

ADVANCES IN PEDIATRIC ENDOCRINOLOGY

January 2013
SPECIAL EDITION

SAVE THE DATE

Brain Attack and Cerebrovascular Disease Update 2013

March 8, 2013
New York Academy of Medicine
New York, NY

Brain Tumor Biotech Summit 2013

June 7, 2013
Weill Cornell Medical College
New York, NY

Advanced Endoscopic Skull Base and Pituitary Surgery, Hands-on Symposium

June 14-15, 2013
Weill Cornell Medical College
New York, NY

For more information and to register, visit nyp.org/pro or e-mail jeg9059@nyp.org



Top Ranked Hospital in New York.
Twelve Years Running.

NewYork-Presbyterian Hospital
is ranked 10th in the nation in
Pediatric Endocrinology.

Clinicians and Researchers Focus on Advancing Expertise in Spectrum of Pediatric Endocrinopathies

NewYork-Presbyterian Morgan Stanley Children's Hospital and NewYork-Presbyterian Phyllis and David Komansky Center for Children's Health are both important centers for innovation in research and clinical care in a variety of pediatric endocrinopathies, with expertise in such disorders as congenital adrenal hyperplasia (CAH), thalassemia, vitamin D deficiencies, and polycystic ovary syndrome.

Work on Congenital Adrenal Hyperplasia Recognized for Excellence

The clinical expertise and research in CAH at the NewYork-Presbyterian Komansky Center for Children's Health have been recognized by the CARES Foundation, the main patient and family support group for CAH. NewYork-Presbyterian Hospital was named as a Comprehensive Care Center of Excellence for CAH—the first such center in the nation to be so acknowledged. “What sets us apart from other programs that competed for this award,” said Maria Vogiatzi, MD, Chief of Pediatric Endocrinology at the Komansky Center for Children's Health, “is the fact that we have developed strong and meaningful collaborations with a group of specialties with expertise in CAH, so we can provide comprehensive care and serve as a ‘medical home’ for these patients.”

Over the past few years, the Division has become a referral center for CAH for the New York tristate area, and now serves a growing number of patients with the disease. In addition to excellence in clinical care, faculty has established educational conferences for patients and their families. With this award, the Division plans to expand these educational activities, develop practice protocols toward transitioning pediatric patients over to the adult clinical service, and increase its involvement in research. “We hope, with the establishment of the Center, to increase the number of our clinical protocols,” said Dr. Vogiatzi. “As our patient population grows, we want to get involved with outcomes research, test new drugs, and establish new therapies.”

Current research in CAH involves studies on stress doses of steroids during an acute illness or



physical stress. “Our understanding about optimal steroid doses during an illness or surgery for patients with CAH is at the moment incomplete,” said Dr. Vogiatzi. “We hope that the study will provide valuable information that will help in the management of these patients.” In addition to this project, faculty members at Weill Cornell Medical College are involved with research that addresses issues around quality of life in patients with CAH. At an earlier stage, Dr. Vogiatzi and collaborators examined the role of growth hormone alone or in combination with pubertal suppression with gonadotropin-releasing hormone analog to improve growth and final height in children with CAH.

“The children typically grow well, but for a number of them the window of growth is much shorter,” Dr. Vogiatzi said. “The study was meant to help children with CAH who had an unfavorable height prediction.” The study, published in the *Journal of Clinical Endocrinology and Metabolism*,¹ showed that such therapy improves final height and can be an alternative treatment for CAH children who typically face a relatively short adult height. Specifically, the researchers treated 34 patients with CAH (19 boys, 15 girls) with growth hormone, alone or in combination with a luteinizing hormone-releasing hormone analog. As a result, all the children reached significantly higher final adult heights than initially predicted. Boys reached 172.0 ± 4.8 cm rather than the predicted 162.8 ± 7.7 cm ($P < 0.001$); girls

See **Endocrinopathies**, page 2

continued from **Endocrinopathies**, page 1

reached 162.2 ± 5.3 cm rather than the predicted 151.7 ± 5.2 cm ($P < 0.001$).

