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HIGHLIGHTED TOPIC | *Central CO_2 Chemoreception in Cardiorespiratory Control*

Carbon dioxide chemoreception and hypoventilation syndromes with autonomic dysregulation

Michael S. Carroll,* Pallavi P. Patwari,* and Debra E. Weese-Mayer

Center for Autonomic Medicine in Pediatrics, Children's Memorial Hospital, Northwestern University Feinberg School of Medicine, Chicago, Illinois

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Carroll MS, Patwari PP, Weese-Mayer DE. Carbon dioxide chemoreception and hypoventilation syndromes with autonomic dysregulation. *J Appl Physiol* 108: 979–988, 2010. First published January 28, 2010; doi:10.1152/japplphysiol.00004.2010.— Respiratory and autonomic disorders of infancy, childhood, and adulthood are a group of disorders that have varying presentation, combined with a range of severity of respiratory control and autonomic nervous system dysfunction. Within this group, congenital central hypoventilation syndrome and rapid onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation, exhibit the greatest respiratory control deficits, requiring supported ventilation as a mainstay of care. The discovery of the key role of the paired-like homeobox 2B gene in autonomic nervous system development, along with the identification of paired-like homeobox 2B gene mutations causing congenital central hypoventilation syndrome, has led to a fruitful dialog between basic scientists and physician-scientists, producing an explosion of knowledge regarding genotype-phenotype correlations in this disorder, as well as important animal models of chemosensory regulation deficit. Though the etiology of rapid onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation is still to be determined, recent studies have begun to carefully delineate the phenotype, suggesting that it too may provide fertile ground for research that both advances our knowledge and improves patient care.

congenital central hypoventilation syndrome; rapid onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation; control of breathing disorders; *PHOX2B* gene

A SUBSET OF RESPIRATORY CONTROL DISORDERS occurs with related autonomic nervous system dysregulation (ANSD). This unique and expanding group of rare disorders has served to broaden our understanding of an emerging collection of diseases that fall within the rubric of respiratory and autonomic disorders of infancy, childhood, and adulthood (RADICA) (105). These are relatively "young" diseases, with the earliest descriptions reported in 1949 for familial dysautonomia (81), in 1965 for what we now call rapid onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) (25), in 1966 for Rett syndrome (80), and in 1970 for congenital central hypoventilation syndrome (CCHS) (58). These disorders have benefited from the emergence of sophisticated, noninvasive monitoring technology (end-tidal carbon dioxide, pulse oximetry, beat-to-beat blood pressure, continuous temperature recording, and creative measures of respiratory effort and airflow), advancement in ventilator support (smaller home ventilators and diaphragm pacing), as well as emergence of autonomic medicine as a distinct discipline (albeit in its infancy). RADICA have a profound impact on the risk of sudden death, neurocognitive outcome, and long-term quality of life. Because they offer an opportunity to study what is essentially an "experiment in nature" (37) that enables an understanding of control of breathing within the autonomic nervous system (ANS), for the purpose of this review we have focused on two examples of RADICA: *1*) CCHS and *2*) ROHHAD.

CCHS

Background. CCHS, first described by Dr. R. Mellins (58), appeared primarily as case reports until the early 1990s, when case series expanded, as three centers for focused CCHS care became more apparent. Clusters of comorbid disorders (aganglionosis of the distal intestine, i.e., Hirschsprung disease, and neural crest tumors), coupled with familial cases of CCHS and consideration of candidate genes in animal models helped narrow the search for genetic causes. Consequently, in 2003 the paired-like homeobox 2B gene (*PHOX2B)* was identified as

* M. S. Carroll and P. P. Patwari contributed equally to this work.

Address for reprint requests and other correspondence: D. E. Weese-Mayer, MD, Professor of Pediatrics, Northwestern Univ. Feinberg School of Medicine, Director, Center for Autonomic Medicine in Pediatrics, Children's Memorial Hospital, 2300 Children's Plaza, Mailstop #165, Chicago, IL 60614 (e-mail: DWeese-Mayer@ChildrensMemorial.org).

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Table 1. *CCHS publications including CO_2 challenge, in chronological order (note no PHOX2B testing available until 2003)*

