hypertension (PH) is an important complication of chronic liver disease. It can also be caused by a wide range of extrahepatic pathologies in children, and is often clinically silent. Acute variceal haemorrhage (VH) is the most serious consequence of portal hypertension associated with significant morbidity and mortality. Management of PH in children consists of medical, endoscopic and surgical approaches which are mainly focused on acute treatment as well as reducing the risk of variceal haemorrhage. Current treatment strategies for children with PH are mostly based on extrapolation of data from adult studies and expert opinion and consensus. A structured protocol, consisting of surveillance endoscopy with primary and secondary prophylactic therapy by endoscopic variceal ligation or sclerotherapy, is increasingly becoming the standard of care. This article discusses the causes and current treatment options for PH in childhood.

Keywords hypersplenism; liver cirrhosis; oesophageal and gastric varices; portal hypertension; splenomegaly

Introduction

Portal hypertension (PH) in children is a major complication arising from liver cirrhosis and extra-hepatic vascular disorders. It is associated with significant morbidity and mortality. It commonly presents catastrophically with variceal haemorrhage (VH), which may occur for the first time in a child with no apparent medical history, particularly if PH is due to a non-hepatic cause. Other common clinical features of PH include splenomegaly, hypersplenism and ascites. Encephalopathy and pulmonary manifestations such as hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPH) are important complications but less commonly encountered in children.

The goals of management of PH are directed at treating its complications. Controversies still surround treatment strategies for prevention or reducing the risk of variceal bleeding and evidence-based recommendations remain scarce.

Portal venous system

The liver receives its blood supply from the hepatic artery and the portal vein (PV). The PV accounts for 75% of the blood supply to the liver and is formed by the union of the splenic vein (SV) and the superior mesenteric vein (SMV). The SMV drains mainly the small intestine, proximal colon and head of the pancreas. The SV drains blood from the spleen and the inferior mesenteric vein (IMV), which receives blood from the distal large bowel. Before reaching the liver, the main PV divides into the left and right portal veins, which in turn divides sequentially into smaller venules. The portal venules and hepatic arterioles ultimately merge into hepatic sinusoids that drain into hepatic veins. Three hepatic veins eventually drain blood from the liver into the inferior vena cava (IVC). A schematic representation of the portal venous system is shown in Figure 1.

Pathophysiology

PH occurs as a result of increased vascular resistance and/or blood volume through the portal venous system. The hyperdynamic circulatory state results from a series of physiologic responses which include splanchnic vasodilatation and activation of the sympathetic nervous system and renin-angiotensin-aldosterone axis, which in turn lead to sodium and water retention, hypervolaemia, increased cardiac output and splanchnic blood inflow.

Normal portal venous pressure is 7–10 mmHg, and hepatic venous pressure gradient (HVPG) ranges from 1 to 4 mmHg. HVPG is the difference between the free hepatic venous pressure (FHVP) and wedged hepatic venous pressure (WHVP) which reflects hepatic sinusoidal pressure. PH is defined as portal pressure greater than 10 mmHg or a HVPG greater than 4 mmHg.

The most significant pathological consequence of portal hypertension is the formation of collateral vessels between the portal venous system and the systemic circulation, leading to the development of varices in the oesophagus, stomach and rectum. In adults, HVPG above 10 mmHg is associated with oesophageal variceal formation and a pressure gradient above 12 mmHg is associated with ascites and variceal bleeding.

Causes

The causes of PH are classified into three categories: prehepatic, posthepatic and intrahepatic, which can be further subdivided into presinusoidal, sinusoidal and postsinusoidal. These are summarized in Table 1.

Prehepatic causes

Portal vein thrombosis (PVT) is the most common cause of extrahepatic portal vein obstruction (EHPVO) in children. Neonatal events such as umbilical vein catheterization, omphalitis and sepsis are common attributable factors, while prothrombotic disorders such as protein C, protein S and antithrombin III deficiencies and factor V Leiden mutations have been found to account for up to 35% of children with PVT. Interestingly, the cause of PVT remains unidentified in about 50% of cases.

Intrahepatic causes

Various intrahepatic presinusoidal, sinusoidal and postsinusoidal causes give rise to increased portal bed resistance within the liver and PH. Presinusoidal causes include congenital hepatic fibrosis and nodular regenerative hyperplasia, which often do not result in impaired liver function. Sinusoidal obstruction is mainly due

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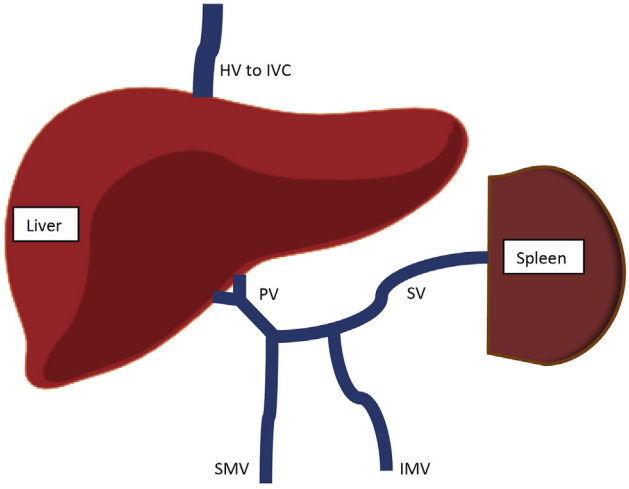

Figure 1 Schematic representation of the portal venous system. (SMV, superior mesenteric vein; IMV, inferior mesenteric vein; PV, portal vein; SV, splenic vein; HV, hepatic veins; IVC, inferior vena cava).

