Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.JournalofSurgicalResearch.com

Metabolic profile of children with extrahepatic portal vein obstruction undergoing meso-Rex bypass

Timothy B. Lautz, MD,[a,*] *Simon Eaton, PhD,*[b] *Lisa Keys, MSN,*[a] *Joy Ito, BA,*[a] *Mario Polo, BSc,*[b] *Jonathan CK. Wells, PhD,*[b] *Agostino Pierro, MD,*[b] *and Riccardo A. Superina, MD*[a]

[a] *Department of Surgery, Ann & Robert H Lurie Children's Hospital of Chicago, Feinberg School of Medicine of Northwestern University, Chicago, Illinois*

[b] *Department of Surgery, Great Ormond Street Hospital and Institute of Child Health, University College London, London, UK*

ARTICLE INFO

Article history:
Received 24 March 2017
Received in revised form
13 September 2017
Accepted 12 October 2017
Available online xxx

Keywords:
Growth hormone
Insulin-like growth factor
Energy expenditure
Caloric intake
Prealbumin

ABSTRACT

Background: Extrahepatic portal vein obstruction (EHPVO) in children is often associated with growth restriction, which improves after the 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 1 year after 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 the 20 children underwent successful meso-Rex bypass at a median age of 4.3 years. Prealbumin level was abnormally low (14.6 ± 3.0 mg/dL) at surgery but improved (17.0 ± 4.3 mg/dL) 1 year later ($P = 0.026$). Mean insulin-like growth factor 1 (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 after 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. Prealbumin and IGF-1 levels improve after a successful meso-Rex bypass.

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 hemorrhage and hypersplenism. Disruption of normal portal venous circulation has been associated with

* *Corresponding author*. Ann & Robert H Lurie Children's Hospital of Chicago, 225 E Chicago Ave, Box 63, Chicago, IL 60611. Tel.: +(312) 227 4210; fax: +(312) 227 9678.
E-mail address: tlautz@luriechildrens.org (T.B. Lautz).

0022-4804/$ – see front matter
https://doi.org/10.1016/j.jss.2017.10.010

symptoms of growth retardation, neurocognitive dysfunction, and mild coagulopathy.[2-5]

Treatment options for EHPVO include the following: Conservative management with beta-blocker therapy and serial endoscopic banding to prevent variceal hemorrhage from the esophagus, portosystemic shunts, including the selective distal splenorenal or nonselective mesocaval shunt, and portal blood flow restoration with the meso-Rex bypass to both decompress the portal system and restore normal physiologic portal venous blood flow. Although 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 after meso-Rex bypass.[2,9] However, the physiologic basis for this observation is poorly understood. The finding by Menon *et al.*[10] that growth improved after portosystemic shunting suggests that portal hypertension itself might be an etiologic factor. It is possible that portal enteropathy leads to malabsorption and increased stool caloric losses. On the other hand, 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 after meso-Rex bypass can be explained by the differences in energy balance and hormonal milieu.

Methods

Between 2009 and 2011, 20 consecutive children aged 2-12 years with EHPVO 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 intrahepatic 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 present 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 1-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 Epi Info and the Centers for Disease Control 2000 standard data (Centers for Disease Control and Prevention, Atlanta, GA). Body composition (body fat and fat-free mass percentages) was determined by bioelectrical impedance analysis (BIA; Rjl Systems Inc, Clinton Township, MI). Prealbumin and transferrin levels were determined as markers of nutritional status.

Growth hormone axis

GH and IGF-1 levels were measured to test the hypothesis that EHPVO is associated with GH 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–McArdle formula [370 + (21.6 × 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 0.4 g D_2O (99.9%) per kg body weight and 3g 10.4 % $H_2^{18}O$ per kg body weight (Cortec Net Sa, Voisins-Le-Bretonneux, France). The test works by approximating the carbon dioxide (CO_2) production during this interval. This is possible because the ^{18}O equilibrates with the total body bicarbonate and dissolved CO_2 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* deuterium/hydrogen content in the urinary water can be used to determine the amount of ^{18}O loss in CO_2, which can be used to estimate total CO_2 production.[12] Urine samples were analyzed for background abundance levels (before dose) and isotopic enrichment (5, 24, 48, and 72 hours after 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 was 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] To ensure that only high-quality isotopic data were analyzed, TEE measurements were only included if isotope space ratio was between within 1.010 and 1.090.[13]