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Helping Kids with Crohn's to Reach New Heights

Doctors have long observed that many children with Crohn's disease experience growth impairment. Their inability to match the physical stature of their peers may be due to poor nutrition, chronic corticosteroid use, and/or longstanding inflammation. Growth impairment affects boys more than girls, while girls tend to have a more severe disease course, including a greater need for surgery, than boys. Could hormones be to blame?

Neera Gupta, MD, MAS, Attending Physician at NewYork-Presbyterian Hospital/Phyllis and David Komansky Center for Children's Health and Assistant Professor of Pediatrics at Weill Cornell Medical College, is leading a clinical study to find out. Supported by more than $3 million in National Institutes of Health funding to Dr. Gupta, the multicenter prospective longitudinal study — headquartered at NYP/Komansky Center — aims to enroll 125 pediatric patients with Crohn's disease (bone age 9-12 years in girls and bone age 10-14 years in boys) who will be followed for two years. Investigators will determine the role of hormones in sex-specific growth impairment, and the impact of inflammation on hormones and sex-specific growth impairment in children with Crohn's disease.

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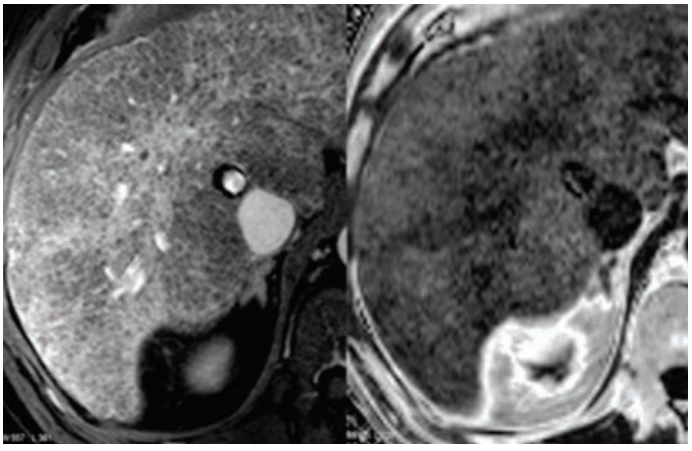

Fibrotic liver (left) and fatty liver. The FLINT trial showed the efficacy of obeticholic acid for improving liver health.

A Promising Treatment for Non-Alcoholic Fatty Liver Disease

Non-alcoholic steatohepatitis (NASH) is estimated to affect 2 to 5 percent of American adults, and there are currently no labelled treatments for this disease. As many as one in four adults with NASH advance to cirrhosis. There has also been an alarming increase in non-alcoholic fatty liver disease (NAFLD) in children, due to the rise in obesity. "We have 8-year-olds with NASH-related cirrhosis," says Joel E. Lavine, MD, PhD, Professor and Vice Chairman of Pediatrics at Columbia University College of Physicians and Surgeons and Chief of Gastroenterology, Hepatology and Nutrition at NewYork-Presbyterian/Morgan Stanley Children's Hospital.

But that may soon change. The findings of the recently completed FLINT Trial (Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment), a Phase IIB study which evaluated the tolerability and efficacy of the drug obeticholic acid, were recently published online in the journal *Lancet* (November 7, 2014). More than twice as many patients with NASH receiving obeticholic acid — 46 percent — experienced improved liver health, compared with just 21 percent of patients receiving a placebo. Improved liver health was defined as a reduction in the NAFLD Activity Score of at least two points, with no worsening of fibrosis.

FLINT was a double blind, placebo-controlled trial of a once-daily dose of 25mg of obeticholic acid or placebo given for 72 weeks in 283 adult patients with biopsy-proven NASH.

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Armed with new data — including serum and urine biomarkers (like inflammatory cytokine and hormone levels), serial measurements of bone age, and clinical variables (such as disease location) — Dr. Gupta and her team will develop separate predictive models for boys and for girls to identify patients at high risk for growth impairment who cannot be treated successfully with standard therapeutic approaches (a sequential "step-up" approach that focuses on inducing a clinical remission and maintaining a clinical response).

