METABOLIC PROFILE OF CHILDREN WITH EXTRA-HEPATIC PORTAL VEIN OBSTRUCTION UNDERGOING MESO-REX BYPASS

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ABSTRACT

BACKGROUND Extrahepatic portal vein obstruction (EHPVO) in children is often associated with growth restriction which improves following restoration of portal venous flow with a meso-Rex bypass, but the physiologic mechanism is unknown. The purpose of this study was to investigate the mechanism of growth delay in children with EHPVO by detailing the metabolic and nutritional profile before and after meso-rex bypass.

METHODS Twenty consecutive children with EHPVO were prospectively studied before and one year following meso-Rex bypass. Caloric balance was determined by investigating caloric intake via a calorie count, total energy expenditure via a doubly-labeled water isotope assay, and stool caloric loss by bomb calorimetry. Laboratory markers of nutrition and growth hormone resistance were tested.

RESULTS Fifteen of 20 children underwent successful meso-Rex bypass at a median age of 4.3 years. Pre-albumin level was abnormally low (14.6 ± 3.0 mg/dl) at surgery but improved (17.0 ± 4.3 mg/dl) one year later (p=0.026). Mean IGF-1 level at baseline was 1.57 standard deviations below normal. IGF-1 levels increased from 88.3 ± 38.9 to 117.3 ± 54.5 ng/ml in the year following surgery (p=0.047). Caloric intake divided by basal metabolic rate (1.90 ± 0.61), total energy expenditure (97.2 ± 15.0% of expected), and stool caloric losses (3.7 ± 1.8% of caloric intake) were all normal at baseline.

CONCLUSIONS Children with EHPVO suffer from malnutrition and growth hormone resistance which may explain their well-established finding of growth restriction. Pre-albumin and IGF-1 levels improve following successful meso-Rex bypass.

KEYWORDS

Growth Hormone; Insulin-like growth factor; Energy Expenditure; Caloric intake; Prealbumin

ABREVIATIONS

EHPVO – extra-hepatic portal vein obstruction

TEE – total energy expenditure

BIA – bioelectrical impedance analysis

INTRODUCTION

Extrahepatic portal vein obstruction (EHPVO) is a major cause of chronic portal hypertension in children and is associated with significant morbidity in affected patients.[1] Symptoms are broadly classified into those attributable to portal hypertension and those related to disruption of normal hepatopetal portal blood flow. Sequelae of portal hypertension include variceal bleeding and hypersplenism. Disruption of normal portal venous circulation has been associated with symptoms of growth retardation, neurocognitive dysfunction, and mild coagulopathy.[2-5]

Treatment options for EHPVO include (1) conservative management with beta-blocker therapy and serial endoscopic banding to prevent variceal bleeding from the esophagus, (2) portosystemic shunts, including the selective distal-splenorenal or non-selective meso-caval shunt and (3) portal blood flow restoration with the meso-Rex bypass to both decompress the portal system and restore normal physiologic portal venous blood flow. While all three treatment strategies have proven effective at preventing variceal hemorrhage, the meso-Rex bypass has been shown to be a superior option for reversing growth restriction, as well as improving coagulopathy and neurocognitive dysfunction.[2-4,6-8]

Restriction in somatic growth is a well-documented complication of EHPVO.[2,5,9] In large cohorts of children, we and others have documented improvement in growth parameters following meso-Rex bypass.[2,9] However the physiologic basis for this observation is poorly understood. The finding by Menon et al that growth improved following portosystemic shunting suggests that portal hypertension itself might be an etiologic factor.[10] It is possible that portal enteropathy leads to malabsorption and increased stool caloric losses. Alternatively, shunting of blood from the liver could result in impaired synthesis of factors needed for normal growth. Disruption of the growth hormone (GH) axis with reduced elaboration of insulin-like growth factor-1 (IGF-1) by the liver in response to GH has been correlated to reduced linear growth and muscle mass in children with EHPVO.[11]

The aim of this study was to test the hypothesis that the previously observed alterations in growth following meso-Rex bypass can be explained by differences in energy balance and hormonal mileu.

