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In This Issue

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UPMC CHILDREN'S HOSPITAL OF PITTSBURGH

A Case of Spinal Muscular Atrophy

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Case Overview

A full-term boy presented at his 2-month-old well-child visit with significant weight loss (50th to 20th percentile) despite no feeding difficulties or intercurrent illness. On examination, he was noted to have poor head control and was referred to the neurology clinic for initial evaluation. His parents reported no developmental regression but did confirm delayed milestone acquisition.

Upon neurologic evaluation, the patient had significant generalized hypotonia with diaphragmatic respiration and absent reflexes. He was admitted to the hospital for further neurologic workup with suspected Spinal Muscular Atrophy (SMA). During this initial hospitalization, he was found to have significant aspiration and underwent a gastrostomy tube placement with Nissen fundoplication. Genetic testing confirmed SMA with two gene copies of SMN2. He was started on Nusinersen (Spinraza®) within two weeks of diagnosis. Following initiation of Nusinersen, the parents reported that he was slowly acquiring new milestones with improved tone. He required no respiratory support at that time.

At 7 months of age, he developed acute respiratory failure secondary to pneumonia, and biphasic noninvasive ventilatory support (NIV) was initiated. He was discharged with the trilogy home ventilator to be used noninvasively during sleep. With intercurrent respiratory illnesses, he would require NIV continuously for a few days. No further hospitalizations occurred. He received gene therapy with Zolgensma® at 9 months of age and continued with his quarterly Nusinersen treatment.

The patient is now almost 3 years of age and has not been hospitalized since 7 months of age. He continues to display significant improvements in his overall motor function. He can independently propel his wheelchair and can stand using a stander. His bulbar muscle strength has improved to the point where he is now safely tolerating small oral feeds with gastrostomy tube supplementation. Furthermore, his most recent polysomnogram showed no evidence of sleep-disordered breathing or alveolar hypoventilation.

Background

SMA is an autosomal recessive neurodegenerative disease caused by a homozygous mutation/deletion in the Survival Motor Neuron 1 (SMN1) gene on chromosome 5q. This gene deletion leads to

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decreased expression of Survival Motor Neuron (SMN) protein, which clinically manifests as muscular weakness and hypotonia. While the exact role of SMN protein within motor neurons is not completely understood, it is believed to play a role in motor neuron development, as SMA is characterized by degeneration of motor neurons in both the spinal cord and the brainstem. Currently, SMA is the leading genetic cause of infant mortality with an incidence of approximately 1 in 11,000 live births and an estimated carrier frequency of 1 in 54.[1-3] Without any form of respiratory support, the historical median life expectancy for a child with SMA Type 1 is approximately 2 years.[1-4] Due to the development of new therapies, the natural history of SMA continues to change rapidly.

SMA has classically been divided into five phenotypes based on the age of symptom onset and the patient's maximal motor function. Type 1 onset occurs by 6 months of age, and patients are unable to sit upright independently. Type 2 onset occurs between 6-18 months, and though patients can sit upright independently, they are unable to ambulate. Type 3 typically presents with mild symptoms after 18 months of age, while Type 4 presents in adulthood. Type 3 and Type 4 patients can generally ambulate independently into adulthood but may lose this ability over time. Type 0 is the rarest and most severe phenotype that begins in utero and results in early mortality. It is associated with congenital heart defects and vascular issues in the extremities affecting perfusion, along with diffuse hypotonia, joint contractures, and pulmonary hypoplasia with significant respiratory distress and chest wall deformities noted at birth.[5,6]

SMA Type 1 (also known as Werdnig-Hoffman Disease) is the most common form of SMA and affects an estimated 60% of all SMA cases. Prior to the advent of new therapies, natural history studies of SMA Type I showed that approximately 68% die within 2 years and 82% by 4 years of age without respiratory and nutritional support.[2] Mortality has been reduced to about 30% by 2 years of age with the use of NIV and gastrostomy placement. The median age of symptom onset is approximately 1.2 months of age, with a median time to full ventilator dependence at approximately 13.5 months of age.[2,7]

