On the Origin of Pediatric Nonalcoholic Fatty Liver Disease

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See “Hepatic Steatosis Is Prevalent in Stillborns Delivered to Women With Diabetes Mellitus” by Deutsch et al on page 152.

When did nonalcoholic fatty liver disease (NAFLD) begin? This is an important question, especially because pediatric NAFLD is becoming more common and because of the significant associated morbidities. What, then, can one say regarding when NAFLD begins?

Many patients seen by gastroenterologists for NAFLD are adolescents or young adults. The question of when NAFLD begins is crucial to help us design more effective interventions. Based on the epidemiologic data, the prevalence of NAFLD among children and adolescents in the United States is high. For example, the prevalence of fatty liver prevalence increases with age ranging from 0.7% for ages 2 to 4 years up to 17.3% for ages 15 to 19 years (6). Fatty liver prevalence increases with age ranging from 0.7% for ages 2 to 4 years up to 17.3% for ages 15 to 19 years (6). Fatty liver prevalence increases with age ranging from 0.7% for ages 2 to 4 years up to 17.3% for ages 15 to 19 years (6). Fatty liver prevalence increases with age ranging from 0.7% for ages 2 to 4 years up to 17.3% for ages 15 to 19 years (6). Fatty liver prevalence increases with age ranging from 0.7% for ages 2 to 4 years up to 17.3% for ages 15 to 19 years (6). Fatty liver prevalence increases with age ranging from 0.7% for ages 2 to 4 years up to 17.3% for ages 15 to 19 years (6). Fatty liver prevalence increases with age ranging from 0.7% for ages 2 to 4 years up to 17.3% for ages 15 to 19 years (6). Fatty liver prevalence increases with age ranging from 0.7% for ages 2 to 4 years up to 17.3% for ages 15 to 19 years (6).

What, then, can one say regarding when NAFLD begins? Clinically, the mean age at presentation has decreased slightly, from 13 to 12 years (10). Whether hepatic steatosis associated with the fetal environment persists to become clinical NAFLD or disappears throughout infancy is unknown. As mentioned, if the onset of NAFLD occurs in the prenatal or neonatal period, then the prevalence of NAFLD in younger children should be higher than reported estimates; however, NAFLD may remain undetected in this demographic because it is a condition that can be relatively asymptomatic, and younger children are much less likely to have screening laboratories. If NAFLD does indeed begin at birth, it has broad implications for how we counsel women even before they are pregnant. Improvement in preconception nutrition and prenatal nutrition would be required. Moreover, infants who are born to women with diabetes mellitus, who were normal weight and did not have diabetes mellitus. Liver fat content was 68% higher in those neonates born to women with diabetes mellitus (controls). For the patients, maternal diabetes was a mixture of gestational diabetes and established type 1 and type 2 diabetes mellitus. The majority of these women were obese (61%) compared with the control group (33%). The main finding of their study was a substantially higher rate of steatosis among patients (79%) versus controls (17%). In addition, the severity of steatosis was greater in the patients and was positively correlated with fetal body weight independent of maternal obesity. Two studies have evaluated hepatic steatosis in neonates through the use of magnetic resonance spectroscopy. Modi et al reported that neonatal body mass index at conception was independently correlated with neonatal hepatic fat content (2). Brumbaugh et al reported on hepatic steatosis in 25 neonates born to women with obesity and gestational diabetes or born to women who were normal weight and did not have diabetes mellitus. Liver fat content was 68% higher in those neonates born to women with obesity and gestational diabetes (3). Surprisingly, neonatal adiposity was not correlated with neonatal liver fat in either study, suggesting that in fetal life the drivers for hepatic fat accumulation may differ from those for adipose storage. In animal models, maternal obesity and overnutrition show a strong association with the early onset of NAFLD in offspring. In nonhuman primates, McCurdy et al demonstrated that maternal obesity and a high-fat diet during gestation promoted fetal hepatic steatosis and oxidative stress during the third trimester (4). Likewise in a mouse model, Bruce et al reported that exposure to a high-fat diet in early development and postweaning periods increased the risk for nonalcoholic steatohepatitis in adult offspring. Wearing these mice to a standard control diet failed to fully reverse NAFLD, suggesting a lasting impact of the maternal environment on pathways of hepatic lipid metabolism (5).