METHODS

Between 2009 and 2011, 20 consecutive children between the ages of 2 and 12 with extra-hepatic portal vein obstruction being evaluated for meso-Rex bypass were enrolled into this prospective study. The study was approved by the Institutional Review Board at Children's Memorial Hospital (now the Ann & Robert H Lurie Children's Hospital of Chicago) and informed consent was obtained from all families. Our standard preoperative evaluation was performed in all cases, including duplex ultrasound of the liver, cross-sectional imaging of the superior mesenteric vein and intra-hepatic portal veins by computed tomography or magnetic resonance venography, and laboratory evaluation including complete blood count, comprehensive chemistry panel, coagulation panel, and hypercoaguable workup. For the

purposes of the current study, additional information about the body composition, nutritional status, and metabolic profile was obtained as detailed below. Evaluation was performed at the preoperative and at the one year postoperative visits. Long term follow up on growth parameters was captured when available. Patients in whom meso-Rex bypass was not technically feasible and required intraoperative conversion to a portosystemic shunt were not included in the final analysis.

Growth Parameters, Body Composition and Nutritional Parameters

Height and weight were recorded and converted to standard deviation z-scores using EpiInfo and the Centers for Disease Control 2000 standard data (Centers for Disease Control, Atlanta, GA). Body composition (body fat and fat-free mass percentages) was determined by bioelectrical impedance analysis (BIA; RJL Systems, Clinton Township, MI). Pre-albumin and transferrin levels were determined as markers of nutritional status.

Growth Hormone Axis

Growth hormone and insulin-like growth factor-1 (IGF-1) levels were measured to test the hypothesis that EHPVO is associated with growth hormone resistance. IGF-1 z-scores were calculated based on the reference mean and standard deviations in our laboratory based on age and gender.

Caloric Intake

Parents met with a clinical nutritionist who provided them with instructions on completing a 3-day food journal for their child. Average daily caloric intake was calculated based on these calorie counts. Calorie counts were normalized against basal metabolic rate (BMR) to account for expected variations based on age and gender. BMR was calculated using the Katch-McCardle formula [370 + (21.6 x lean body mass)] where lean body mass was determined by BIA analysis.

Total Energy Expenditure

Total energy expenditure (TEE) was determined by a doubly-labeled water isotope assay. Doubly-labeled water ($D_2{}^{18}O$) is formed by combining 0.4g D_2O (99.9%) per kg body weight and 3g 10.4 % $H_2{}^{18}O$ per kg body weight (CortecNet; Voisins-Le-Bretonneux, France). The test works by approximating the carbon dioxide production during this interval. This is possible because the ^{18}O equilibrates with the total body bicarbonate and dissolved carbon dioxide via the action of carbonic anhydrase and can therefore leave the body as $CO^{18}O$ in addition to losses as H_2O via the usual routes. However, the deuterium remains confined to the body's water stores and therefore only leaves the body as water. Therefore the faster rate of decrease of $^{18}O/^{16}O$ versus D/H content in the urinary water can be used to determine the amount of ^{18}O loss in carbon dioxide, which can be used to estimate total carbon dioxide production.[12] Urine samples were analyzed for background abundance levels (pre-dose) and isotopic enrichment (5, 24, 48 and 72 hours post-dose) by isotope ratio mass spectrometry equilibration expressed relative to Vienna - Standard Mean Ocean Water, as described previously.[13] Dilution spaces and isotope elimination rates were calculated by back extrapolation, and CO_2 production calculated from the deuterium and ^{18}O dilution spaces and elimination rate constants. Oxygen consumption was

predicted from CO_2 production using an assumed respiratory quotient of 0.85. TEE was calculated using Weir's equation.[14] In order to ensure that only high quality isotopic data were analysed, TEE measurements were only included if isotope space ratio was between within 1.010 and 1.090.[13]

Stool Caloric Losses

Caloric losses in the stool were determined by bomb calorimetry. Parents were provided with a collection system and biohazard bags to collect all stool output over the same 3-day period as the calorie count and TEE assay. Specimens were frozen and sent to Covance Laboratories (Madison, WI) for determination of total caloric content by bomb calorimetry. Results were expressed as average stool caloric loss per day, and compared to caloric intake to determine the fraction of calories lost in the stool.