Beyond CAH, the Division continues its pioneering work in the area of endocrinopathies related to thalassemia and iron overload. Dr. Vogiatzi and her colleagues were one of the first groups to describe high rates of osteoporosis in these patients beginning at a very young age.² The studies, which included patients from all major thalassemia programs in the United States and Canada, showed suboptimal bone accrual in children and adolescents with thalassemia; proved associations between severity of osteoporosis and fractures; and described the prevalence of growth, endocrine, and vitamin D abnormalities among the various thalassemia syndromes in North America.^{3,4} Dr. Vogiatzi and her collaborators are now using mouse models of thalassemia to understand the mechanism by which erythropoiesis and iron overload affect bone remodeling.^{5,6}

NewYork-Presbyterian Hospital was named as a Comprehensive Care Center of Excellence for congenital adrenal hyperplasia—the first such center in the nation to be so acknowledged.

At present, both the NewYork-Presbyterian Komansky Center for Children's Health and NewYork-Presbyterian Morgan Stanley Children's Hospital are designated New York State newborn screening programs for CAH. Dr. Vogiatzi and Sharon Oberfield, MD, Director of Pediatric Endocrinology, Diabetes, and Metabolism at Morgan Stanley Children's Hospital, are board members of the CARES Foundation.

Adolescent Bone Health Studied in Connection With Bariatric Surgery

Researchers at Morgan Stanley Children's Hospital have been studying adolescent bone health before and after bariatric surgery. The work is especially important as childhood obesity continues to rise and an increasing number of adolescents are undergoing bariatric surgical procedures.

In a study presented at The Endocrine Society's 2012 annual meeting, Marisa Censani, MD, Pediatric Endocrinology Fellow at Morgan Stanley Children's Hospital, and her colleagues sought to determine vitamin D deficiency in morbidly obese adolescents being evaluated for bariatric surgery.⁷ The investigators reviewed medical records of 236 adolescent patients evaluated for bariatric surgery between March 2006 and June 2011; of these records, 219 had data on vitamin D levels. Vitamin D levels were deficient (< 20 ng/mL) in 53% of patients, and inversely associated with body mass index ($r = -0.28$; $P < 0.0001$). The strongest predictor of low vitamin D levels was race: 82% of blacks, 59% of Hispanics, and 37% of white patients were vitamin D-deficient.

"We found over half of all the obese adolescents who present for bariatric surgery are vitamin D-deficient," said Dr. Censani. "We found the most obese adolescents had the lowest vitamin D

levels; we also noted that African Americans were at greatest risk for vitamin D deficiency. Our data suggested that all morbidly obese adolescents should be screened for vitamin D deficiency, and those who are deficient should be treated."

She added, "The data extend previously reported adult findings to the adolescent population—that the high prevalence of vitamin D deficiency varies according to the extent of obesity and race."

Previously, at the 2011 American Society of Bone Mineral Research (ASBMR) annual meeting, Dr. Censani received an ASBMR President's Poster Competition Award for a pilot study on the effects of laparoscopic adjustable gastric banding (LAGB) and weight loss on bone turnover markers. "It had been shown that there are increased bone turnover and decreased bone mineral density (BMD) in adult patients pre- and post-bariatric surgery,"

said Dr. Censani. "No one had looked prospectively at adolescent patients undergoing bariatric surgery and the effects on bone turnover markers that could reflect long-term bone health."

"As our patient population grows, we want to get involved with outcomes research, test new drugs, and establish new therapies."

—Maria Vogiatzi, MD

The researchers examined 2 markers, one of bone formation, osteocalcin, and one of bone resorption, C-telopeptide. They conducted a pilot study on 11 patients, measuring the markers at baseline and 12 months after LAGB. At this age, bone turnover markers are expected to either level off on a plateau or begin to decline. Instead, bone turnover markers rose sharply by 12 months after bariatric surgery, with osteocalcin increasing 3.5-fold and C-telopeptide doubling ($P < 0.001$ for both).

"The concern is that we shouldn't be seeing this amount of bone turnover in this patient population at this particular stage and age," said Dr. Censani. "Adolescence is a time of peak bone mineral accrual and anything that occurs during that time that might provoke a detriment to peak bone mass could affect the strength of bones long-term." The next step for Dr. Censani is a more longitudinal study of the effects of bariatric surgery on bone turnover markers and BMD in the adolescent patient population. "I want to make sure that we're doing everything we can to be advocates for these patients and make sure that they stay as healthy as they need to be."

