

FOCUS ON PEDIATRIC PULMONOLOGY

Affiliated with Columbia University College of Physicians and Surgeons and Weill Cornell Medical College

Understanding Serious Asthma Could Help All Kids Breathe Easier

Asthma is the most common respiratory disease in children, affecting 10 percent of kids up to age 17 — some 7 million in the United States alone — and accounting for hundreds of thousands of emergency room visits and millions of missed school days.

While most cases of asthma can be traced to allergic triggers of inflammation, a subset of young patients has nonallergic asthma that is not associated with inflammation — making it especially challenging to manage. Asthma is also more prevalent among inner-city children. At NewYork-Presbyterian Hospital, pulmonology specialists are identifying molecular drivers of nonallergic asthma and shedding light on the characteristics of asthma in inner-city children.

Tiny Fats, Big Power

Investigators from NewYork-Presbyterian Hospital/Weill Cornell Medical Center and NewYork-Presbyterian Hospital/Columbia



University Medical Center collaborated with researchers from SUNY Downstate Medical Center to show that overactivity in a gene called *ORMDL3* interrupts the synthesis of lipid molecules called sphingolipids. Reduced production of sphingolipids is a hallmark of nonallergic asthma and is linked to increased bronchial hyperactivity. The findings (which were published in the May 22, 2013 issue of *Science Translational Medicine* and highlighted in the *New England Journal of Medicine* and the *Wall Street Journal* in September 2014) draw attention to a new pathway in asthma

pathogenesis that could become a target for novel therapies.

Prior genome-wide association studies identified variations in the *ORMDL3* gene in up to 30 percent of children with asthma. An overactive *ORMDL3* gene has become the most consistent

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Helping Kids to Get Quality Shut-Eye

Video games, homework, sports, and other activities all threaten the ability of children to get enough sleep, and sufficient high-quality sleep once they are slumbering. The noise of city streets, chaotic lifestyles, and overcrowded living conditions may compound the problem for urban youth. Pediatric sleep specialists are now assessing the factors that impair sleep among minority children living in New York City and formulating interventions to improve their sleep habits.

“Even adding as little as 28 extra minutes of sleep a night has been shown to improve cognitive function,” explains Beverley Sheares, MD, Associate Attending Physician at NewYork-Presbyterian/Morgan Stanley Children’s Hospital and Associate Professor of Pediatrics at Columbia University College of Physicians and Surgeons. She and her team have been examining sleep behaviors and nightly sleep duration among urban minority 5- and 6-year-olds through a National Institutes of Health-funded study. This age represents a time when children start going to school every morning, but their parents may still be running the household on a less structured preschool schedule. Children end up going to bed late, even though they have to get up earlier the next morning. The result: sleep deprivation, which has



been shown to impair academic success as well as immune function.

“The literature on sleep habits among nonwhite children shows that they get less sleep than their white counterparts,” says Dr. Sheares. “This disparity may account for a portion of the academic achievement gaps we observe between these groups.” During the study, a counselor visits the homes of study participants to identify modifiable factors that may interfere with the ability of children to obtain a solid night’s sleep. They found that in many

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homes, there is a television in the room where the children sleep, and most of the children have no set bedtimes.

The counselors are working with the parents to make positive changes, such as ensuring that children don't sleep in the same room where a television is located, modifying lighting, and setting regular bedtimes. The investigators are also learning about cultural differences in children's sleep preferences. In some cultures, children and parents like to sleep together, while in other groups,

children prefer to sleep with their siblings.

The researchers are now using actigraphy — a watchlike device the user wears — to objectively assess how much sleep children are getting, and finding that parents often overestimate their children's actual sleep duration. "This is a novel approach and has provided us with quite a bit of information, which we can continue to use to improve the sleep behaviors of urban children," Dr. Sheares concludes.

DEDICATED PEDIATRIC SLEEP LABS

Both NewYork-Presbyterian/Morgan Stanley Children's Hospital and NewYork-Presbyterian Hospital/Phyllis and David Komansky Center for Children's Health have sleep laboratories just for children and adolescents. The Pediatric Sleep Disorders Center at NYP/Morgan Stanley Children's is accredited by the American Academy of Sleep Medicine and features three board-certified sleep pulmonologists. The Weill Cornell Pediatric Sleep and Breathing Disorders Center was recently expanded and also features a board-certified sleep pulmonologist. Both centers perform the full range of sleep studies required to diagnose a sleep disorder, including daytime and overnight studies (with a parent or guardian sleeping in the same room as the child). Sleep studies are conducted by friendly sleep technicians who are experts in performing sleep studies in children. The labs may be used to assess and diagnose the following pediatric sleep disorders:

- Insomnia
- Parasomnias
- Sleep schedule abnormalities
- Airway obstruction/sleep apnea
- Excessive daytime sleepiness (such as narcolepsy)
- Sleepwalking
- Behavioral sleep problems
- Movement disorders, including periodic limb movement disorder and head banging



To learn more about the pediatric sleep labs or to refer a patient, call:

NewYork-Presbyterian/Morgan Stanley Children's Hospital:
(212) 305-2406 or (212) 305-5122

Weill Cornell Pediatric Sleep and Breathing Disorders Center:
(646) 962-3410

Respiratory Support for Children with Neuromuscular Disease

The Neuromuscular Disease Clinic at NewYork-Presbyterian/Morgan Stanley Children's Hospital provides diagnostic testing and treatment for children with respiratory problems associated with muscular dystrophy and other neuromuscular diseases, such as spinal muscular atrophy (SMA). Pulmonologists are members of the clinic's multidisciplinary care team. Andrei Constantinescu, MD, PhD, Assistant Attending Physician and Assistant Professor of Pediatrics at Columbia University College of Physicians and Surgeons, directs the clinic's respiratory care component.