Statistical Analysis

The Shapiro-Wilk test was applied to each continuous variable to determine whether it was normally distributed. Normally distributed variables were summarized as mean ± standard deviation. Variables with a non-normal distribution were summarized as a median (interquartile range [IQR]). Changes from the pre- to post-operative measurements were compared using the paired t-test for normally distributed variables and the related-samples Wilcoxon signed rank test for non-normally distributed variables. Correlation between two continuous variables was assessed by Pearson Correlation. A $p < 0.05$ was considered significant. All analyses were performed using IBM SPSS, version 18.

RESULTS

Between 2009 and 2011, 20 consecutive patients who underwent surgery for EHPVO were enrolled in this study. There were 13 boys and 7 girls. Median age at surgery was 4.3 years (IQR 5.2) with a range of 2.3 to 11.3 years. Meso-Rex bypass was performed in 16 patients (80%), while 3 underwent distal splenorenal shunt, and one required a meso-caval shunt. One child died in the early postoperative period after meso-Rex bypass of complications of pulmonary hypertension. Analysis of outcomes was limited to the 15 surviving patients who underwent meso-Rex bypass except when otherwise indicated. Follow up imaging one year following surgery demonstrated shunt patency in 14 of 15 patients. All conclusions about significant pre- to post-operative comparisons are unchanged if the patient with the occluded shunt at one-year follow up is excluded.

Growth parameters and body composition

Mean weight (-0.33 ± 0.99) and BMI (-0.50 ± 0.86), but not height (0.16 ± 1.3) z-scores were below average before surgery. At one year follow up, there was no change in regards to weight (-0.18 ± 0.93; p=0.50), height (0.29 ± 1.23; p=0.43) or BMI (-0.53 ± 1.52; p=0.86) (Table 1). Likewise, for the 12 patients with long-term follow up (median duration 57 months), there was no change in regards to weight (-0.23 ± 1.41; p=0.87), height (0.21 ± 1.04; p=0.39) or BMI (-0.55 ± 1.79; p=.93). There were only 5 (33%) patients with BMI more than one standard deviation below average at baseline. In this small cohort of patients, neither the weight (-0.18 ± 0.93, p=0.50) nor the BMI (-0.53 ± 1.52, p=0.86) improved

significantly in the first year after surgery. Mean body fat percentage as measured by bioelectrical impedance analysis was 22.6 ± 9.2% before surgery and 21.3 ± 8.1% one year after surgery (p=0.25).

Nutritional laboratory assessment

Mean pre-albumin level at the time of surgery was 14.6 ± 3.0 mg/dl (reference 18.0-36.0) which improved to 17.0 ± 4.3 mg/dl after surgery (p=0.026) (Figure 1). There was no change in serum transferrin levels between the preoperative (274.7 ± 36.8 mg/dl) and one-year postoperative visits (264.5 ± 25.0 mg/dl, p=0.33).

Growth Hormone axis

Median growth hormone level was 1.7 ng/ml (IQR 3.7) prior to surgery and 2.4 ng/ml (IQR 4.8, p=0.36) one year after meso-Rex bypass. Mean IGF-1 level increased from 88.3 ± 38.9 to 117.3 ± 54.5 ng/ml in the year following meso-Rex bypass (p=0.047). Compared to our laboratory's standards for age and gender, the IGF-1 z-score was abnormally low prior to surgery (-1.57 ± 0.80) and there was a non-significant trend towards improvement one year after surgery (-1.19 ± 1.03, p=0.21).   A correlation between the pre- to post-operative changes in IGF-1 and pre-albumin levels was observed but did not reach statistical significance (Pearson's r 0.486, p=0.066).

Caloric Intake

Average daily caloric intake, determined by a 3-day food diary was compared to basal metabolic rate calculated based on fat-free mass using the Katch-McArdle formula. This ratio was unchanged at 1.90 ± 0.61 before surgery and 2.07 ± 0.57 one year after meso-Rex bypass (p=0.45).

