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Clinically Evident Portal Hypertension: An Operational Research Definition for Future Investigations in the Pediatric Population

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Abstract

Portal Hypertension (PHT) is a major cause of morbidity and mortality in pediatric liver diseases. Thus, research into causes and disease modifiers in PHT in these conditions is vitally important. PHT is rarely directly or indirectly measured in the assessment of children with chronic liver disease. A straightforward, reproducible definition of portal hypertension could be invaluable for consistently identifying patients with portal hypertension and for grouping these patients according to their risk of complications from their disease. We propose the term Clinically Evident Portal Hypertension (CEPH) to denote clinical findings that demonstrate evidence of elevated portal pressure. When CEPH criteria are met, PHT is highly likely to be present, although it is likely that PHT exists for variable periods of time prior to meeting CEPH criteria. Use of this research definition of CEPH will allow for consistent identification of these patients by clinicians in nearly any clinical setting and serve as a clinical milepost that may dictate future prognosis in pediatric patients with cirrhosis.

Portal hypertension (PHT) is the result of complex pathophysiologic processes that can affect patients across the spectrum of liver disease. Prolonged increases in portal pressure can result in life-threatening complications and lead to an array of chronic morbidities including variceal hemorrhage, hypersplenism, hepatopulmonary syndrome, hepatorenal syndrome, and ascites. PHT occurs as a result of increased portal resistance, increased portal

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blood flow, or a combination of both. PHT is most accurately identified by direct measurement of portal pressures, although in practice this rarely happens. An alternative is to assess portal pressure indirectly via the Hepatic Venous Pressure Gradient (HVPG). HVPG is measured in some adults and is a key element in the research definition of Clinically Significant Portal Hypertension (CSPH) defined by the Baveno VI workshop (1). While PHT is physiologically defined as an HVPG of greater than 5 mm Hg, the clinical consequences of PHT occur when HVPG exceeds 10 mm Hg. In adult patients, HVPG measurements greater than 10 mm Hg are associated with presence of esophageal varices and HVPG greater than 12 mm Hg is associated with variceal bleeding and ascites(2). Due to the relationship between a measurement of HVPG above 10 mm Hg and complications of portal hypertension, the concept of CSPH has been introduced to denote portal hypertension in adult patients associated with an HVPG >10mm Hg(3). Further, CSPH in adults is correlated with histologic evidence of cirrhosis (4).

In the Childhood Liver Disease Research Network (ChiLDReN), we previously have utilized a definition of PHT based on splenomegaly and platelet count or the presence/history of complications of PHT applied to children with biliary atresia (BA) who had received their hepatoporoenterostomy prior to enrollment in the study (5). This definition was also applied in a study of cholestatic infants with BA enrolled at the time of diagnosis and in a baseline study of patients with alpha-1 antitrypsin deficiency (6, 7). In these studies, definite PHT was defined as either the presence of both thrombocytopenia —platelets less than 150,000/mm³— and splenomegaly —defined as spleen palpable on physical exam 2 cm below the costal margin—, or the presence of a manifestation of PHT including ascites, gastrointestinal bleeding, or hepatopulmonary syndrome (HPS).

In pediatric liver disease, direct or indirect measurement of portal pressure is rare and not typically performed in routine clinical practice. As a result, the gold standard definitions that define adult criteria for PHT are difficult to obtain with regularity on many children with pediatric liver disease. In addition, there are some data suggesting that HVPG may not always be accurate in the estimation of portal pressure in BA due to veno-venous collaterals (8, 9). Given the prevalence of BA in children with PHT, this is a major confounder. In addition, routine HVPG measurements in adults are done under sedation, while general anesthesia is required in most children. The effect of general anesthesia on HVPG is not well understood. This creates a major impediment in advancing the study of PHT in pediatrics and necessitates the definition of PHT to be assessed by clinical criteria.

The research definition of PHT that was previously utilized in ChiLDReN has some limitations. First, gastrointestinal bleeding is an uncommon event and therefore underestimates the prevalence of patients with gastroesophageal varices, especially if one's clinical practice does not involve screening for or pre-emptively treating gastroesophageal varices (10). Gastrointestinal bleeding may also be from sources such as ulcers or gastritis unrelated to PHT. Ascites was not clearly defined and thus the definition used in application could range from true clinically significant ascites requiring medical therapy, to a small amount of fluid in the peritoneal cavity noted on imaging, to an erroneous assessment of abdominal distension due to organomegaly or gas. HPS, also appearing in the definition, is uncommon and the definition of HPS is not standardized across all centers.