Dr. Gupta has already published research showing that insulin-like growth factor 1 levels were more compromised in boys with Crohn's disease than in girls, possibly explaining their greater risk for shorter height. "In males, inflammation seems to more adversely affect levels of hormones that are important in growth, and this may help explain their increased susceptibility to growth impairment," Dr. Gupta explains. "The male-female dichotomy in risk for growth impairment in Crohn's disease is a window for understanding the effects of inflammation on growth in both sexes."

Growth impairment affects boys with Crohn's disease more than girls, while girls tend to have a more severe disease course.

Current treatment strategies for improving growth impairment and final adult height in pediatric patients with Crohn's disease are suboptimal. Identifying risk factors for growth impairment and understanding the underlying mechanisms of the observed sex differences may guide the development of new targeted medical treatments to improve height velocity and final adult height. For example, biologic agents like infliximab are currently used when other therapies have failed (the step-up approach). Since children with Crohn's disease remain growth-impaired despite the incorporation of biologic agents into the Crohn's disease arsenal, Dr. Gupta theorizes that infliximab should be introduced as first-line therapy (a "top-down" approach) in high-risk children — as identified by the new predictive model she plans to develop — since there is a narrow therapeutic window when clinicians can intervene effectively. After the current study is complete, the next step will be an interventional clinical trial assessing such novel therapeutic approaches (comparing a top-down versus a step-up approach) in high-risk children.

"Determining which children are high-risk and appropriate candidates for the early introduction of high-level medications — the top-down treatment paradigm — would represent a major turning point in the management of children with Crohn's disease," she asserts. "The findings of this research will significantly improve our understanding of growth impairment in Crohn's disease and possibly other chronic pediatric inflammatory conditions, and ultimately lead to improvements in the care we provide to our patients."

For more information about pediatric IBD care at NYP/Komansky Center or to refer a patient, contact (646) 962-3869.

Gut Feelings: Getting to the Root of GI Problems in Autism

The mice behaved differently than their peers. They showed obsessive-compulsive tendencies, repeatedly climbing up and down a water bottle. They had an increased sensitivity to sound. Their vocalization after birth was delayed. And they preferred socializing with inanimate objects.

What accounted for the differences? These mice were bred to have the most common genetic serotonin transporter mutation found in human autism. Researchers at Vanderbilt University developed this mouse model, and investigators at NewYork-Presbyterian/Morgan Stanley Children's Hospital are now using it to discern why children with autism have more gastrointestinal disorders than those without autism. Their findings may lead to novel therapies for children with autism and digestive problems. They are the only researchers in the New York City area doing this type of work.

Up to 95 percent of the body's serotonin is produced in the gut, with the remainder in the brain. "Because serotonin plays such critical roles in the intestine, we sought to determine if there were intestinal defects associated with this mutation," explains Kara Gross Margolis, MD, Attending Physician and Assistant Professor of Pediatrics at Columbia, who is leading the research with Michael Gershon, MD, Professor of Pathology and Cell Biology. Individuals with autism have GI problems at four times the rate of those without autism, including motility disorders such as chronic constipation and diarrhea and gastroesophageal reflux disease. GI problems have also been strongly correlated with difficult and worrisome behaviors in children with autism spectrum disorders.

Dr. Margolis and her team found that the mice with the autism gene possessed major abnormalities in the development of their enteric nervous systems, leading to severe constipation, disordered intestinal contraction, altered intestinal permeability, and a predisposition to intestinal inflammation. The scientists are now looking at the pathways that control the development of intestinal motility and inflammatory abnormalities, and initial studies suggest that the team may be able to reverse them.