Total Energy Expenditure

Average daily energy total expenditure was determined by doubly-labeled water analysis over a 3-day period and reported as the percent expected based on weight and gender standards [15]. Among all 18 patients with EHPVO who underwent doubly-labeled water analysis prior to surgery, the mean TEE was 98.4 ± 13.6% of expected based on weight and gender. Among the patients who underwent successful meso-Rex bypass, there was no change in TEE from 96.5 ± 15.5% before surgery to 100.6 ± 17.2% after surgery (p=0.522).

Stool caloric losses

To determine whether portal hypertensive enteropathy leading to impaired absorption might be causing excessive stool caloric losses, a 3-day total stool collection was analyzed by bomb calorimetry. The ratio of average daily stool caloric loss to caloric intake was analyzed to determine the fraction of caloric intake being lost in the stool. The mean stool caloric losses in children with EHPVO was normal prior to surgery (3.7 ± 1.8%; reference <5%). There was a non-significant trend towards decreased stool caloric losses one year later (2.7 ± 0.9%, p=0.082).

DISCUSSION

Although this prospective study lacked the power needed to re-demonstrate the previously documented improvement in somatic growth among children with EHPVO following meso-Rex bypass, it does help delineate the metabolic and nutritional profile of these children. As such, the current findings provide valuable insights into prior observations and direction for future studies. By better understanding the mechanism of growth restriction in children with EHPVO, it may be possible to design targeted interventions to improve growth in this patient population, especially in the subset of patients who are unable to undergo successful restoration of physiologic hepatic blood flow.

In our prior review of 45 children who underwent successful meso-Rex bypass between 1997-2007, we found that mean height and weight of children with EHPVO was below average. At 1-2 years following surgery, z-scores for height had increased from -0.42 to -0.14 (p = .026), weight from -0.49 to 0.35 (p < .001) and BMI from -0.22 to 0.48 (p < .001).[2] Likewise, in a comparison of 65 children with EHPVO who underwent meso-Rex bypass to 16 who underwent a portosystemic shunt, we found that among patients with below average preoperative weight-for-age, the improvement was greater after meso-Rex bypass (0.84 ± 0.98) than portosystemic shunt (0.17 ± 0.79, p=0.044).[6] Elsewhere, in a study of 11 children who underwent meso-Rex bypass, Stringer et al reported that mean BMI standard deviation scores increased from -0.44 ± 1.28 to 0.46 ± 1.08 (p=0.003).[9]

Growth restriction among children with EHPVO has also been demonstrated in studies from India. Mehrota et al compared 33 consecutive children assessed for EHPVO to 35 age and gender matched siblings. After limiting analysis to the 22 patients who were considered well-nourished (weight-for-height z-score within 1 standard deviation of the controls), they found that mean height z-score (-1.88 ± 1.33) was lower than that of the controls (-1.06 ± 0.64).[11] Likewise, Sarin et al compared 61 children with EHPVO to 183 healthy, matched controls and found that despite similar nutrition (weight-for-height z-scores), there was a much higher incidence of stunted growth in the EHPVO group. More than 50% of children with EHPVO had height less than 90% of normal.[5] Finally, Menon et al reported that weight and height were more than two standard deviations below normal in 57% and 37% of children with EHPVO, respectively.[10]

Our current study, within limits, provides important insight into the etiology of growth restriction in children with EHPVO. In agreement with prior studies,[11] we found that IGF-1 is abnormally low. IGF-1 is produced in the liver in response to growth hormone. It is therefore conceivable that an anatomic abnormality which disrupts normal hepatopetal blood flow to the liver could interfere with this growth hormone axis. On a patient level, IGF-1 levels increased significantly following restoration of portal blood flow by the meso-Rex bypass. When converted to z-scores based on age and gender, this trend persisted but did not reach statistical significance. There was also a nearly-significant correlation between the postoperative change in IGF-1 levels and pre-albumin levels. This is an important area for future study.