The clinic is an active recruiting ground for clinical trials assessing innovative therapies for children with neuromuscular disease. Researchers are participating in clinical studies of the natural history of children with varying degrees of SMA involvement, and exploring their pulmonary and motor function. Over the last two years, investigators have been assessing a new therapy

that targets the *SMN2* gene. Patients with SMA have a mutated, dysfunctional form of the *SMN1* (Survival of Motor Neuron) gene, but all of them have one or more functional *SMN2* genes. Upregulating *SMN2* through targeted therapy ramps up production of the SMN protein, which in higher amounts mitigates the effects of mutant *SMN1* gene.

NYP/Morgan Stanley Children's researchers have been collaborating with Isis Pharmaceuticals, Inc. to evaluate an antisense oligonucleotide called ISIS-SMN_{Rx} which raises SMN protein production by targeting the *SMN2* gene. Results so far have shown that ISIS-SMN_{Rx} can improve function and symptoms in children with SMA, including the frequency of colds and other respiratory exacerbations. Assessment of this drug is ongoing, including the development of a blinded, placebo-controlled study.

Understanding Serious Asthma (continued from page 1)

genetic factor identified so far in asthma. Using mouse models, the researchers found that inhibition of the serine palmitoyl-CoA transferase (SPT) enzyme, which is required for sphingolipid synthesis, produced asthma in mice and in human airways, as it did in mice that had a genetic defect in SPT. The airway hyperactivity seen in the mice was not linked to elevated levels of inflammation. Moreover, the scientists observed a decreased response of the lung and airways to magnesium, which is often used in the emergent care of patients having asthma attacks as a means of relieving their chest tightness.

“Our model shows that asthma can result from having too little of a type of sphingolipids,” says Stefan Worgall, MD, PhD, Chief of the Pediatric Pulmonology, Allergy and Immunology Division at NewYorkPresbyterian Hospital/Phyllis and David Komansky Center for Children’s Health and Distinguished Professor of Pediatric Pulmonology at Weill Cornell Medical College. “These findings reveal a completely new pathway for asthma pathogenesis. Our findings are not only valuable for understanding the pathogenesis of this complex disease, but provide a basis for the development of new therapies, especially asthma agents based on a patient’s genotype.” He and his colleagues are now measuring sphingolipid levels in the breath condensate of children with asthma, with preliminary data demonstrating evidence of sphingolipid abnormalities.

Why Do More Obese Children Have Asthma?

The results could also help explain why obesity is a risk factor for asthma, since obese individuals tend to have sphingolipid abnormalities. Emilio Arteaga-Solis, MD, PhD, Assistant Attending Physician at NewYork-Presbyterian/Morgan Stanley Children’s Hospital and Assistant Professor of Pediatrics at Columbia University College of Physicians and Surgeons, is exploring the hormonal regulation of lung function and its potential link to obesity-associated asthma by investigating the role of adipocyte-derived hormones and their contribution to airway physiology and pathology. His recent studies demonstrated that leptin regulates airway diameter through a novel neuronal pathway that is altered in obesity. Dr. Arteaga-Solis is now studying the function of other adipocyte-derived hormones in lung physiology and how they affect both allergen-related and obesity-induced asthma.

His recent identification of increased parasympathetic activity in genetically and diet-induced obese mice implied that anticholinergic agents may be beneficial for treating obesity-associated asthma. In fact, treatment of animal models of obesity with anticholinergic

agents alleviated their asthma. Dr. Arteaga-Solis is now collaborating with the Inner-City Asthma Consortium to determine if ipratropium bromide — a short-acting anticholinergic agent — may be more effective for treating obese asthmatic children than patients of normal weight.

“Our investigators have taken clinical observations to the laboratory and back to the clinic. These findings indicate that certain drugs that are active in the nervous system may have a place in the treatment of asthma,” notes Meyer Kattan, MD, Chief of the Division of Pulmonology at NYP/Morgan Stanley Children’s and Professor of Pediatrics at Columbia.



Asthma in the City

As one of only nine clinical research sites in the National Institutes of Health-funded Inner-City Asthma Consortium, NYP/Morgan Stanley Children’s

investigators are studying environmental and psychosocial factors related to asthma in inner-city children, as well as issues related to healthcare delivery. The earliest studies of the group identified cockroach allergen as a trigger of asthma symptoms. Subsequent studies showed that reducing the exposure of children with asthma to house dust mites, secondhand smoke, cockroaches, pets, rodents, and mold improved their symptoms.

Armed with this knowledge and the results of other investigations, the Inner-City Asthma Consortium has shifted its focus to improving asthma treatment. An observational study is examining genetic, environmental, and immune factors that play a role in the development of asthma in inner-city children by closely following a cohort of more than 500 children from before birth until age 7 years. Another investigation is seeking to clarify why some children with asthma fare better than others, and to see whether children with asthma have epigenetic differences from children with no asthma or allergies.

NYP/Morgan Stanley Children’s investigators played a key role in refining the use of omalizumab (Xolair®) subcutaneous injection, an anti-IgE therapy which is given once or twice a month and is very effective for reducing viral exacerbations of asthma — especially in the fall, when emergency room visits for asthma peak. But it is also very expensive — prohibitively so for some families. The researchers found that even giving the injection just a few months each year was still beneficial for reducing asthma exacerbations, but at a lower expense for families.

Concludes Dr. Kattan, “Understanding asthma in the most severely affected patients helps us to understand more about asthma in general, which could lead to better treatments for all patients.”

As part of a national consortium, investigators are studying factors related to asthma in inner-city children.

Focus on Pediatric Pulmonology

New York-Presbyterian Hospital
3959 Broadway
New York, NY 10032
www.nyp.org/kids

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