The link between autism and digestive problems is not surprising, given that the enteric nervous system develops in similar ways as the central nervous system. "So

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The drug's strong efficacy was first identified in January 2014; treatment was stopped early and all patients were moved into the 24-week follow-up phase, and they no longer needed end-of-treatment liver biopsies (which carry their own risks). Given the drug's efficacy profile, it may eventually be assessed in children with NASH.

While the treatment of patients in FLINT took place at the University of California, San Diego (UCSD), Dr. Lavine — who was previously on the UCSD faculty — continued as one of the principal investigators of FLINT, which is funded through the National Institutes of Health NASH Clinical Research Network. Dr. Lavine serves as Co-Chair of the NASH Clinical Research Network Steering Committee and was one of the *Lancet* report co-authors. "Given the lack of approved pharmacologic therapies for NASH, these findings are very exciting," he says.

There's been an alarming increase in pediatric fatty liver disease, largely due to obesity.

Obeticholic acid selectively binds to and induces activity in the farnesoid X receptor (FXR), a nuclear hormone receptor that regulates glucose and lipid metabolism. In prior studies, the drug decreased insulin resistance and hepatic steatosis in animal models, and also reduced insulin resistance, body weight, and markers of liver fibrosis among patients with NAFLD and type 2 diabetes (*Gastroenterology.* 2013;145:574-582). "These data show that this drug may not only make it possible to stop the progression of cirrhosis, but actually reverse it," adds Dr. Lavine.

The Fatty Liver Clinic for Children

NAFLD is now recognized as the most common cause of liver disease among children in the United States. If left undetected and untreated, NAFLD can lead to significant liver injury. NYP/Morgan Stanley Children's has established a weekly clinic dedicated to the study and care of children with fatty liver disease. Patients have the opportunity to enroll in clinical trials, such as the NIH-funded multicenter CyNCh (Cysteamine Bitartrate Delayed-Release for the Treatment of Nonalcoholic Fatty Liver Disease in Children) Trial, of which Dr. Lavine is the principal investigator. This study enrolled 169 boys and girls ages 8-17 years with NAFLD. Participants are receiving enteric-coated cysteamine or placebo by mouth twice a day for a year. Cysteamine is an antioxidant that Dr. Lavine showed in a pilot study to have efficacy against NASH.

"For many people, following a weight loss plan can be daunting, especially if they have limited access to healthy food options and infrequent opportunities for physical activity," said Dr. Lavine. "We expect this study will move us closer to finding a safe and effective treatment for children with fatty liver disease."

For more information about the children's fatty liver disease clinic at NYP/Morgan Stanley Children's or to refer a patient, call (212) 305-NASH or (212) 305-5903, or e-mail fattyliver@columbia.edu.

when there are abnormalities in brain development, like autism, it is more likely that there will be abnormalities in gut development," says Dr. Margolis. "We hope that by elucidating and reversing defects in the enteric nervous system, these therapies may also help correct abnormalities in the brains of individuals with autism."

While her group and others have determined that serotonin plays a critical role in the modulation of intestinal inflammation, it was Dr. Margolis' team that found that only one part of serotonin synthesis is responsible for gut inflammation. They showed that tryptophan hydroxylase 1 (TPH1), the enzyme responsible for serotonin production in the gut, promotes inflammation, while TPH2 (which governs serotonin in the enteric neurons) has a protective effect. They were the first to show that blocking TPH1 while maintaining levels of TPH2-derived serotonin would be a critical concept in the treatment of intestinal inflammatory disorders (*Gut.* 2014;63:928-37). This study has led to Phase II clinical trials in patients with inflammatory bowel diseases.

Dr. Margolis concludes, "We think that these findings will change the paradigm by which people think of the relationship between autism and GI, and enhance our understanding of the critical role serotonin plays in enteric nervous system development and GI function."

Individuals with autism have GI problems at four times the rate of those without autism.

NewYork-Presbyterian AMAZING THINGS ARE HAPPENING HERE FOR KIDS

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