Our work also helps to rule out several factors which might have been hypothesized to influence the growth profile of these children. We had hypothesized that disruption of normal portal venous blood

flow might create a situation wherein total energy expenditure would be increased before surgical correction, and would be normalized by meso-Rex bypass but this was not borne out in our data.   Total energy expenditure was normal for weight and gender and did not change significantly following surgery. The finding by Menon et al that growth restriction improved in children with EHPVO following distal splenorenal shunt suggested that growth restriction might be a sequela of portal hypertension itself, and not related to disruption of physiologic portal venous flow.[10] Based on his finding, we hypothesized that portal hypertension might cause portal enteropathy and subsequent malabsorption. However, our results demonstrate that stool caloric losses were only 3.7% of total caloric intake. Although comparison data in children is lacking, in healthy adults, stools losses of up to 5% are normal,[16] suggesting that malabsorption was not significant. We also found that caloric intake normalized to basal metabolic rate was normal in children with EHPVO and did not change following meso-Rex bypass. Therefore, inadequate caloric intake cannot be blamed.

The present study suffers from several important limitations, but also highlights key areas for future investigation.   Owing to the rarity of this disease, the number of patients who could be enrolled in the study was small, and the analysis was further restricting due to the patients who required conversion to portsosystemic shunts. Furthermore, the extent of growth restriction in this group was not as significant as had been observed in our prior retrospective study.[2] As such, we were limited in our ability to identify associations between growth restriction and the various aspects of the metabolic and nutritional profile. Nonetheless, our findings suggest that future investigation should focus on the role of growth hormone resistance attributable to altered portal venous blood flow.

In conclusion, children with EHPVO suffer from malnutrition and growth hormone resistance as evidenced by low pre-albumin and IGF-1 levels, respectively. These results help explain the well-established finding of growth restriction in children with EHPVO. Improvements in pre-albumin and IGF-1 levels following meso-Rex bypass may partially explain the increase in somatic growth which has been previously observed. Future studies should explore this axis further, specifically focusing on those children with the most marked growth deficits before meso-Rex shunt.

FIGURE LEGENDS

Figure 1: Changes in patient-level nutritional status following meso-Rex bypass. Pre-albumin level was abnormally low (14.6 ± 3.0 mg/dl) in children with EHPVO but increased significantly to 17.0 ± 4.3 mg/dl after surgery (p=0.026).

Figure 2: Patient level changes in the growth hormone axis. (a) Standard deviation scores for insulin-like growth factor-1 (IGF-1) were abnormally low in children with EHPVO (-1.57 ± 0.80) and there was a non-significant trend towards improvement one year after surgery (p=0.21). (b) The raw IGF-1 levels increased significantly over this time period (p=0.047).

Figure 3: Patient level changes in total energy expenditure. (a) Total energy expenditure in kcal/kg/day is shown before surgery and at one year following meso-Rex bypass. (b) Total energy expenditure as percent expected based on weight and gender was normal in children with EHPVO and did not change significantly following meso-Rex bypass (p=0.522).