Classification and causes of PH in children

Classification	Causes
Prehepatic	Portal vein thrombosis
	Congenital or acquired stenosis of portal vein
	Splenic vein thrombosis
Intrahepatic	
Presinusoidal	Congenital hepatic fibrosis
	Polycystic liver disease
	Nodular regenerative hyperplasia
	Myeloproliferative diseases (lymphoma, leukaemia)
	Granulomatous diseases (schistosomiasis, sarcoidosis, tuberculosis)
	Non-cirrhotic portal fibrosis/Idiopathic PH
Sinusoidal	Liver cirrhosis (independent of cause)
Post-sinusoidal	Veno-occlusive disease
Posthepatic	Budd-Chiari syndrome
	IVC obstruction
	Constrictive pericarditis
	Right heart failure

Table 1

to liver cirrhosis, independent of the underlying primary liver disease. The increase in intrahepatic vascular resistance in cirrhosis is due to two factors: the 'mechanical factor' is related to hepatic architectural derangement caused by fibrosis and nodule formation, while the 'dynamic factor' is related to vasoconstrictive effect from vasoactive endogenous factors. Post-sinusoidal obstruction is best represented by veno-occlusive disease (VOD), or sinusoidal obstruction syndrome, which occurs as a result of conditioning treatment administered prior to haematopoietic stem cell transplantation (HSCT). VOD is characterised by microthrombosis and sclerosis of hepatic venules, and presents with hyperbilirubinaemia, hepatomegaly and ascites typically within 3 weeks from HSCT.

Posthepatic PH

Posthepatic PH can be due to a hepatic venous outflow obstruction (Budd Chiari syndrome), which is uncommon in children, or cardiac disorders with increased right atrial pressure. In posthepatic portal hypertension, chronic venous congestion results in hepatomegaly and can eventually lead to liver dysfunction and cirrhosis.

Clinical presentation

The main clinical manifestations of PH in children are gastrointestinal haemorrhage, splenomegaly and ascites. Abnormal abdominal venous patterning (caput medusa) may also provide an important clue to underlying portal hypertension. Other complications that are less common include hepatorenal syndrome, pulmonary vascular disease, growth failure and encephalopathy. In patients with extrahepatic portal hypertension or compensated liver disease, there may be no prior symptom and the first indication of portal hypertension may be gastrointestinal bleed or an incidental finding of splenomegaly.

Gastrointestinal bleeding: gastrointestinal haemorrhage is usually from ruptured oesophageal varices, but may also be secondary to portal hypertensive gastropathy, gastric antral vascular ectasia, or gastric, duodenal, peri-stomal or rectal varices. VH has been reported to occur in 17%–29% of children with biliary atresia in retrospective cohorts, and nearly half to two-thirds of children with EHPVO by 16–18 years of age. The age of the first bleeding episode is related to the underlying aetiology of PH. Reported median ages at presentation of first VH was 3.8 years in patients with EHPVO, 17 months – 3 years in patients with biliary atresia, and 11.5 years in patients with cystic fibrosis-related liver cirrhosis.

VH has been observed to occur more often in children with intercurrent upper respiratory infection and febrile illnesses. The factors postulated to contribute to rupture of varices include increased abdominal pressure from coughing and sneezing, increased cardiac output during febrile episode, and use of non-steroidal anti-inflammatory medication.

Splenomegaly: splenomegaly is a common clinical finding in children with PH and can be an incidental discovery on routine physical examination. The haematological consequence of hypersplenism, including thrombocytopenia and leucopenia, often misleads clinicians into performing a work-up for haematological causes, resulting in delayed diagnosis of PH. Liver function test (LFT) and Doppler ultrasonography are therefore advisable in the evaluation of children with splenomegaly and hypersplenism. When portal pressure is relieved either with liver transplantation or porto-systemic shunt surgery, splenomegaly and hypersplenism are expected to improve over time.

Ascites: ascites develops when hydrostatic pressure exceeds oncotic pressure within the hepatic and mesenteric capillaries, and the fluid shift overcomes the drainage capacity of the lymphatic system. Ascites is usually seen in patients with PH due to cirrhosis. Increased sodium and fluid retention contributes to further fluid accumulation in the peritoneal space. Treatment of ascites includes salt and fluid restriction, and diuretic therapy. Spironolactone is the first-line diuretic as its property as an

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