The cohort of Patel et al included a majority of African American women (54%), followed by whites (27%) and a minor proportion of Hispanics (9%); however, these findings are not consistent with the epidemiology of NAFLD known in children. Hispanic children have the highest rate of hepatic steatosis, followed by whites, and then African American children, who have the lowest rate (6). In addition, other observations have suggested that African American children and adolescents tend to show a lower degree of fatty liver disease, even when controlling for obesity and insulin resistance (7). Thus, whether these new data are generalizable or not is unclear. Additionally, if NAFLD begins at birth, we would expect to see greater numbers of infants, toddlers, and young children with NAFLD. Based on data from the Study of Child and Adolescent Liver Epidemiology, the prevalence of NAFLD is extremely low in this age group and, in fact, is actually extremely low before 8 years of age. Fatty liver prevalence increases with age ranging from 0.7% for ages 2 to 4 years up to 17.3% for ages 15 to 19 years (6).

Fetal liver development begins at week 4 of gestation. During most of gestation, the developing fetal liver is in constant flux. In the environment of maternal obesity, the fetoplacental unit develops under conditions of both excess nutrients and inflammation. The increased substrate load creates a concentration gradient, driving lipid flux to the fetus. Excess fetal lipid exposure in early to midgestation may therefore use the liver and other developing organs as ectopic sites of excess lipid deposition in the absence of adipose tissue, resulting in whole-body insulin resistance and susceptibility to fatty liver throughout life. The postnatal persistence of increased hepatic steatosis may result from changes to hepatic de novo lipogenesis, fatty acid oxidation, or lipoprotein export. Maternal obesity appears to prime de novo lipogenesis (8). Bruce et al demonstrated reduced fatty acid oxidation in adult mice that had been exposed to a maternal high-fat diet and those postweaning high-fat diet were unable to clear increased levels of intrahepatic lipid (5). During this critical period when fetal development is “plastic,” the fetus is constantly experiencing a rapid cell proliferation, making it sensitive to environmental challenges. Therefore, neonatal overfeeding and postweaning high-fat diet could prime hepatic lipid synthesis pathways, which are associated with the onset and long-term risk for NAFLD, both developmentally and biochemically (8,9).

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women with diabetes mellitus—likely a high-risk group—would warrant close monitoring of nutritional status throughout childhood with anticipatory guidance provided to enhance awareness of potential for NAFLD development.

REFERENCES


**Taking Full Measure of the Pediatric Ulcerative Colitis Activity Index**

Oren Koslowe and Joel R. Rosh

See “Feasibility and Validity of the Pediatric Ulcerative Colitis Activity Index in Routine Clinical Practice” by Dotson et al on page 200.

The ability to accurately monitor disease activity in pediatric inflammatory bowel disease (IBD) has always been seen as an important goal. In addition to measuring treatment response in the individual patient, such a tool would facilitate the design of clinical trials for drug development. A reliable “scoring system” would generate a more consistent language for clinicians to discuss and describe disease status. The Physician Global Assessment (PGA) was the first scale used to measure, in a somewhat qualitative manner, the clinical status of pediatric patients with IBD. PGA became the standard with which newer clinical scoring systems have been compared (1).

The Pediatric Ulcerative Colitis Activity Index (PUCAI) was developed as a “pediatric friendly” tool in that it does not require an endoscopic evaluation. Perhaps the best demonstration to date of the PUCAI was the Outcome of Steroid Therapy in Colitis Individuals trial, which showed the use of daily PUCAI assessment in determining which patients should be moved on to second-line therapy when hospitalized for intravenous steroid treatment for severe ulcerative colitis (UC) (2). In our own pediatric IBD center, we have found it clinically helpful to calculate PUCAI scores when seeing our patients with UC in either the office or hospital setting, but how universal is the PUCAI? Can it be reliably used in various clinical settings by clinicians with a range of IBD clinical experience?

These important and practical questions are addressed head-on by Dotson et al in this issue of the *Journal of Pediatric Gastroenterology and Nutrition* (3). Using the large database created and maintained by the quality improvement network of Improve Care Now, the authors were able to look at data from thousands of clinical visits by pediatric patients with UC. The easy-to-use nature of the PUCAI was evidenced by the high rate (96%) of completed PUCAI assessments in this cohort. Using simultaneously assigned PGA scores, the authors were able to validate the PUCAI measurements and showed them to be responsive to change. The PUCAI was most accurate in distinguishing patients at the ends of the clinical spectrum and less so in distinguishing moderate from severe disease activity. As the authors point out, this is partially explained by the fact that the studied population was ambulatory, whereas the most severely active patients were hospitalized. One can appropriately wonder about the clinical impact of distinguishing ambulatory moderate from severe patients with UC because clinical disease activity and treatment plans are likely similar in both of these cases.

