Adult Identified with Congenital Central Hypoventilation Syndrome--Mutation in PHOX2b Gene and Late-Onset CHS

To the Editor:

In light of our recent review of the genetic basis for congenital central hypoventilation syndrome (CCHS) (1), we bring to your attention a 35-year-old adult recently identified as having had late-onset CHS and the CCHS-mutation in PHOX2b.

One year ago this patient presented with a history of snoring “for his whole life,” nocturnal gasping, and “stopping breathing and turning blue.” During polysomnography he had 46 obstructive events (38 hypopneas, 8 apneas), 16 central apneas, and an apnea–hypopnea index of 77 events/hour, with an SaO₂ nadir of 65% in room air and 80% with supplemental oxygen. He temporarily responded to Bi-Pap with supplemental oxygen during sleep, but within 6 months was referred for uvulopalatopharyngoplasty. He was readmitted 48 hours after discharge with intermittent confusion, difficulty staying awake, and respiratory failure (awake arterial Pco₂ of 73 mm Hg). His admission hematocrit was 73%, body temperature was 35.5°C, chest X-ray revealed cardiomegaly, and ECG revealed right axis deviation, enlargement, and hypertrophy. He required intubation and mechanical ventilation, then a tracheostomy; however, mechanical ventilation was discontinued. We were contacted by the family when an arterial blood gas assay upon awakening revealed a Pco₂ of 129 mm Hg (pH 7.03). Because of his daughter’s diagnosis of late-onset CHS 3 years before, and documentation that she is heterozygous for the CCHS-related PHOX2b polyalanine expansion mutation, we conducted the same assay with the father’s DNA. Figure 1 demonstrates the identical mutation in the 4-year-old daughter and the father, as well as in the 2-year-old daughter, who also has alveolar hypoventilation (all three have a genotype of 20/25). In retrospect, we learned that the father uses Dextrenal “stay on task,” has symptoms compatible with autonomic nervous system dysregulation (low body temperature, postural hypotension, pinpoint pupils minimal reactive to light, no shortness of breath despite markedly increased carbon dioxide levels), and has wakened with headaches and periods of disorientation for several years.

On the basis of this remarkably late presentation of the alveolar hypoventilation component of CHS, we suggest that adult pulmonologists and intensivists consider the possibility of late-onset CHS, confirmable by PHOX2b assay, when caring for adults with hypercarbia of unknown etiology. From a scientific perspective, this case raises the possibility of a regulatory gene that modifies the expression or activity of PHOX2b, determining the severity of the autonomic dysregulation in late-onset CHS.

Conflict of Interest Statement: D.E.W.-M. is named on a patent application for the PHOX2b assay but has not received any financial benefit from this application; E.M.B.-K. is named on a patent application for the PHOX2b assay but has not received any financial benefit from this application; L.Z. is named on a patent application for the PHOX2b assay but has not received any financial benefit from this application.

Debra E. Weese-Mayer
Elizabeth M. Berry-Kravis
Lili Zhou
Rush University Medical Center
Chicago, Illinois

References


Omalizumab and Changes in Airway Hyperresponsiveness

To the Editor:

The article by Djukanovic and colleagues (1) provides insight into the antiinflammatory effects of anti-IgE monoclonal antibody in individuals with mild-to-moderate persistent asthma. However, no effect upon nonspecific airway hyperresponsiveness (AHR) to methacholine was observed after treatment for 16 weeks with omalizumab.

Methacholine is a direct bronchoconstrictor stimulus, which acts upon effector cells such as smooth muscle, causing contraction and narrowing of the airway. Bronchoprovocation with indirect stimuli such as adenosine monophosphate (AMP) and mannitol is considered to be particularly relevant to real-life situations, as cold air, exercise, and allergen also act in a similar fashion in terms of release of proinflammatory mediators such as histamine and leukotrienes from primed mast cells (2). This in turn leads to smooth muscle contraction. Indeed, shifts in the AMP threshold concentration are more closely related to underlying airway inflammation, particularly with sputum eosinophils and exhaled nitric oxide (3, 4), and associated with symptoms of atopic asthma than are direct stimuli such as methacholine (3, 5). Improvements in the AMP threshold concentration are also greater with antiinflammatory therapy than are effects upon the methacholine threshold dose or concentration (6). Moreover, AHR to methacholine is often associated with changes in airway caliber (not observed with omalizumab in the present study) rather than with underlying atopy and inflammation (5).

Thus, despite a significant reduction in airway eosinophils, it may not be surprising that AHR was not altered with omalizumab. It may well be that omalizumab does in fact reduce AHR, but that a more physiologically and clinically relevant bronchoconstrictor stimulus is required to demonstrate it. The jury must...
therefore still be out in deciding whether anti-IgE therapy does in fact attenuate AHR in individuals with asthma.

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Graeme P. Currie
Aberdeen Royal Infirmary
Aberdeen, United Kingdom

Sudip Saha
Raigmore Hospital
Inverness, United Kingdom

Daniel K. C. Lee
Ipswich Hospital
Ipswich, United Kingdom

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From the Authors:
We thank Drs. Currie, Saha, and Lee for their thoughtful comments regarding the observations made in our study that anti-IgE treatment does not alter methacholine responsiveness (1). They are right when they say that this treatment might have had an effect on adenosine monophosphate (AMP), mannitol, and cold air/exercise responsiveness, as these reflect, at least in part, mast cell activation. It is, indeed, also possible that responsiveness to other stimuli, such as Bradykinin, may have also been reduced. Thus, they are right that the jury is still out as to whether airway responsiveness to stimuli other than methacholine, which we investigated in our study, may be affected by this treatment.

Notwithstanding the above comments, we remain surprised that omalizumab did not have larger effects on methacholine reactivity given its large effects on airway eosinophilia and other markers of airway inflammation. This finding, in our view, is worthy of further study so that we may better understand the relationship between airway inflammation and methacholine airway responsiveness, a key characteristic of asthma.

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Ratko Djukanovic
University of Southampton
Southampton, United Kingdom

John V. Fahy
University of California
San Francisco, California

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