Therefore, a surrogate operational *research* definition for the clinical signs and symptoms of PHT for pediatrics is needed. The surrogate needs to be easily applied using routinely available clinical information. We propose the term Clinically Evident Portal Hypertension (CEPH) to denote clinical findings that demonstrate evidence of elevated portal pressure in the setting of cirrhosis. When CEPH criteria are met, portal hypertension is highly likely to be present, although portal pressures may be elevated in the absence of meeting these criteria. “Evident” was chosen instead of “significant”, since the clinical significance of the findings needs to be determined prospectively. CEPH should be considered a stage of progression of disease and not a measurement of portal pressure. CEPH, as defined here, does not necessarily apply to patients with pre-hepatic or post-hepatic causes of PHT. Ascites is uncommon in extrahepatic portal vein obstruction and varices may have a very different natural history in post-hepatic cause of PHT. Individuals who meet CEPH criteria are likely to have had portal hypertension for months to years prior to meeting those criteria. The definition of CEPH has evolved from investigations conducted by the ChiLDReN and is proposed as follows and listed in Table 1.

Definite CEPH (dCEPH): One or both of:

- **Clinical Findings**, which consists of both:
 - Splenomegaly (spleen size > 2 cm below the costal margin by physical examination) **and**
 - Platelet count < $150 \times 10^9/\text{L}$ ($= 150,000/\text{mm}^3 = 150,000/\text{micro-L} = 150,000/\mu\text{L} = 150,000/\text{mL}$)
- **Manifestations**, which consist of at least one of:
 - Clinically evident ascites (defined below) or
 - Endoscopic evidence of esophageal or gastric varices

Possible CEPH (pCEPH): Absence of manifestations listed above and only one of:

- Splenomegaly (spleen size > 2 cm below the costal margin by physical examination) or
- Platelet count < $150 \times 10^9/\text{L}$ ($= 150,000/\text{mm}^3 = 150,000/\text{micro-L} = 150,000/\mu\text{L} = 150,000/\text{mL}$)

Absent CEPH (aCEPH): Absence of any of the above manifestations or findings

CEPH is an operational clinical research definition of portal hypertension that utilizes standardized physical examination findings and laboratory values that may be applicable to patients in any setting irrespective of geography or available clinical resources. Based on the definition of CSPH (1), it is reasonable to consider that children who develop clinical manifestations of portal hypertension such as hypersplenism, thrombocytopenia, gastroesophageal varices, or ascites must have an elevated portal pressure in order to manifest these findings. Reports of PHT in the pediatric medical literature generally are single center, extend across different eras of medical therapies, and are inconsistent in the definition of PHT. The pediatric PHT workshops at both the Baveno V and Baveno VI

conferences similarly do not provide a clear, concise definition of PHT in the pediatric population (11, 12). Thus, there is an unequivocal need for standardization in defining such a condition with a wide clinical spectrum.

The new definition of CEPH leverages operationally defined clinical manifestations of portal hypertension, the elements of which are specified next.

Splenomegaly:

Splenomegaly in CEPH is denoted as a spleen that is palpable more than 2 cm below the costal margin. This definition was chosen because the finding of splenomegaly is clinically significant and reproducible in the hands of an experienced clinician. Splenomegaly noted on ultrasound (or other cross-sectional imaging techniques) should correlate with the physical exam. Spleen size may not be uniformly recorded on ultrasounds in clinical practice (5). For these reasons, the definition of CEPH does not include measurement of spleen size on imaging. Two centimeters was chosen as clinically significant and avoids the occasional finding of a palpable spleen tip in normal children. It is recognized that assessing spleen size in children requires a dedicated effort on the part of the clinician, especially in uncooperative children.

It is worthwhile to note that patients with Biliary Atresia Splenic Malformation (BASM) have been demonstrated to have complications from PHT (13–15). Yet, due either to asplenia, or polysplenia, detection of dCEPH may be difficult in these patients. A special protocol of screening patients with BASM (especially those with asplenia) for esophageal varices may be appropriate. In the future, the use of transient elastography may be an alternative approach. For research outcome purposes, however, these patients will not be considered to have developed dCEPH until they manifest varices or ascites.

Thrombocytopenia:

Thrombocytopenia, defined as a platelet count $< 150,000/\text{mm}^3$, has long been recognized as a potential marker of portal hypertension. A database study of patients with compensated cirrhosis and without varices demonstrated that platelet count was the first hematologic index to become abnormal (16). Further, clinicopathologic studies in non-cirrhotic portal hypertension consistently demonstrated thrombocytopenia in that population of patients (17). Thus, ChiLDReN utilized a platelet count of $150,000/\text{mm}^3$ as a cut-off definition for thrombocytopenia in the initial description of portal hypertension of the study in BA. It is important to note, however, that some patients, particularly those under 2 years of age, may have evidence of and complications from PHT despite normal platelet count, so this definition must be evaluated with that fact in mind (5). pCEPH may be more significant in children under the age of 2 years. Clinicians should also be aware of the rare circumstance when there may be other causes of thrombocytopenia that could complicate the interpretation of thrombocytopenia in chronic liver disease (e.g., malignancy, immune-mediated destruction, or splenic vein thrombosis).