In performing their study, the authors clearly demonstrate the power of a multicenter quality improvement network. Dotson et al provide an important multicenter validation of the PUCAI as a facile, responsive clinical measurement. It is reassuring to see that the same clinical tool used in pediatric IBD centers can easily be implemented across different practice sites and settings. In addition to its clinical use, the PUCAI has also been used in clinical trials, but, because our understanding of the natural history of IBD has advanced, so have our treatment and clinical trial goals. Symptom relief is an important short-term goal, but the long-term treatment for IBD requires a positive effect on the natural course of the disease. This is most likely predicted by sustained mucosal healing, and, accordingly, assessment of mucosal integrity and the ability of a therapy to “turn off the inflammation” are likely to be part of any future pediatric IBD clinical trial.

Such measurement was a major focus of the 2 Gastroenterology Regulatory Endpoints and Advancement of Therapeutics workshops held by the Food and Drug Administration in 2012 and 2013 (4). What is emerging is the concept of a composite score that will factor in clinical, endoscopic, and patient-reported outcomes. The idea is not that the PUCAI is ineffective or even outdated, but rather that it is time to build upon its success with the next-generation activity index.

It is recognized that many of our colleagues share a hesitancy regarding mucosal assessment of disease activity in pediatric
patients. This reluctance is becoming replaced by the realization that we can do more for our patients than ever before. Such enhanced therapeutic capabilities need to be strengthened by our use of the most definitive outcome measures. There are some data to suggest that the PUCAI can predict endoscopic findings (5), and this and the role of surrogate fecal inflammatory markers need to be studied further. We await the day, hopefully in the near term, when we will glean useful diagnostic and therapeutic information from ongoing translational investigations of the clinical, genetic, and microbiome aspects of pediatric IBD such as are being performed in the Crohn’s & Colitis Foundation of America–funded RISK and National Institutes of Health–funded PROTECT (Predicting Response to Standardized Pediatric Colitis Therapy) studies (6).

The mantra that good data are needed for good studies could not be more true than in a field as complex as pediatric IBD, and there is no doubt that Dotson et al have done an excellent job in reinforcing the use and ease of use of the PUCAI. Although more work needs to be done, the pediatric gastrointestinal community has served our patients well by coming together both here and abroad to form large, multicenter collaborations such as Improve Care Now. Perhaps the most important way clinical indices have helped move the field forward is that they taught us the power of measurement and the need to do so accurately.

REFERENCES


Delivery Mode Shaped the Gut Microbiome in Chinese Newborns

Yao Yang and Jianzhong Hu

See “Bacterial Community Structure Associated With Elective Cesarean Section Versus Vaginal Delivery in Chinese Newborns” by Yu et al on page 240.

Microbes that live on and inside the human body (microbiota) consist of more than 100 trillion microbial cells and outnumber the host cells. Commensal bacteria provide a wide range of metabolic functions that the human body lacks. They facilitate diverse processes such as digestion, absorption, and storage of nutrients, and protection against pathogen colonization through competition for nutrients, secretion of antimicrobial substances, and microniche exclusion. Commensal bacteria also promote angiogenesis and development of the intestinal epithelium and have been shown to be essential for the normal development and function of the immune system. Although we know the essential role of the microbiome in maintaining the health status of the host, little is known about when the initial colonization of gut microbiome occurs. Recent evidence suggested that the initial colonization may be before birth (1,2) and seeded from the maternal environment. Furthermore, in early childhood, the gut microbiome was unstable and affected by birth mode, antibiotic usage, changes on feedings, and many other environmental factors.

In this issue of the Journal of Pediatric Gastroenterology and Nutrition, Yu et al describe how 41 Chinese newborns were recruited and their day 2 and day 4 postdelivery fecal samples were characterized to compare the composition and diversity of the intestinal microbiota by the delivery status, vaginally (VD) or by cesarean section (CD) (3). In spite of the experimental design in the Yu et al study using the denaturing gradient gel electrophoresis approach and Sanger sequencing being less informative than the bacterial 16S ribosomal RNA deep sequencing approach, it was concluded that the composition and overall structure of gut microbiome in infants was substantially different by delivery mode in Chinese newborns, which is consistent with the findings by other ethnic groups (4,5). In particular, a sample from VD infants showed enrichment of Escherichia coli and Bacteroides, which are commonly found in gut microbiota, whereas enriched Staphylococcus in CD infants was commonly found on skin. Those differential microbiome signatures suggest the possible seeding origins of varied bacterial strains in the infant gut; however, commonly found vagina-enriched Lactobacillus was observed in neither VD nor CD samples of the present study. Interestingly, when comparing day 2 and day 4 samples, it was observed that certain taxa such as Veillonella and a Neisseria mucosa strain were present only in day 4 samples and they are not differentiable by delivery mode. Those taxa may be seeded through later contact with the parents or the caregivers.

