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Extrahepatic Portal Vein Obstruction in the Pediatric Age: A Medical Challenge

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Keywords

Cavernous transformation of portal vein, Esophageal varices, Infant, Follow-up guidelines

Abbreviations

EHPVO: Extrahepatic Portal Vein Obstruction; PHT: Portal Hypertension; EGD: Esophagogastroduodenoscopy; EV: Esophageal Varices; EVL: Endoscopic Variceal Ligation

Introduction

Extrahepatic portal vein obstruction (EHPVO), although rare in children, is a significant cause of portal hypertension (PHT) which leads to life-threatening gastrointestinal bleeding in the pediatric age group. PHT may also lead to other complications such as hypersplenism, cholangiopathy, ascites, and even hepatopulmonary syndrome and portopulmonary hypertension that may require organ transplantation.

Finding a cavernous transformation of the portal vein with evidence of collateral circulation in a pediatric patient is a challenging condition for professionals, since PHT may lead to severe complications during childhood and can compromise growth and development.

Pathogenesis

The most common causes of PHT in children are EHPVO and biliary atresia. When PHT appears, collaterals develop in response to the elevation of the portal pressure in the esophagus, cardia of the stomach, anus and falciform ligament, through remnants of the fetal umbilical circulation and retroperitoneum. At the prehepatic obstruction (EHPVO), collaterals attempt to bypass the blockage and enter directly into the liver at the *porta hepatis* by shaping a cavernous transformation of the portal vein. The obstructed portal vein will be replaced by a network of hepatopetal collateral veins that connect the patent portion of the vein upstream to the patent portion downstream [1]. Despite the formation of collateral veins, PHT persists as a consequence of increased cardiac output and decreased splanchnic arteriolar tone [2]. Furthermore, antral, duodenal and biliary veins are markedly enlarged due to the occlusion of the trunk of the portal vein.

Etiology

EHPVO is the most common cause of prehepatic PHT in children. When a cavernous transformation of portal vein is detected, the differential diagnosis is quite heterogeneous. It could be consequence of neonatal omphalitis, catheterization of the umbilical vein, pylephlebitis related to appendicitis or other intra-abdominal infections or sepsis [3]. The direct injury to the portal vein due to umbilical catheterization is one of the major risk factors for EHPVO. A prolonged placement or misplacement of the catheter or the use of hyperosmolar solutions are common features associated with this complication. EHPVO has also been reported as a consequence of perinatal events such as asphyxia, persistent pulmonary hypertension, sepsis and presence of congenital heart disease [4].

Factor V Leiden and acquired JAK2 (JAK2V617F) mutation have been detected in adult patients with EHPVO. Nevertheless, none of these prothrombotic hereditary mutations have been found in children with EHPVO [5]. With regard to acquired causes of trombophilia, it has been described an association of EHPVO with anti-phospholipid syndrome and paroxysmal nocturnal hemoglobinuria [4].

The factor causing the blocking of the portal vein remains unknown in more than 65% of cases. In fact Ando, et al. determined that many cases were caused by an embryological malformation resulting in a tortuous, abnormal portal transformation [6].

Clinical Manifestations

Most of the pediatric cases of PHT associated to EHPVO are diagnosed at the age of 10-14 years [7,8]. Life-threatening hematemesis and melenas are the most frequent presentation with variceal bleeding as the most common cause [9]. The risk of first-time bleeding for pediatric patients with PHT associated with EHPVO is 22%, but increases to 38% in children with known varices over a 5-year period [10]. The risk of variceal bleeding in children with portal vein obstruction was expected to decrease in adolescence because of the development of spontaneous portosystemic collaterals. However, there are studies that refute this hypothesis. In this regard, Lykavieris, et al. followed a group of children with EHPVO up to 24-years-old and observed a steady risk of variceal bleeding with growth [11].

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Chronic complications such as hypersplenism, cholangiopathy, ascites, hepatopulmonary syndrome and portopulmonary hypertension are associated with EHPVO in children. An unexplained pancytopenia associated with hypersplenism is an important clinical feature that should be recognized early. Some of these patients undergo an extensive hematological study, including bone marrow biopsy, before EHPVO is suspected. Jaundice caused by cholestasis is observed in those cases where the portal cavernoma compresses the bile duct. Ascites may appear after a bleeding episode, associated to decreased serum albumin levels. Intrinsic liver disease and infections should be ruled out in these cases. Dyspnea, exercise intolerance and finger clubbing are clinical signs of hepatopulmonary syndrome. Hepatopulmonary syndrome and portopulmonary hypertension are severe complications that may require hepatic transplantation. Moreover, approximately 50% of children with EHPVO will have growth retardation.

