0031-3998/05/5704-0471
PEDIATRIC RESEARCH
Vol. 57, No. 4, 2005
Printed in U.S.A.

DOI: 10.1203/01.PDR.0000158667.41282.F1

COMMENTARY

Functional Brain Deficits in Congenital Central Hypoventilation Syndrome

Commentary on the articles by Woo *et al.* on page 510 and Macey *et al.* on page 500.

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The present issue of *Pediatric Research* provides two reports of functional brain deficits detected by functional magnetic resonance imaging (fMRI) in patients with congenital central hypoventilation syndrome (CCHS) compared with age-matched controls (1,2). Woo *et al.* (1) used cold pressure challenge and Macey *et al.* (2) hyperoxia to induce these deficits. The results constitute the first evidence of functional brain abnormalities in specific locations, thereby providing information on the brain sites that generate some of the clinical characteristics of CCHS (3,4).

CCHS is a very rare disorder of autonomic nervous system control (5). Sleep-dependent hypoventilation, especially during nonrapid-eye-movement sleep, is the hallmark of CCHS (3,4,6). There is considerable within-and between-patient variability in the severity of hypoventilation (3,4,6). Hypoventilation is present during wakefulness in the most severe cases (3,4). A functional characteristic of CCHS patients is absence or marked blunting of the ventilatory response to sustained hypercapnia and to sustained hypoxia (7). Peripheral chemoreceptors are functional in the milder cases (8). In addition to respiratory abnormalities, CCHS patients have functional disorders of the autonomic control of heart rate and blood pressure, with a reduced influence of breathing on cardiac rate variation (9,10), diminished blood pressure dipping at night (11), and reduced short-term variability of heart rate and blood pressure (12). Deficiencies also include loss of dyspnea (13) and reduced anxiety (14). This complex phenotype of CCHS suggests widespread functional brain deficits, although these had not been investigated until the present studies by Woo *et al.* (1) and Macey *et al.* (2).

A genetic etiology for CCHS has long been hypothesized. A few mutations have been identified in genes for the *RET* and endothelin pathways, which are involved in autonomous nervous system development (15). Recent studies have shown that *Phox2b* is the main disease-causing gene for CCHS (16–20). Most of the heterozygous mutations consist in alanine expansions within the polyalanine stretch of *Phox2b* exon 3 (16–20), and several genotype-phenotype associations have been established (18–20).

Studies in transgenic mice have produced data on the homozygous and heterozygous *Phox2b* knockout phenotypes (21–23). Homozygous *Phox2B*-deficient mice die shortly after midgestation because of complete absence of noradrenergic neurons, including those of the locus ceruleus (21). The *Phox2b* deficient embryos lack sympathetic, parasympathetic, and enteric ganglia (21). In homozygous *Phox2b*-deficient mice, the neural crest-derived carotid body degenerates, as do the three visceral sensory ganglia (geniculate, petrosal, and nodose), whereas the nucleus of the solitary tract, which integrates all visceral information, never forms (21). Heterozygous *Phox2b*-deficient newborn mice have abnormal function of chemical respiratory control and dysgenesis of the petrosal chemoreceptors, which may underlie the neonatal respiratory phenotype (22) characterized by abnormally long sleep apneas during the first days of life (Durand E, *et al*., unpublished data). Thus, the respiratory phenotype of heterozygous *Phox2b* mice partly models the respiratory phenotype of CCHS patients. However, the links between recent advances in knowledge about genetic and neurodevelopmental abnormalities in CCHS are not clearly established.

Woo *et al.* examined functional brain responses to a hyperoxic challenge (1). They exposed 14 mildly affected CCHS patients and 15 age-matched controls to hyperoxia for 2 min. During the hyperoxic challenge, the CCHS patients had alterations in early-onset and later respiratory patterns, as well as in respiratory-related heart rate variability, as previously described (10). Using fMRI to assess blood oxygen level-dependent signals in the brain, Woo *et al.* (1) obtained the following results in CCHS patients exposed to hyperoxia: (i) comparable cerebellar and dorsal medial thalamic responses to those in controls; (ii) abnormal medullary and pontine responses in areas targeted by *Phox2b* expression; (iii) an early increase in activity in the right amygdala in response to hyperoxia, contrasting with the normal transient decline in the controls; (iv) absence of the late right insular response noted in the controls.

Macey *et al.* examined functional brain deficits during cold pressure challenge in 13 patients with mild CCHS and in 14

Received January 4, 2005; accepted January 19, 2005.
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age-matched controls (2). They previously showed that CCHS patients lacked the normal respiratory-rate slowing and diminished respiratory-related heart-rate variation in response to cold pressure challenge (23). In the present fMRI study, in both groups, cold pressure challenge failed to recruit the dorsal medullary areas, including the nucleus tractus solitarius, and the dorsal pons, containing the locus ceruleus, which would be affected by *Phox2b* expression. In the CCHS patients, signals were markedly reduced in the cerebellar cortex and deep nuclei; basal ganglia; mid-to-posterior cingular, insular, frontal, and anterior cingulate cortices; and temporal cortices. Thus, this study of responses to cold pressor challenge revealed deficiencies in brain areas that are not targeted by *Phox2b* expression. These results extend previous fMRI studies by the same group showing abnormal cerebellar and limbic responses to respiratory and cardiovascular challenges such as forced expiratory maneuvers, hypoxia, and hypercapnia (24–26). Taken in concert, the fMRI data reported in this issue of *Pediatric Research* document widespread deficiencies in cerebral integrative respiratory and cardiovascular control mechanisms in CCHS patients.

In summary, for the first time, new functional imaging techniques provided data on brain responses to respiratory and cardiovascular challenges in CCHS patients relative to controls. However, the CCHS patients in both studies were ventilator-dependent while sleeping but not while awake. Given the considerable interindividual variability of the CCHS phenotype, the relevance of the results to patients with less severe or more severe CCHS needs to be examined. Nevertheless, in both studies, functional evaluations of respiratory and cardiovascular integrative mechanisms showed that areas other than those targeted by *Phox2b* expression had abnormal and/or aberrant, possibly adaptive, responses. So far, it is unclear whether these functional alterations are secondary to a developmental abnormality in *Phox2b* expression or to other genetic deficits in CCHS patients. Therefore, despite recent advances in molecular genetics, the mechanisms underlying this rare disorder remain unclear. Further studies investigating functional brain deficiencies in CCHS patients and transgenic models could improve our understanding of the complex pathophysiological mechanisms involved in CCHS.

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