Initially, SMA Type 1 patients present with a variety of symptoms including the inability to sit upright, poor head control, and overall muscular weakness. While the diaphragm is not affected, weak intercostal muscles result in a baseline paradoxical breathing pattern (inward motion of the chest during inspiration) and the development of a structurally bell-shaped upper torso and pectus excavatum. Bulbar denervation results in characteristic tongue fasciculations, in addition to a weak suck and swallow. Patients are at increased risk for nutritional growth failure, aspiration pneumonia, and frequent lower respiratory tract infections from insufficient airway clearance with a weak cough. Pulmonary compromise remains the primary cause of death in SMA.[1,2]

Historically, there were no effective therapeutic options for SMA, and management primarily consisted of supportive care. Treatment targets for SMA involve two genes, Survival Motor Neuron 1 (SMN1) and Survival Motor Neuron 2 (SMN2). SMN1 is the primary gene involved in the production of functional SMN protein. In humans, SMN2 is a similar gene that differs from SMN1 by approximately 11 nucleotides and codes for the same SMN protein. The difference between the two is located at an exon splice enhancer site that regulates the inclusion of Exon 7. While SMN2 produces some functional SMN protein, nearly 90% of the mRNA coded by SMN2 is nonfunctional due to splicing that excludes Exon 7. This produces a smaller protein that is quickly degraded by the body. Patients that possess a higher copy number of SMN2 produce more functional SMN protein and usually display a milder phenotype.[1,2,5,8]

In 2016, the U.S. Food and Drug Administration (FDA) approved Nusinersen, the first treatment for patients with SMA. Nusinersen is an antisense oligonucleotide drug that modifies the splicing of SMN2 to include Exon 7, thereby promoting increased production of the full-length functional SMN protein.[3,4,8] It is administered by repeated intrathecal injections due to its inability to cross the blood-brain barrier, with four loading doses of 12 mg in the first two months of treatment, followed by routine doses approximately every three months. Nusinersen has been found to be well-tolerated in infants and children with SMA.

This therapy option has drastically changed the clinical landscape for SMA patients. A clinical trial examining Nusinersen versus a sham control showed a benefit-risk assessment in favor of Nusinersen,[4] which caused early termination of this trial and expedited FDA approval. All patients were then subsequently enrolled in an open-label extension study to receive Nusinersen. Overall, the risk of death or the use of chronic ventilation was approximately 47% lower in those treated with Nusinersen as compared to a sham control. Furthermore, postmortem studies demonstrated that Nusinersen caused an increase in the amount of full-length SMN2 mRNA, as well as SMN protein compared to untreated SMA infants.[9] Nusinersen also demonstrated progressive improvement in overall motor function and survival in treated infants. While age-appropriate function was not achieved, many of the Nusinersen treated patients developed the ability to sit independently and exhibited improvements in other motor functions such as head control and the ability to roll over.

Although Nusinersen has significantly affected the natural history of SMA in a positive direction, it is not a cure for the disease. Patients with more advanced disease at the time of Nusinersen treatment displayed less dramatic functional improvement,

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New R01 Study to Probe Connections Between Obesity and Asthma

The incidence of both obesity and asthma has been rising steadily in the United States. Centers for Disease Control and Prevention (CDC) data show that obesity rates in children and adolescents have increased three-fold since the 1970s.[1] Rates of asthma also have been on the increase. National prevalence data from the CDC as of 2018 show that more than 5.5 million children and adolescents under the age of 18 in the United States have asthma.[2]

Evidence exists for an association between both diseases, such that people with obesity are at higher risk of asthma. Furthermore, individuals with asthma and obesity tend to have more severe asthma, worse symptom control, and a reduced response to asthma medications. However, the exact molecular and genetic mechanisms by which obesity may influence asthma in childhood are complex and not entirely known.

Erick Forno, MD, MPH, ATSF, assistant professor of pediatrics at the University of Pittsburgh and the Division of Pediatric Pulmonary Medicine at UPMC Children's Hospital of Pittsburgh, obtained new R01 funding in March from the National Heart, Lung, and Blood Institute (NHLBI) at the National Institutes of Health (NIH) for studies[3] that will probe the mechanisms by which obesity affects asthma in children and adolescents.

The central hypothesis of Dr. Forno's studies is that obesity affects childhood asthma through epigenetic regulation and trans-criptomic activity within adipose tissue. Epigenetic regulation is one of the ways the body regulates which genes are turned on or off; transcriptomic activity measures how much of each gene is being produced.

