Correspondence

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 Sa_{O_2} 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 P_{CO_2} 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 P_{CO_2} 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 Dexadrine to "stay on task," has symptoms compatible with autonomic nervous system dysregulation (low body temperature, postural hypotension, pinpoint pupils minimally reactive to light, no shortness of breath despite markedly increased carbon dioxide levels), and has awakened 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

1. Weese-Mayer DE, Berry-Kravis EM. Genetics of congenital central hypoventilation syndrome: lessons from a seemingly orphan disease. *Am J Respir Crit Care Med* 2004;170:16–21.

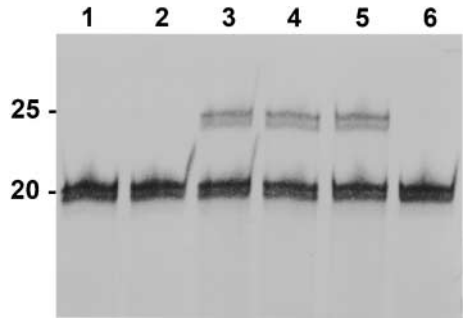

Figure 1. *PHOX2b* mutation analysis in family with late-onset CHS. *Lanes 3* (father with late-onset CHS), *4* (4-year-old affected daughter), and *5* (2-year-old affected daughter) show an expansion mutation with genotype 20/25. *Lanes 1*, *2* (parents of father with late-onset CHS), and *6* (wife of father with late-onset CHS) show a normal 20/20 genotype. *PHOX2b* genotyping was performed as described previously (2).

2. Weese-Mayer DE, Berry-Kravis EM, Zhou L, Maher BS, Silvestri JM, Curran ME, Marazita ML. Idiopathic congenital central hypoventilation syndrome: analysis of genes pertinent to early autonomic nervous system embryologic development and identification of mutations in Phox2b. *Am J Med Genet* 2003;123A:267–278.

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.

Conflict of Interest Statement: G.P.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; S.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; D.K.C.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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

References

1. Djukanovic R, Wilson SJ, Kraft M, Jarjour NN, Steel M, Chung KF, Bao W, Fowler-Taylor A, Matthews J, Busse WW, *et al.* Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. *Am J Respir Crit Care Med* 2004;170:583–593.
2. Currie GP, Jackson CM, Lipworth BJ. Does bronchial hyperresponsiveness matter in asthma? *J Asthma* 2004;:41:247–258.
3. Van Den Berge M, Meijer RJ, Kerstjens HA, de Reus DM, Koëter GH, Kauffman HF, Postma DS. PC(20) adenosine 5′-monophosphate is more closely associated with airway inflammation in asthma than PC(20) methacholine. *Am J Respir Crit Care Med* 2001;163:1546–1550.
4. van Den Toorn LM, Prins JB, Overbeek SE, Hoogsteden HC, de Jongste JC. Adolescents in clinical remission of atopic asthma have elevated exhaled nitric oxide levels and bronchial hyperresponsiveness. *Am J Respir Crit Care Med* 2000;162:953–957.
5. De Meer G, Heederik D, Postma DS. Bronchial responsiveness to adenosine 5′-monophosphate (AMP) and methacholine differ in their relationship with airway allergy and baseline FEV(1). *Am J Respir Crit Care Med* 2002;165:327–331.
6. Wilson AM, Lipworth BJ. Dose–response evaluation of the therapeutic index for inhaled budesonide in patients with mild-to-moderate asthma. *Am J Med* 2000;108:269–275.

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.

Conflict of Interest Statement: R.D. has been consulting for Aventis and has received payments for lectures sponsored by GlaxoSmithKline and has received sponsorship for basic research from AstraZeneca, Cambridge Antibody Technology, Immunex, GlaxoSmithKline, and Bayer, and in addition has received funding from GlaxoSmithKline for participating in two multicenter studies of the anti-inflammatory effects of Advair and is one of the cofounders and paid consultant of Synairgen in which he has shares; J.V.F. received a research grant from Novartis/Genentech for his participation as an investigator in the study examining the effects of omalizumab on airway inflammation in asthma.

Ratko Djukanovic
University of Southampton
Southampton, United Kingdom
John V. Fahy
University of California
San Francisco, California

References

1. Djukanovic R, Wilson SJ, Kraft M, Jarjour NN, Steel M, Chung KF, Bao W, Fowler-Taylor A, Matthews J, Busse WW, *et al.* Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. *Am J Respir Crit Care Med* 2004;170:583–593.