Novel Techniques Used in Studying Polycystic Ovary Syndrome

Researchers at Morgan Stanley Children's Hospital also are using novel techniques to study fat deposition in the livers of adolescent girls with polycystic

ovary syndrome (PCOS). Their focus is non-obese girls, who are affected more often by PCOS than is commonly thought. Patients with PCOS are at risk for insulin resistance, which involves fat deposition in the liver. “The gold standard for determining if the liver is affected is a liver biopsy, but that is extremely invasive,” said Aviva Sopher, MD, Pediatric Endocrinologist at Morgan Stanley Children’s Hospital, and Assistant Professor of Pediatrics, Columbia University College of Physicians and Surgeons. “These girls are relatively healthy, so we wouldn’t want to subject them to such an invasive procedure.”

Instead, Dr. Sopher and her colleagues are using imaging techniques and experimental blood tests to look for fat or inflammation in the liver. Magnetic resonance spectroscopy is used to study fat deposition in the liver and the calf muscle. Magnetic resonance imaging of the body is used to examine visceral and subcutaneous adipose tissues as well as liver fat. Dual-energy x-ray absorptiometry is performed to look for overall projected body fat and bone density.

Recruitment is under way for a study of liver apoptosis markers. “It is definitely cutting-edge,” said Dr. Sopher. “There was one study done in adult women with PCOS that showed that some of the women had higher apoptosis markers in the PCOS group. So I was interested in seeing if in this young group who are non-obese we also see similar findings.”

“No one had looked prospectively at adolescent patients undergoing bariatric surgery and the effects on bone turnover markers that could reflect long-term bone health.”

—Marisa Censani, MD

Dr. Sopher’s current and projected studies build on the Columbia University team’s previous work in PCOS. In a study presented at The Endocrine Society’s 2011 annual meeting, Dr. Sopher, as principal investigator, and her colleagues

found that adolescents with PCOS (n=6) had similar BMD to controls (n=9)—despite their hypothesis that patients with PCOS would have lower BMD.⁸ They concluded that in PCOS, the bone-enhancing effects of hyperinsulinemia and hyperandrogenemia might compensate for the detrimental effects of low estradiol.

“We’re trying to determine if the bones are protected or not protected in these girls who have polycystic ovary syndrome.”

—Aviva Sopher, MD

The issue remains a subject of study, said Dr. Sopher. “We’re trying to determine if the bones are protected or not protected in these girls who have PCOS. It could have long-term implications because adolescence is when you have your peak bone mineral deposition. In the long term, it would be a concern: Are these girls more at risk for osteoporosis or not?”

At the Pediatric Academic Societies 2010 annual meeting, Dr. Sopher and her colleagues presented a study of intramyocellular lipid deposition in 13 adolescent girls (6 with PCOS, 7 controls).⁹ Intramyocellular lipid deposition was found to be an early marker of insulin resistance in both groups. In an

interventional, double-blinded, randomized controlled trial for which Dr. Sopher is now recruiting, PCOS patients will receive either metformin or placebo. The aim is to see the effect of metformin not only on basic parameters but on liver fat

deposition and apoptosis markers. “These clinical studies are being done in these young, healthy, adolescent girls, since this is a key time to see the effect of the disorder at such a young age and also potentially prevent long-term problems with diabetes and cardiovascular disease,” Dr. Sopher said.

References

1. Lin-Su K, Harbison MD, Lekarev O, Vogiatzi MG, New MI. Final adult height in children with congenital adrenal hyperplasia treated with growth hormone. *J Clin Endocrinol Metab*. 2011;96(6):1710-1717.
2. Vogiatzi MG, Macklin EA, Fung EB, et al. Bone disease in thalassemia: a frequent and still unresolved problem. *J Bone Miner Res*. 2009;24(3):543-557.
3. Vogiatzi MG, Macklin EA, Fung EB, et al. Prevalence of fractures among the thalassemia syndromes in North America. *Bone*. 2006;38(4):571-575.
4. Vogiatzi MG, Macklin EA, Trachtenberg FL. Differences in the prevalence of growth, endocrine and vitamin D abnormalities among the various thalassaemia syndromes in North America. *Br J Haematol*. 2009;146(5):546-556.
5. Tsay J, Yang Z, Ross FP. Bone loss caused by iron overload in a murine model: importance of oxidative stress. *Blood*. 2010;116(14):2582-2589.
6. Vogiatzi MG, Tsay J, Verdellis K. Changes in bone microarchitecture and biomechanical properties in the th3 thalassemia mouse are associated with decreased bone turnover and occur during the period of bone accrual. *Calcif Tissue Int*. 2010;86(6):484-494.
7. Censani M, Stein EM, Oberfield SE, et al. Vitamin D deficiency is prevalent in morbidly obese adolescents prior to bariatric surgery. Presented at: The Endocrine Society 2012 annual meeting; June 23-26, 2012; Houston, TX.
8. Gerken AT, Oberfield SE, Libby IB, et al. Adolescents with Polycystic Ovary Syndrome (PCOS) have similar Bone Mineral Density (BMD) and Bone Mineral Content (BMC) to controls (C). Presented at: The Endocrine Society 2011 annual meeting; June 4-7, 2011; Boston, MA.
9. Oberfield SE, Sopher AB, Gerken AT. Approach to the girl with early onset pubic hair. *J Clin Endocrinol Metab*. 2011;96(6):1610-1622.