Clinically Evident Ascites:

The definition of clinically evident ascites is denoted by treatment with diuretics in patients older than 6 months of age. Ascites from PHT occurs when hydrostatic and osmotic pressure within hepatic and mesenteric capillaries produce a net transfer of fluid from blood vessels to lymphatic vessels at a rate that exceeds the drainage capacity of the lymphatics. Ascites may be suggested by a history of recent increases in weight on physical exam by shifting dullness or fluid wave, or by abdominal imaging, either ultrasound, CT, or MR. Physical exam findings are insensitive with inadequate specificity, while ultrasounds can detect even a small amount of free fluid that may or may not be ascites or clinically relevant (18). Furthermore, a small amount of ascites detected on imaging with no clinical sequelae does not require treatment, while a large amount of ascites with clinical relevance will be treated with diuretics as the first line of therapy by most clinicians. Therefore, rather than rely on insensitive and poorly correlative physical exam measures or overly sensitive imaging studies, a reasonable definition of ascites is presence of fluid in the abdomen that causes the clinician to treat ascites with diuretics.

Gastroesophageal Varices:

Instead of the finding of gastroesophageal varices manifesting as gastrointestinal bleeding, this definition uses any endoscopic evidence of gastroesophageal varices. As a result, this definition encompasses the number of patients who have evidence of gastroesophageal varices on screening or surveillance endoscopy but who have not had a variceal bleeding event. The presence of gastroesophageal varices in pediatric patients is consistent with the definition of CSPH in adult patients. It is presumed that in children with chronic liver disease who have significant gastrointestinal hemorrhage, endoscopy will be performed and varices will be identified. As such, bleeding *per se* is not part of the defining features of CEPH. Additionally, the presence of gastroesophageal varices on cross-sectional imaging exhibits poor specificity and is not a reliable indicator of the presence of varices compared to endoscopy, considered the gold standard (19). Application of CEPH as a research definition needs to account for clinical practice variations vis-a-vis screening for varices as this may affect the timing of detection and, therefore, the declared time of onset of CEPH.

A number of clinical manifestations for portal hypertension were not included in the definition of CEPH and are described next.

Hepatopulmonary Syndrome:

HPS is absent from the definition due to the inconsistency in recording and applying clinical criteria associated with the condition. For instance, due to the invasive nature of the test and complexities in execution due to orthodeoxia, arterial blood gas sampling is used inconsistently with children who may have HPS. In a cross-sectional study of patients with BA, every patient noted to have HPS also met the study's criteria for portal hypertension, either due to the presence of both splenomegaly and thrombocytopenia, or the presence of another manifestation of portal hypertension such as ascites or variceal hemorrhage (5). Therefore, it was concluded that it was extremely unlikely for HPS to be the sole

manifestation of PHT, and, due to inconsistency in patients meeting defining criteria for HPS, it was not included in the definition of CEPH.

Portal Gastropathy:

Portal hypertensive gastropathy (PHG) is characterized by dilation of the mucosal and submucosal vessels of the stomach. PHG can appear as discrete cherry-red spots with a lacy, mosaic pattern. Bleeding from PHG is usually chronic and should be suspected in cirrhotic patients with chronic iron deficiency anemia. There are numerous studies that describe the incidence of PHG in patients with portal hypertension, in patients with severe PHT, and in end-stage liver disease (10, 20, 21). Worsening PHG is correlated with the presence of portal hypertension and more advanced cirrhosis (22). However, PHG has not been shown to be a risk factor for bleeding in multivariate analyses. Clinically, PHG is not observed in the absence of splenomegaly, thrombocytopenia, or esophageal varices. While the presence of PHG in the setting of previously known portal hypertension is associated with good inter-observer reliability (23), there are few studies that distinguish PHG from other etiologies of gastropathy in the absence of PHT. Therefore, the literature does not give enough guidance for the use of the presence of PHG alone as a marker of PHT.

