Role of the Microbiome in Celiac Disease

RESEARCHERS AT THE CENTER FOR CELIAC

Research and Treatment at Mass General Hospital for Children (MGHfC) are investigating whether imbalances in the gut microbiome play a critical role in the loss of tolerance in celiac disease, an autoimmune disorder in which gluten triggers a reaction that damages the small intestine in genetically vulnerable people. The microbiome exerts an epigenetic influence on how risk genes are expressed and on immune system dynamics, and its composition and metabolites differ among individuals, based on their genes, diet, and history of infection and antibiotic treatment, explains Alessio Fasano, MD, director of the Center and chief of the Department of Pediatric Gastroenterology and Nutrition at MGHfC. Dr. Fasano is leading the large, international Celiac Disease Genomic Environmental Microbiome study (CDGEMM) to further investigate this hypothesis.

Autoimmune diseases are thought to result from three components: a genetic predisposition, an environmental trigger and an auto-antibody that attacks the body’s own tissues. Celiac disease is considered a model for the study of autoimmunity because all three components are known: HLA-DQ2 and -DQ8 genes; gluten as a trigger; and immunoglobulin A antibody. While a necessary environmental trigger, gluten is not sufficient to initiate autoimmunity, explains Dr. Fasano. Identifying the additional environmental factors contributing to the loss of gluten tolerance could lead to predictive markers for autoimmunity and new approaches for preventing the onset of celiac disease.

Dr. Fasano has previously demonstrated that celiac disease can have adult onset, suggesting that genetically susceptible people may tolerate gluten until additional events cause them to develop autoimmunity.1 He investigated some of the possible contributing factors in a 10-year intervention study with 700 children. The study found that introducing gluten to babies at 12 months instead of six months delayed, but did not prevent, the onset of celiac disease. Breastfeeding also did not prove protective, but vaginal birth did when compared to caesarean birth,2 possibly, Dr. Fasano hypothesized, because of the influence of the microbiome.

For the current CDGEMM study, researchers will analyze the genetic makeup of the infants and environmental variables that contribute to the development of celiac disease: timing of gluten introduction, method of delivery (caesarean or vaginal birth) and other factors. They will also analyze the gut microbiome, its metabolites and their dynamic interplay with diet and other changes in the child’s health and environment.

The researchers hope to define biomarkers that predict the development of celiac disease before it happens, and to identify metabolite pathways with implications for treatment and prevention of celiac disease and, by extension, other forms of autoimmunity.

Obesity Interventions for Children and Adolescents

**OBESITY IN CHILDREN** causes serious co-morbidities with lifelong consequences for their health. Children with a body mass index (BMI) ≥ 95th percentile are at risk for cardiovascular disease, type 2 diabetes, fatty liver disease and obstructive sleep apnea, which increases the risk for attention difficulties and school failure.

MassGeneral Hospital for Children (MGHfC) provides clinical services for the prevention, management and treatment of obesity. One example is the Raising Healthy Hearts Program, a preventive cardiology clinic that cares for children whose underlying condition is obesity and where patients require weight management. Co-locating weight management with specialties that manage cardiovascular
disease and diabetes, according to Elsie Taveras, MD, MPH, chief of the division of general pediatrics and director of pediatric population health management, allows the hospital to integrate weight management as a core clinical service.

Dr. Taveras also oversees a research program focused on obesity prevention and management in infancy through adolescence and for pregnant women and mothers. Her ongoing study, Connect 4 Health, is creating linkages between clinical services and community resources to reduce childhood obesity.

This study used census tracks and electronic health records to identify “hot spots” in eastern Massachusetts where more than 15% of children aged 2–19 have BMIs that are greater than or equal to the 95th percentile. Researchers identified positive outliers (children with healthy weight management) in those neighborhoods, and interviewed them and their families to discover their successful strategies. Commonly, the families leveraged opportunities in the community for healthier nutrition and physical activity, such as farmers markets, indoor playgrounds for winter or wellness centers. Participating pediatricians are connecting obese patients with health coaches who encourage and facilitate use of these resources.

**Surgical Treatments**

Bariatric surgery, long recognized as the most effective treatment for severe obesity in adults, is increasingly used in adolescents aged 13–22 who cannot manage their weight through diet and lifestyle. The MGHfC Adolescents Weight Loss Surgery (AWLS) Program, directed by surgeon Janey Pratt, MD, treats patients with an average BMI of 50 who weigh up to 500 pounds and have been obese since childhood.