Top Ranked Hospital in New York.
Twelve Years Running.

ADVANCES IN PEDIATRIC ENDOCRINOLOGY

Important news from NewYork-Presbyterian Pediatric Endocrinology.

Current research projects, clinical trials, and advances in the diagnosis and treatment of pediatric patients with diabetes and endocrine diseases

NewYork-Presbyterian Hospital
525 East 68th Street
New York, NY 10065

Non-Profit
US Postage
PAID
Syracuse, NY
Permit No. 999

Genetics Research Across Medical Specialties Now Yielding Secrets and Improving the Practice of Medicine

The decoding of the human genome and subsequent concerted efforts by physician-scientists to decipher the relationships between specific genes and the diseases they influence have already yielded tremendous advancements in medicine. This work is fostering important strides in understanding and caring for people with diseases affecting all health systems, and much of the laboratory and translational studies, as well as clinical research, are being done at Columbia University College of Physicians and Surgeons, Weill Cornell Medical College, and NewYork-Presbyterian Hospital.

Pulmonology has begun to explore the use of gene-based vaccines targeted against pulmonary infectious organisms. At Weill Cornell Medical College, a team led by Stefan Worgall, MD, PhD, Division Chief of the Pediatrics Pulmonology, Allergy and Immunology Division, has developed capsid-modified adenovirus vectors^{1,2} to heighten immune responses from genetic vaccines against both *Pseudomonas aeruginosa* and respiratory syncytial virus.

Nephrologists and psychiatrists, meanwhile, were interested in the results of a large multinational study led by Ali Gharavi, MD, Associate Director of the Division of Nephrology at NewYork-Presbyterian/Columbia.³ The study is the first to link congenital kidney disease with neurodevelopmental disorders, and found that 10% of children born with

kidney defects have genomic alterations that have been linked with neurodevelopmental delay and mental illness. The finding is important because it paves the way for identifying subgroups of patients with kidney defects whose treatment will be guided by specific genetic information.

Researchers, led by Antonio Iavarone, MD, Professor of Pathology and Neurology at Columbia's Institute for Cancer Genetics at the Herbert Irving Comprehensive Cancer Center at NewYork-Presbyterian/Columbia, conducted genetic analyses of patients with glioblastomas, searching for evidence of gene fusions.⁴ They found the most common fusions involving the fibroblast growth factor receptor (*FGFR1* or *FGFR3*) and transforming acidic coiled-coil (*TACC1* or *TACC3*) genes. The protein produced by the fusion of *FGFR-TACC*

disrupts the mitotic spindle, causing aneuploidy, and from there tumorigenesis. The finding is important because it provides researchers with a protein target for a cancer that is especially difficult to treat.

As the field of clinical genetics continues to grow so too the physician-scientists at Columbia University College of Physicians and Surgeons, Weill Cornell Medical College, and NewYork-Presbyterian Hospital will continue to be at the forefront of integrating genetics into all specialties.

References

1. Halbreiner M, Pagovich O, Finnin E, et al. Disrupted adenovirus-based vaccines against small addictive molecules circumvent anti-adenovirus immunity. *Human Gene Ther.* 2012 Nov 9. [Epub ahead of print]
2. Krause A, Worgall S. Delivery of antigens by viral vectors for vaccination. *Ther Deliv.* 2011;2(1):51-70.
3. Sanna-Cherchi S, Kiryluk K, Burgess KE, et al. Copy-number disorders are a common cause of congenital kidney malformations. *Am J Hum Genetics.* 2012;91(6):987-997.
4. Singh D, Chan JM, Zoppoli P, et al. Transforming fusions of *FGFR* and *TACC* genes in human glioblastoma. *Science.* 2012;337(6099):1231-1235.