EARLY POSTNATAL MALNUTRITION INDUCED BY LOW-PROTEIN LOW-FAT DIET CAUSES INTESTINAL DYSMOTILITY

Peace N Dike[1], Geoffrey A Preidis[2], Krishnakant G Soni[2], Tripti Halder[2], Margaret E Conner[3]

[1] Baylor College of Medicine, Department of Pediatrics, Gastroenterology, Hepatology & Nutrition

[2] Baylor College of Medicine and Texas Children's Hospital, Pediatrics, Gastroenterology, Hepatology, & Nutrition

[3] Baylor College of Medicine , Molecular Virology and Microbiology, Molecular Virology and Microbiology

Background: Gastrointestinal (GI) dysmotility is observed in states of protein-calorie malnutrition. In patients with kwashiorkor, marasmus, and mild malnutrition, early contrast studies evidenced decreased intestinal tone. Similarly, sigmoidoscopy performed on children with severe kwashiorkor revealed “hypotonicity and laxity” of the distal colon. In other states of malnutrition, such as anorexia nervosa and small-for-gestational-age neonates, GI dysmotility is often present in the form of constipation and feeding intolerance. Mechanisms by which malnutrition causes GI dysmotility remain unclear. Objective: To model malnutrition-associated GI dysmotility in mice and to gain insight into possible underlying mechanisms.

Materials/Methods: Early postnatal malnutrition was induced by giving low-protein, low-fat “regional basic diet” (RBD) chow to lactating dams starting on pup day of life 8. Control litters were given isocaloric chow of normal macronutrient composition. Pups were weaned to the RBD or control chow and tested at 2 months of age. Upper GI tract motility was assessed by fluorescein isothiocyanate-dextran gavage and colonic motility was assessed by rectal bead latency. Intestinal segments were evaluated by light microscopy, and mucosa thickness, crypt depth, and muscularis interna and externa thicknesses were measured. Additional segments of the colon were analyzed ex vivo by force transduction to determine the contractile response to cholinergic stimulation. Finally, colon contents were analyzed by targeted LC/MS-MS to measure concentrations of pro-kinetic metabolites.

Results: RBD young adult males were underweight and stunted compared to RBD females. Gastric emptying was delayed in RBD young adult females but not males. A trend towards prolonged bead expulsion time was observed only in RBD young adult females. No histologic differences were observed. Force transduction studies demonstrated an exaggerated response to cholinergic stimulation in RBD young adult mice. LC/MS-MS revealed significant decreases in 16 of 19 bile acids in the colon of RBD young adults versus controls.

Conclusions: In our diet-induced model of early postnatal malnutrition, GI transit is delayed in a sex-specific manner. RBD mice also have decreased quantities of bile acids, potent prokinetic agents, in the colon. These data lead us to hypothesize that intestinal bile acid signaling abnormalities, which result from impaired hepatic bile acid biosynthesis in malnutrition, may contribute to malnutrition-induced GI dysmotility.