Dr. Forno's studies will recruit cohorts of children and adolescents with asthma, obesity, or both, as well as control populations, in whom they will perform extensive phenotyping and obtain subcutaneous and intra-abdominal adipose tissue for study. The investigation will assess body mass index (BMI) in the study cohorts, along with other indices of adiposity and body composition measured by anthropometry and impedance analysis.

Dr. Forno will examine the risk of asthma in children and adolescents with and without obesity; among children and adolescents with asthma, he will evaluate severity outcomes, including exacerbations, symptoms, and lung function. Dr. Forno will then study the top identified targets in the laboratory using normal and asthmatic bronchial epithelial and airway smooth muscle cells.

Dr. Forno previously received a K08 award from the NHLBI to study obesity and asthma in children[4], and the current award is partly built on findings from that research.

Clinically Significant Research

"Our new studies are innovative in that they will focus on the 'source' tissue of children with asthma who are obese, rather than using blood biomarkers or mediators, and by validating the effect of the top results on the 'target' tissues," says Dr. Forno. "Revealing the pathways in adipose tissue associated with asthma in the context of obesity will have critical implications for understanding this phenotype. It will allow us to identify ways to improve the management of these patients and may help identify therapeutic targets."

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2. https://www.cdc.gov/asthma/most_recent_data.htm
3. Obesity and Childhood Asthma: The Role of Adipose Tissue. 1R01HL149693-01. Principal investigator: Erick Forno, MD, MPH, ATSF.
4. Obesity and Asthma Subphenotypes and Underlying Pathways. 5K08HL125666-04.

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suggesting that earlier initiation of treatment may maximize its efficacy. Patients who ultimately received permanent ventilator assistance while receiving Nusinersen did so within 13 weeks of receiving their first dose of Nusinersen. Meanwhile, there were several patients receiving Nusinersen who died, did not achieve any normal motor development, and required nutritional and ventilatory support during the trials.[4] These outcomes highlighted the need for early initiation of therapy. Most states have worked to quickly include SMA in their newborn screening programs.

Research continued into other SMA therapies, and a gene replacement therapy was FDA approved in 2018 for the treatment for SMA. This gene therapy, AVXS-101 (Onasemnogene Abeparvovec, Zolgensma®), is an adeno-associated viral vector that carries SMN1 DNA encoding functional human SMN with a continuous promoter.[10,11] Inside the cell, it causes the expression of SMN1 mRNA, thereby increasing the amount of functional SMN protein. Children who were in the first gene replacement trial received a single intravenous infusion shortly after birth and have demonstrated longer event-free survival as compared to historical cohorts. Moreover, patients demonstrated improved motor function and achievement of milestones, including the ability to sit upright independently with improved feeding, swallowing, and ventilatory status.[8] This August, another SMN2 modifier, risdiplam (Evrysdi™), was approved by the FDA for patients 2 months of age and older.[5,6] Risdiplam is a daily orally administered medication.

Conclusion

Recent treatment advances have drastically changed the clinical landscape of SMA and improved the mortality and morbidity previously associated with this disease. Children on treatment are showing improved motor function, achievement of milestones, and decreased reliance on nutritional and respiratory support.

However, as this new cohort of SMA patients ages, new challenges are occurring in this population with increased incidence of scoliosis and the need for adaptive equipment to continue to support and nurture their new independence. A strong multidisciplinary neuromuscular clinic is critical to continue to help these young pioneers thrive.

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Searching for Mechanistic Targets to Treat Severe, Drug-Resistant Asthma

Research Assistant Professor **Michelle Manni, PhD**, from the UPMC Children's Hospital of Pittsburgh Division of Pediatric Pulmonary Medicine, studies the immunological mechanisms of severe, steroid insensitive asthma. She also investigates the immune mechanisms that underlie the pathogenesis of acute asthma exacerbations and obesity-associated asthma.

In March, Dr. Manni received her first National Institutes of Health (NIH) R01 grant to continue her studies of the IL-22 signaling pathway in the context of severe and treatment-resistant asthma. This translational work utilizes a preclinical animal model and human samples, aiming to uncover new therapeutic targets for severe asthma treatment.

Severe and Refractory Asthma — Prevalence and Morbidity

Allergic asthma is a heterogenous respiratory disease that affects approximately 300 million people worldwide. Although the majority of patients have mild to moderate, well-managed disease, approximately 5% to 10% of asthmatics have severe refractory disease, which accounts for more than half of the disease-related health care costs. As the incidence of asthma continues to rise, studies linking immune and pathophysiologic mechanisms to asthma endotypes are crucial to establishing more targeted and effective therapies.