Diagnosis of EHPVO

To establish the diagnosis of EHPVO different methods have been used. The ultrasound allows the assessment of liver and spleen echogenicity and size and presence of cavernous transformation of the portal vein. Ultrasound is also recommended during follow-up in order to detect the dilatation of the biliary tree. The Doppler ultrasound is used to assess patency of portal and splenic veins and to determine the direction of blood flow [12]. Computed tomography and magnetic resonance imaging angiography should be the first option to assess the anatomy of the portal system, especially in those cases where surgery is considered [13].

Invasive techniques, such as endoscopic retrograde cholangiography and transvenous insertion of balloon catheter in the hepatic vein, might be helpful for the study of biliary factors that cause PHT and the measurement of wedged and free hepatic venous pressures, respectively. These techniques are rarely used in children due to the high risk of pancreatitis and bleeding, respectively. Moreover, they are not relevant in EHPVO as biliopathy is caused by an extrinsic compression of the cavernoma and hepatic vein pressure gradient is normal in this condition [8].

Detection of Varices

The most recent adult guidelines for the management of PHT [14,15] strongly support the performance of an esophagogastroduodenoscopy (EGD) at diagnosis to detect the presence of varices. For the management of PHT in adults evidence-based guidelines have been published. However, follow-up and treatment of patients diagnosed at infancy have not been standardized yet. Recommendations are based on opinions by pediatric experts, case series or cohorts [8,16]. These reviews have been performed mostly in prepubescent patients, where physiologic parameters are more diverse from those found in adults. Furthermore, there are technical limitations that hinder the management at this age, such as the inability to perform a variceal ligation in infants. Therefore, diagnostic techniques and treatment algorithms used in adult patients cannot be extrapolated to children.

Flores-Calderón, et al. state that EGD is the best procedure to screen for esophageal and gastric varices and it should be done in every potential case of PHT in children [8]. Unanimous data trends regarding endoscopic features of esophageal varices in children with PHT are scarce. Experts show an excellent agreement for medium and large-sized varices, but weaker on mild disease [17]. The variceal grade findings, such as large tense varices, red spot and gastric varices may help to identify those cases at risk of gastrointestinal bleed.

The role of capsule endoscopy as a minimally invasive tool to screen for EV in adult patients with PHT associated with cirrhosis has been recently evaluated by a Cochrane meta-analysis [18]. Currently, there is insufficient data to conclude that EGD can be replaced by capsule endoscopy for the detection of EV in adults. Data assessing the value of capsule endoscopy in children and in patients with EHPVO are still not available. Considering that most of pediatric patients would not be able to swallow the capsule by themselves, the direct placement of an endoscope into the duodenum with a specific device or a Roth basket would be necessary to perform this procedure [19]. As a consequence, the visualization of the esophagus would not be possible. Even in the case that pediatric patients swallowed an esophageal capsule by themselves, certain handicaps would be present. Such as the distortion of the actual variceal size, the inability to inflate air in the esophagus, required for variceal gradation, and the impossibility to perform therapeutic procedures. These handicaps support the use of EGD as the first choice for the screening of EV.

Follow-up of Varices

For reasons of prevalence and severity the following sections will focus on the management of esophageal varices; the follow-up and treatment of chronic complications of EHPVO will not be discussed. There are not robust recommendations with regard to follow-up times in pediatric PHT [20]. Pediatric patients with EHPVO and small esophageal varices should have an EGD every 1-2 years. However, in the case of medium-large varices a prophylactic endoscopic or medical treatment should be considered [15].

Repetition of these exams would lead to significant healthcare costs and patient discomfort. Therefore, selection of patients at high-risk of variceal bleeding represents a clinical challenge for the hepatologist in order to reduce futile examinations, related costs, and patient's burden. In this regard, several non-invasive examinations try to assess clinically significant PHT in order to define properly the optimum time for the repetition of the EGD [21].

Several studies have tried to identify ultrasonographic predictors of EV in children and adolescents with EHPVO. Presence of abnormal collateral vessels appears to be one of the most sensitive and specific sonographic signs for the diagnosis of PHT [22]. De Alcántara, et al. found that the identification of wall thickening of the gallbladder and gallbladder varices were highly indicative of EV among patients with EHPVO [23]. While several biochemical non-invasive markers have been correlated to liver functional reserve in chronic liver disease, none of them has been able to predict the risk of bleeding in children with EHPVO [24,25]. The Indocyanine Green Retention Test (ICG-r15) is a quantitative function test that reflects the presence, degree and complication of PHT among adult patients with initial cirrhosis [26]. It seems to be a valid tool for the assessment of EV in cirrhosis adult patients. These results have to be validated in a larger population and confirmed by longitudinal analysis. Platelet count, splenic index and platelet-splenic index ratio have demonstrated to act as predictors of EV in children and adolescents with chronic liver disease [24,25]. However, they have not been able to anticipate the progression of EV in patients with EHPVO.