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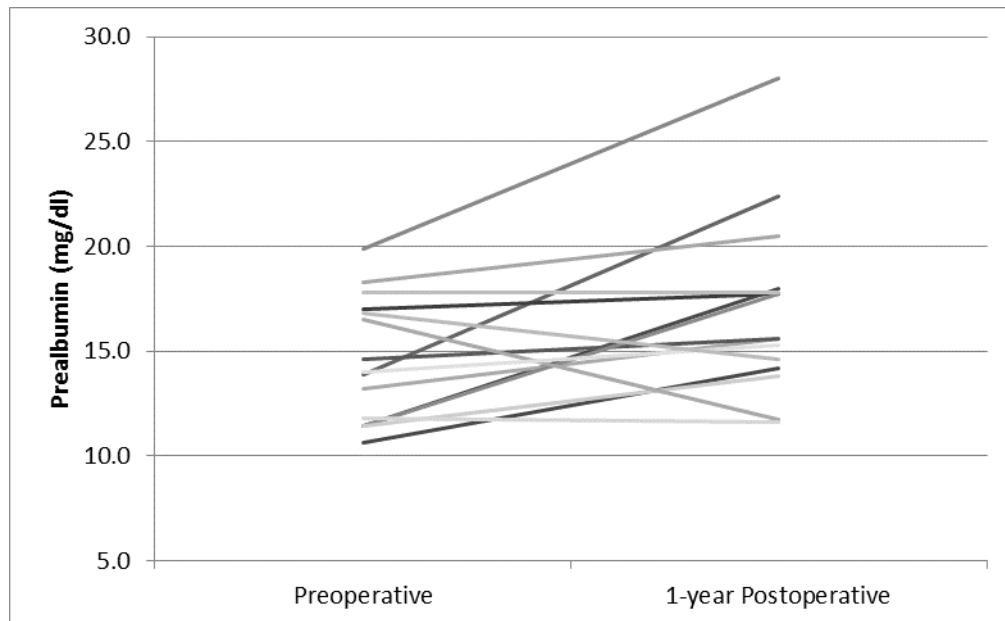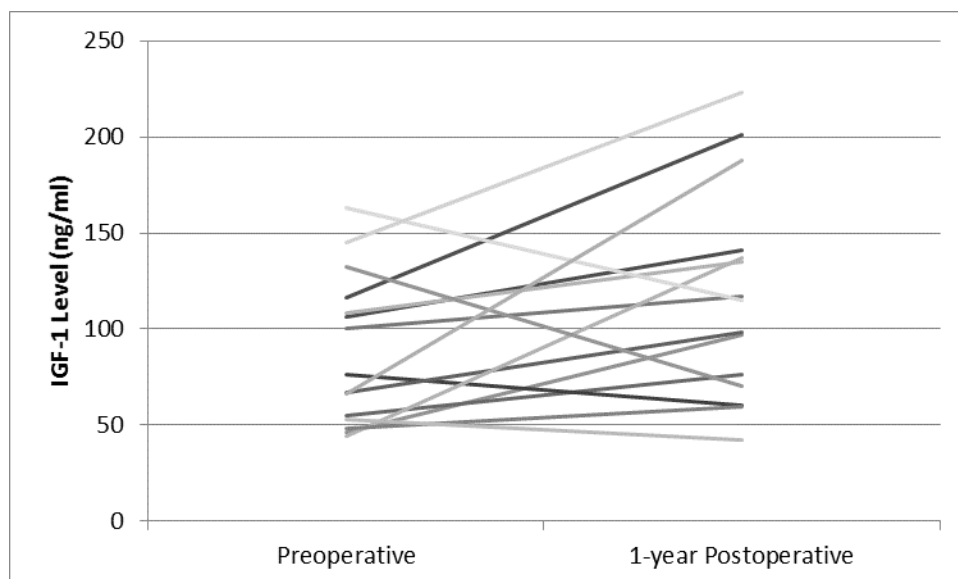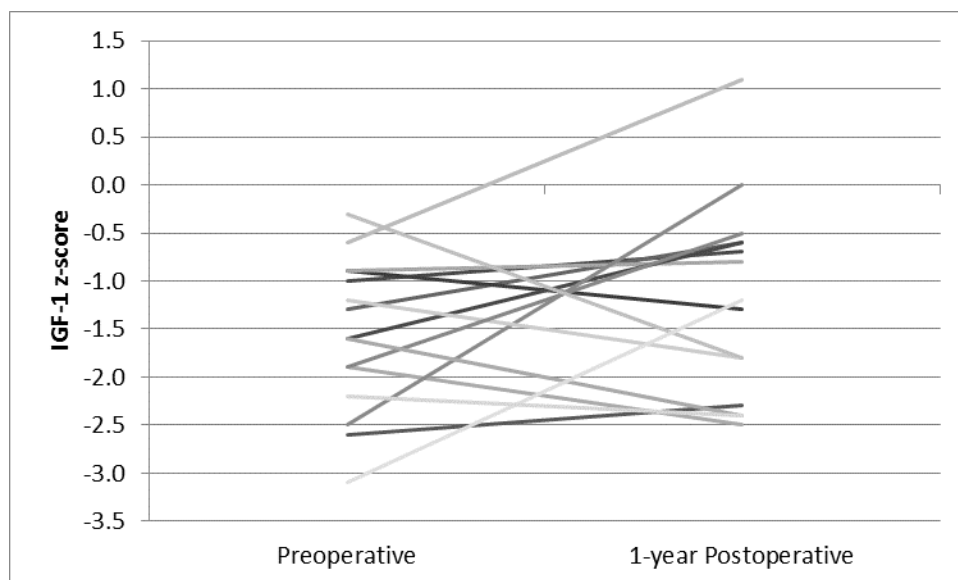
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