IL-22 and Interferon Functions

In severe refractory asthma, allergen-specific steroid-insensitive T helper (Th) 17 and/or Th2 cells are thought to critically orchestrate asthma pathogenesis, resulting in pulmonary inflammation, mucus hypersecretion, and airway hyperresponsiveness. The Th17 immune cytokine interleukin-22 (IL-22) plays a vital role in maintaining epithelial integrity and promoting repair. IL-22 receptor alpha-2 (IL-22Ra2), an endogenous soluble receptor for IL-22, inhibits its activity.

The significance of IL-22 and endogenous IL-22Ra2, as well as the pathways that regulate them in severe asthma, are unknown. Aside from IL-22Ra2, type I IFNs also are immunomodulators that can alter IL-10 and IL-22 signaling in certain inflammatory disease contexts. Based on preliminary and published findings from Dr. Manni and her colleagues, they hypothesize that IL-22Ra2 and type I IFNs perpetuate severe allergic airway disease (AAD) by blocking IL-22 signaling, which is necessary to alleviate AAD and maintain epithelial integrity in the lung.

Study Aims

Dr. Manni's team will investigate whether IL-22Ra2 modulates severe AAD by altering IL-22 bioavailability in the lung. Her research also seeks to determine if type I IFNs influences severe AAD through IL-22 signaling. Finally, Dr. Manni's investigation will examine if IL-22 is protective by signaling through the pulmonary epithelium during severe asthma.

Clinical Significance

Severe, drug-resistant asthma is a growing public health issue in the United States and worldwide that causes thousands of deaths every year and creates a large burden on the health care system. Despite advancements in treatments, a significant portion of asthmatics fail to achieve asthma control, and nearly half of all asthmatics do not exhibit a type 2, eosinophil-dominant phenotype, especially those with severe refractory disease. As much less is known about pathogenic mechanisms in non-type 2 asthma, an unmet clinical need exists to better understand these subsets of disease. The goal of Dr. Manni's work is to model these clinical subsets in mice to investigate the molecular mechanisms underlying the disease. This work will contribute to the understanding of asthma pathogenesis and aid in the development of more targeted therapeutic approaches.

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Division of Pediatric Pulmonary Medicine Recent Published Research

The Division of Pediatric Pulmonary Medicine at UPMC Children's Hospital of Pittsburgh is a national and global leader in the research of pediatric pulmonary diseases and conditions including asthma, cystic fibrosis, sleep disorders, and neuromuscular conditions affecting the lungs.

Division faculty, residents, and fellows have published more than 30 studies, review articles, and commentaries to date in 2020.

Learn more about UPMC Children's research and active clinical trials by visiting **CHP.edu**.

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About The Division of Pediatric Pulmonary Medicine

The Division of Pediatric Pulmonary Medicine provides consultative services for the diagnosis, evaluation and management of diseases of the respiratory tract and sleep disorders. A multidisciplinary team of physicians, certified registered nurse practitioners, registered nurses, registered respiratory therapists, registered dieticians, and social workers offers patient management, patient/family education and support services.

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- Cystic fibrosis
- Home mechanical ventilation
- Interstitial lung disease
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- Neuromuscular diseases with respiratory complications
- Sleep disorders (sleep apnea, narcolepsy, behavioral sleep problems)

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Obesity and Asthma *Continued from Page 3*

Further Reading

A selection of previously published research by Dr. Forno and colleagues on childhood asthma and obesity includes the following papers.

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Regionally, nationally, and globally, UPMC Children's Hospital of Pittsburgh is a leader in the treatment of childhood conditions and diseases, a pioneer in the development of new and improved therapies, and a top educator of the next generation of pediatricians and pediatric subspecialists. With generous community support, UPMC Children's Hospital has fulfilled this mission since its founding in 1890. UPMC Children's is recognized consistently for its clinical, research, educational, and advocacy-related accomplishments, including ranking 15th among children's hospitals and schools of medicine in funding for pediatric research provided by the National Institutes of Health (FY2019) and ranking on *U.S. News & World Report's* Honor Roll of America's Best Children's Hospitals (2020–21).

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