Treatment of Varices

Primary prophylaxis

Adult guidelines recommend non-selective β-blockers (propranolol or nadolol) or endoscopic variceal ligation (EVL) for the prevention of first variceal hemorrhage in patients with medium/large varices that have not bled but have a high risk of hemorrhage (red wale marking on endoscopy). However, on those with medium/large varices, but a low risk of bleeding (no red wale marking) non-selective β-blockers would be preferable. In the latter an EVL should be considered if there are contraindications, intolerance or non-compliance to this medication. In the case of small varices that have not bled, but have criteria for increased risk of hemorrhage, non-selective β-blockers should be considered. Sclerotherapy should not be used for primary prevention of variceal bleeding, since a prospective trial comparing prophylactic sclerotherapy vs. sham therapy was terminated 22.5 months after its initiation because the mortality rate was significantly higher in the first group [27].

There are no randomized trials assessing the efficacy of propranolol as primary prophylaxis in children with EV. The few cohort studies carried out did not include the measurement of

hepatic venous pressure gradient before and after the beginning of the treatment [28]. Currently, there is not enough information to recommend its use in children with EHPVO [8].

The role of prophylactic or pre-emptive EVL is still controversial in children also because of lack of trials. EVL has been shown to be superior to sclerotherapy, in efficacy and safety terms. Prophylactic sclerotherapy has been abandoned worldwide [9]. Children with large varices should be considered for primary prophylaxis with EVL on a case-by-case basis. EVL may be considered in selected children within defined clinical circumstances: conditions where the clinician feels the risk of mortality from first variceal hemorrhage is greater than that of children in general [8,16,29]. Nevertheless, EVL is not feasible in infants because available devices cannot be used with small pediatric endoscopes. EST should be considered as the only option to obliterate large varices below one year of age [30].

Secondary prophylaxis

Non-selective beta-blockers have been used in combination with EVL for secondary prophylaxis in adult patients with prehepatic PHT [15]. However, there are no data regarding its use in children. Studies in this regard are needed.

With regard to endoscopic procedures, in pediatric patients with prehepatic PHT variceal eradication by EST is achieved in 80 to 100% of cases and the rate of recurrence of EV is 10 to 40% after eradication. Gastrointestinal rebleeding is frequently caused by gastric varices and occurs in 0 to 42% of cases. Bypass surgery is necessary in 4 to 13% of cases. Otherwise, EVL controls EV bleeding in 96% of the cases. Obliteration of the varices is achieved in 16 to 100% of cases treated, with 2 to 4 sessions being necessary to achieve obliteration. Recurrence of EV in pediatric patients has been reported to be from 5% to as much 75% [31].

By comparison with EST, EVL requires fewer sessions (3-9 vs. 6.1) and as such, fewer anesthetics procedures; there are few major complications (25 vs. 4%), whereas there is no difference in control of bleeding or in the obliteration of EV, which is achieved in 91.7% and 96%, respectively ($p < 0.61$) [31].

Surgery

Regarding to the meso-Rex bypass procedure, there is controversy with regard to the legitimacy of using this procedure in an asymptomatic child, including those who have not yet had a variceal bleed. One approach would suggest the assessment of surgery feasibility within all children with a cavernous transformation of portal vein and PHT. With prehepatic PHT, children may have normal parenchyma and liver function for decades, as there is little or absent ongoing damage occurring downstream of the portal blockage. Such patients may have a patent intrahepatic portal system that is surgically accessible at the level of the Rex recessus and thus may benefit from a restoration of the portal venous system by meso-Rex bypass. Children with a thrombosed left portal vein within the Rex recessus who cannot benefit from meso-Rex bypass should be continued on a conventional endoscopic program and conservative management. They would become candidates for portosystemic shunt when complications could not be medically or endoscopically managed [32]. Another approach would be to defer surgery until there is significant disease associated.

Conclusion

Data for guiding the follow-up and management of complications of PHT in children are scarce. Difficulties in recruiting patients into multicenter studies and the lack of official approval make the situation of obtaining robust data on the adequacy and timing of the different examinations and interventions in children with EHPVO quite unlikely. Special emphasis should be pointed in the management of PHT in infants, whose steady damage may lead to greater morbidity and mortality in a particularly susceptible period of life. Furthermore, available tools are scarce and unsupported in this age. In conclusion, multicenter trials would be required for follow-up and treatment standardization in PHT in the pediatric age group.

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