Hepatorenal Syndrome:

Hepatorenal syndrome (HRS) occurs as a result of a cascade of events associated with intense dilatation of the splanchnic arterial vasculature in the setting of cirrhosis or acute liver injury and resulting in profound renal arterial vasoconstriction and progressive renal failure. Acute renal dysfunction occurs in a significant number of hospitalized patients with cirrhosis. HRS seems to be an extension of pre-renal azotemia. The actual frequency of HRS in pediatric patients is unknown (24). Several studies have attempted to define criteria for HRS in pediatrics modified from adult data, with criteria including cirrhosis with ascites, serum creatinine level doubling from baseline, and no or insufficient improvement in serum creatinine level 48 hours after diuretic withdrawal and adequate volume expansion with IV albumin (24, 25). Other criteria include absence of shock, no evidence of recent use of nephrotoxic agents, and absence of intrinsic renal disease (26). While the criteria in pediatrics have not been defined in the medical literature, all patients with hepatorenal syndrome will have met already the criteria for dCEPH due to the presence of clinically evident ascites. While an important outcome measure, the inclusion of hepatorenal syndrome as a necessary feature in the definition of dCEPH is thus unnecessary.

Hepatic Encephalopathy:

Hepatic encephalopathy (HE) encompasses a number of potentially reversible neuropsychiatric abnormalities that can be seen in patients with cirrhosis or portosystemic shunting. Effects are thought to be secondary to increased levels of potentially neurotoxic substances, such as ammonia, in the systemic circulation that cross the blood-brain barrier. Manifestations range from mild to severe and are grouped into stages (27). In children, HE is associated with cerebral atrophy and impaired cognitive function that may persist even after liver transplantation (28). Patients with HE are at risk of cerebral edema secondary to

astrocyte swelling from ammonia metabolism. However, in patients with cirrhosis who have chronically elevated ammonia levels, brain osmoregulatory mechanisms often are able to compensate (29). Minimal hepatic encephalopathy (MHE) is the mildest form of HE in which patients have no overt symptoms but may have subtle motor and cognitive defects and impairment on neuropsychological tests(30). The assessment of MHE in a young child is quite challenging in the absence of rigorous neuropsychological testing, which is not frequently performed in a routine outpatient setting. Studies suggest that up to 50% of children with chronic liver disease have MHE which negatively affects brain function and school performance (31, 32). While hepatic encephalopathy may be an important outcome measure in patients with CEPH, it is unlikely that the presence of HE alone will suffice to identify PHT.

Portopulmonary Hypertension:

Portopulmonary hypertension (POPH) arises from increased pulmonary vascular resistance, resulting in elevated mean pulmonary artery pressure. It is diagnosed by right heart catheterization. Since POPH is defined by the presence of pulmonary hypertension in the setting of portal hypertension, it cannot be a diagnostic criterion for clinically evident portal hypertension.

In conclusion, as the care of children with chronic liver disease improves, understanding within the settings of individual diseases of the natural history, progression, and manifestations of complications of PHT will be vitally important in determining the effectiveness of potential therapies and making interventions that can improve the quality of life of these patients. A straightforward, reproducible definition of portal hypertension is invaluable for consistently identifying patients with portal hypertension and for grouping these patients according to their risk of complications from their disease. Use of this research definition of CEPH will allow for consistent identification of these patients by clinicians in nearly any clinical setting independent of clinical practice. This will allow more direct comparison of clinical outcomes across different research protocols conducted worldwide. This is a reproducible definition for research outcomes and, as more prospective studies in children with liver disease are performed, will serve as a clinical milestone that may dictate future prognosis in pediatric patients with cirrhosis.

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What is Known:

- Direct or indirect measurement of portal pressure are rare in clinical pediatric practice
- Current research definitions of portal hypertension (PHT) are non-standardized and may underestimate the prevalence of PHT

What is New:

- We propose clinically evident PHT to serve as an operational research definition for PHT
- This definition will allow for prospective cohorting of patients to determine their risk for future complications of PHT

Table 1:**Definition of Clinically Evident Portal Hypertension (CEPH)**

<p><i>Definite</i> CEPH (dCEPH): <u>One or both of</u>:</p> <ul style="list-style-type: none"> • Clinical Findings, which consists of <u>both</u>: <ul style="list-style-type: none"> ◦ Splenomegaly (spleen size > 2 cm below the costal margin by physical examination) and ◦ Platelet count < $150 \times 10^9/L$ (= 150,000/mm³ = 150,000/micro-L = 150,000/μL = 150,000/mcL) • Manifestations, which consist <u>of at least one of</u>: <ul style="list-style-type: none"> ◦ Clinically evident ascites (defined below) or ◦ Endoscopic evidence of esophageal or gastric varices
<p><i>Possible</i> CEPH (pCEPH): Absence of manifestations listed above and <u>only one of</u>:</p> <ul style="list-style-type: none"> • Splenomegaly (spleen size > 2 cm below the costal margin by physical examination) or • Platelet count < $150 \times 10^9/L$ (= 150,000/mm³ = 150,000/micro-L = 150,000/μL = 150,000/mcL)
<p><i>Absent</i> CEPH (aCEPH): Absence of any of above manifestations or findings</p>