The patients undergo one of two procedures: Roux-en-Y gastric bypass or a vertical sleeve gastrectomy (which causes fewer short-term complications and vitamin deficiencies). Among the MGHfC patients, diabetes is resolved within days in 80% of bypass and 50% of sleeve procedures; both procedures resolve sleep apnea 70% of the time as a result of weight loss. Dr. Pratt and colleagues have shown that weight loss and the resolution of diabetes happen independently of one another via different metabolic pathways controlling gastrointestinal hormone balances. She is now interested in whether bariatric surgeries would be more beneficial in morbidly obese children aged 10–12, before the onset of life-limiting comorbidities.

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The Concussion Spectrum: Tracing the Impact

**DESPITE GROWING CONCERN** about long-term deficits caused by repetitive mild concussive injuries in student athletes, researchers still lack a rigorous scientific consensus on clinical measures, diagnosis and treatment of mild concussion. A diverse clinical and research program at the MassGeneral Hospital for Children (MGHfC) Sports Concussion Program, led by Grant Iverson, PhD, is designed to address this research gap, improving clinical care by translating and applying findings about concussion in adult and animal studies to children and adolescents. Current aims of the program include assessing cognition more reliably and accurately, providing better rehabilitation services, and determining the roles of rest and exercise in rehabilitation.

**Concussions Diagnosed in Athletes**
The signs and symptoms that clinicians use to diagnose concussion are not consistent among specialties. What a sports medical team may call a concussion, an emergency physician may not, explains director of Pediatric Neurosurgery at MGHfC Ann-Christine Duhaime, MD. She believes that the term “concussion spectrum” more accurately encompasses the variable consequences of head impacts. The field of biomechanics offers promising leads to better explore the nature of concussive injury. For instance, sports helmets equipped with impact monitoring/measurement technology present a novel opportunity to study concussions and neuropsychological changes in student athletes. Dr. Duhaime and a multidisciplinary team found that the symptoms leading to concussion diagnosis by college athletic personnel were more diverse and subjective than expected. Surprisingly, symptoms often began hours or days after a game or practice, and many were not associated with a specific impact event. Moreover, there was no specific “threshold” of measured acceleration force that consistently caused a concussion and below which symptoms did not occur. Even without symptoms or diagnosis of concussion, repeated impact events may cause long-term harm in some people.

**The Vulnerable Period in Mice**
Because many questions about concussions cannot be mechanistically studied in humans, Michael Whalen, MD, a pediatric intensivist at MGHfC, has developed clinically relevant adult and adolescent mouse models of repetitive mild concussions that mimic both the lack of histopathology and the impact plus free head acceleration. The 4.2-FOLD INCREASE in diagnosed concussions from 1998 to 2008 for girls and boys in high school sports may partially reflect more awareness of the signs and symptoms of concussion, leading to increased reporting.

**COGNITIVE LEARNING** is measured by a decline in latency in finding a hidden or visible platform on the Morris water maze. Top panel shows decline in cognitive outcome in a five-hit mouse concussion model when closed head injuries (CHIs) are spaced a day apart, without a recovery period. Middle panel shows lack of long-term deficit at six months when concussions are spaced two weeks apart. Bottom panel shows emergence of cognitive deficits when concussions are spaced two weeks apart (recovery period) AND a higher height is used for the weight drop: With more severe injury, the two-week rest period that was protective in the middle panel is no longer safe. Researchers do not know how to judge injury severity in a human with concussion, so the “safe” rest period is still uncertain for any given level of concussive injury.
mechanisms of injury seen in sports-related concussions. Validating the concept of a period of vulnerability between injuries, he found that mice whose brains had time to recover did not exhibit long-term deficits following subsequent concussions. Mice that received subsequent injuries within the period of vulnerability, however, experienced cognitive effects that were cumulative and persistent and/or permanent. Dr. Whalen is studying molecular and cellular pathways induced by concussion, and whether their time course and resolution reflects the protective rest interval between injuries.

**What Is Known About the Role of Rest?**

In humans, a recovery period following a concussion can prevent an overlapping injury when the brain is vulnerable. But contrary to standard belief, MGHfC experts do not advise extreme physical and cognitive rest (staying in bed in a dark room with no reading, screen time or socializing). The evidence does not support those recommendations, Dr. Iverson concluded in a review article, but rather suggests that too much rest can prolong symptoms, delay recovery and cause psychological distress. A better strategy is to refrain from activities that risk overlapping injuries to the head and brain, and to gradually resume physical and other activities unless they cause significant headaches or other symptoms.

The MGHfC Concussion Clinic individualizes treatments to ensure a safe, swift and durable return to school and sports; both overlapping injury and too much rest make it more difficult to achieve that outcome. The researchers hope their work facilitates the development of evidence-based guidelines for better diagnosis and treatment of concussions.

6 Unpublished data, Whalen Lab, MGHfC.