Overall, the Yu et al study demonstrated the effect of delivery mode on the diversified intestinal microbiota in Chinese newborns. With the economic expansion in the last 20 years in China, dramatic changes have occurred in the entire society, and increasing elective CD and many other environmental factors may affect the gut microbiome abundance and composition in early life and increase the risk in an infant’s later development. Therefore, a more extensive multicenter study is essential to evaluate samples obtained from a larger Chinese population using more advanced technology with a high sensitivity and resolution to fully assess the impact of the delivery mode on the intestinal microbiota of Chinese infants.
REFERENCES


Can Lipidomics Conceal the Key for Understanding Celiac Disease?

Birgitta Strandvik

See “Low n-3 Long-Chain Polyunsaturated Fatty Acids in Newly Diagnosed Celiac Disease in Children With Preexisting Type 1 Diabetes Mellitus” by Tárnok et al on page 255.

Despite intensive research to disclose the mechanism behind celiac disease (CD), it remains a challenge, and during the last decades the diagnosis has even extended to include pathological changes in relation to many other diseases, which from the beginning were considered unrelated to the typical intestinal pathology. Other puzzling factors are the variability of age at debut of symptoms and the variability of the symptoms (1). A clear link that has convincingly been shown to the human leukocyte antigen (HLA) class II molecules, HLA-DQ2 and HLA-DQ8, binding inflammatory CD4+ T-cell specific for gluten-derived peptides modifying glutamine by specific tissue transglutaminase. The typical picture is the chronic inflammation of the small intestine, and although it mainly or completely resolves with use of the gluten-free diet (2,3), its persistence in many cases has mainly been referred to incomplete dietary treatment, even though the proof for that is not always shown.

HLA-DQ2/8 is common in the human population, but only 1% of carriers develop CD. An increased risk for the disease in relatives with the same HLA haplotype has not given a clue to other factors of importance. The new development of single nucleotide polymorphisms has allowed for genome-wide association studies, which in CD may explain approximately 50% of the genetic variation of the disease (4). Most of these loci are related to immunology showing overlap in expression of many other autoimmune diseases. High variants of genome-wide association studies are located in noncoding regions of the genome, which suggests that the genetic variation may be an effect of the influence on gene expression rather than intragenetic changes (4).

Fatty acids are potent modifiers of gene expression (5). The Western diet has changed markedly during the last decades in fat quality composition, with an increase in vegetable oils giving high levels of linoleic acid, the precursor of arachidonic acid, substrate for a cascade of proinflammatory eicosanoids. This can be balanced by the anti-inflammatory lipid mediators from the omega-3 fatty acids, necessary to resolve inflammation. The dietary fatty acids influence the composition of membranes differently in different tissues, and this can interfere with membrane protein function, such as receptors, channels, and enzymes.

Tárnok et al (6) report in this issue of the *Journal of Pediatric Gastroenterology and Nutrition* about the difference in long-chain polyunsaturated fatty acids in children with CD with and without preexisting type 1 diabetes mellitus. Both conditions are characterized by severe inflammation. The results confirm findings by others that the fatty acid profile in plasma regarding omega-3 fatty acids may be related to diabetes mellitus (7), but found no difference in plasma fatty acid profile between patients with CD and controls. A study in CD with a small group of patients found 30% lower docosahexaenoic acid in the plasma of patients with CD, which, however, was not significantly different from the controls (8). Tárnok et al (6) conclude that a lack of difference in plasma does not necessarily exclude a difference in the target organ, that is, the intestine. Such a conclusion is supported by findings in animal experiments that showed different fatty acid profiles in different intestinal segments not reflected in plasma (9) and also by studies in CD not showing similar fatty acid profiles in plasma and the intestinal mucosa (8). Of more interest may be that neither the fatty acid pattern nor the electrophysiological abnormalities in the mucosa were normalized in patients with CD in remission with normal morphology (8,10). An intrinsic abnormality in the mucosa may therefore contribute to gluten sensitivity. Furthermore, in vitro studies have shown that docosahexaenoic acid can be of importance by modulating the inflammation in intestinal epithelial cells exposed to gliadin peptides via inhibition of the arachidonic acid–liberating enzyme, phospholipase A2, which is the rate-limiting enzyme in the arachidonic acid cascade (11).

In view of the strong activity of the eicosanoid system in the intestinal tract (12), it would be of value if more research were focused on the mucosa and its cell populations in relation to fatty acid profiles and lipid mediators. A balance between the omega-6 and omega-3 fatty acids is crucial for the resolution of inflammation and preventing transformation to a chronic condition (13). Fatty acids have a strong impact on immunology besides locally acting on membrane composition and function. The modifying role of breastfeeding on the symptoms of CD would be 1 target for such studies because the fatty acid composition of breast milk is dependent on maternal diet and reflects the high omega-6 intake in the Western diet (14). Finding a treatment directed to inaccuracies in the basic mucosa may even open a possibility for prevention.

REFERENCES