Citation	Ref. No.	*N*	Type of Study	Genotype	Age at Onset	Age at Test	Challenge Method	State	Gas Mixtures $CO_2/O_2/N_2$	Results and Comments
Mellins, 1970	58	1	CR	NA	12 days	12 mo	RB, SP: >100	W	4% CO_2	Case compared to 30 previous, mostly adult-onset cases with reduced CO_2 sensitivity. Established definitional diagnostic criteria and behavioral state dependence
Shannon, 1976	83	2	CR	NA	birth	4 mo	D	R	5% CO_2	Compared 6 unmatched controls. Decreased VT to challenge
Haddad, 1978	37	2	CR	NA	birth	1–2 mo	SP: 48–75, D	W/R/N	2% CO_2	No response in f or VT to challenge
Wells, 1980	110	1	CR	NA	birth	19 mo	SP: 71	W/S	U/A & 100%	No ventilatory response in R or N
Fleming, 1980	28	1	CR	NA	birth	9 mo	D	W/R/N	4% CO_2	No ventilatory response in W or R, small response in N. Parents also challenged; mother shows very low normal response
Guilleminault, 1982	34	1	CR	NA	early	2 mo	D	W/S	4.75% CO_2, 7.25% CO_2	Minimal ventilatory response to 4.75%; some response to 7.25%
		1				16 mo	D	W/S	2% CO_2, 5% CO_2	Some response to 5%; stage-dependent arousals
Oren, 1987	66	6	CR/CU	NA	early	5 wk + follow	D	W	3.5% CO_2/A	Ventilatory response muted or absent
Paton, 1989	72	5	CU	NA	<1 yr	6–11 yr	RB-13	W	5% CO_2/95% O_2	No consistent ventilatory response to challenge
Marcus, 1991	56	8	CU	NA	<1 yr	0.4–12 yr	D/RB	S	10% CO_2/A	7/8 cases aroused to challenge with no ventilatory response, but required more time (reached higher $P_{ET}CO_2$)
Weese-Mayer, 1992	109	32	CU	NA	early	median: 3 mo	SP: >70, CB	W/S	U	No ventilatory response to challenge
Shea, 1993	85	5	CU	NA	birth	8–17 yr	RB-2, CB	W	14% CO_2/A	Blunted ventilatory response. No subjective "breathlessness"
Gozal, 1993	32	5	CM	NA	<1 yr	9–14 yr	RB-U	W	15% CO_2, 5% CO_2/95% O_2, 5% CO_2/0% O_2/95% N_2	Designed to elicit mainly transient peripherally mediated response. No significant case-control differences in CO_2 response slopes; significant changes in VT (and f in some challenges)
Nakahara, 1995	60	1	CR	NA	birth	birth	U	W/S	U	Normal response in W; flat in S
Kerbl, 1996	44	1	CR	NA	birth	8 mo	RB	W/S	U	Blunted f and arousal response to challenge
Croaker, 1998	14	5	CR	NA	birth	birth	SP: varied	W/S	U	No ventilatory response to hypercapnia
Macey, 2003	51	14	CA	NA	U	8–15 yr	D	W	5% CO_2/95% O_2, 0% CO_2/15% O_2/85% N_2	Measured fMRI global BOLD response. Gases measured in subset. Muted hypercapnic response in cases
Macey, 2004	53	12	CM	U	U	8–15 yr	D	W	5% CO_2/95% O_2, 0% CO_2/15% O_2/85% N_2	Slow/muted response. Slow f response to hypercapnia
Bajaj, 2005	7	1	CR	NPARM	pre	pre	SP: 120	S		No ventilatory response in extreme preterm with Hirschsprung disease
Chiaretti, 2005	13	3	CM	U	1–4 wk	1–3 mo	SP: 75	S		No ventilatory response
Harper, 2005	38	14	CA	U	U	8–15 yr	D	W	5% CO_2/95% O_2, 0% CO_2/15% O_2/85% N_2	Measured fMRI localized BOLD response. Most areas muted or inverse response in cases. Group differences in midline dorsal medulla, etc.
Chen, 2005	12	5	CA	U	<1 yr	mean: 21 yr	RB-13	W	5% CO_2	No ventilatory response, with normal cardiovascular response. BP response preserved
Antic, 2006	3	5	CR	20/25	varied	22–36 yr	CB, SP: 60–82	W/S		Mild phenotype in adult diagnoses (LO-CCHS) with possible antecedent symptoms
Bachetti, 2006	6	2	CR	U	birth	3 mo, <15 mo	V	N	U	No ventilatory response
Barratt, 2007	8	1	CR	20/25	32 yr?	41 yr	RB	W	U	No quantification
Diedrich, 2007	18	1	CR	20/25	U	27 yr	CB	W	U	Blunted response to challenges. No EMG response to breath hold. Reduction in some HRV measures. BP similar to control
Doherty, 2007	19	5	CR	20/25	varied	4–41 yr	RB-5	W	7% CO_2/93% O_2	LO-CCHS. Reduced response in all *PHOX2B* mutation-confirmed family members

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Table 1.—*Continued*

Citation	Ref. No.	*N*	Type of Study	Genotype	Age at Onset	Age at Test	Challenge Method	State	Gas Mixtures $CO_2/O_2/N_2$	Results and Comments
Huang, 2008	40	7	CM	20/25–27	U	mean: 13 yr	V	W/N/R	U	More severe hypoventilation in N and R. Arousals in 41% of sleep trials. Summary data pooled from 7 CCHS and 2 non-CCHS with normal genotype
Lee, 2009	47	3	CU	20/25	22–30 yr	22–53 yr	RB-7	W	5% CO_2	Reduced slope response to CO_2 challenge
Fine-Goulden, 2009	24	1	CR	20/25	12 yr	12 yr	SP: >112	S		Respiratory failure after anesthesia

N, no. of subjects exposed to hypercapnic challenges. *PHOX2B*, paired-like homeobox 2B gene. Type of Study: CR, case report; CU, cohort, unmatched; CM, cohort, matched; CA, cohort, approximately matched. *PHOX2B* Genotype: NA, not available pre-2003; U, unknown; not tested; NPARM, nonpolyalanine repeat mutation; 20/25 and 20/25–27, *PHOX2B* genotype reflecting the heterozygous condition [and confirming the diagnosis of congenital central hypoventilation syndrome (CCHS)]. Nos. refer to the no. of alanines on each allele in *exon 3* of the *PHOX2B* gene. The normal individual has 20 alanines on each allele. The child with CCHS has one allele with 20 alanines and the second allele with anywhere from 24 to 33 alanines. Hence the genotype of the normal individual is 20/20, and the genotype options for CCHS patients with a polyalanine repeat expansion mutation will have a range of 20/24–20/33. Challenge Method: RB, rebreathing; SP: *x*, spontaneous hypercapnia to *x* mmHg; D, direct through ventilator, pneumotach, or mask; RB-*x*, rebreathing, with *x* liter reservoir; CB, voluntarily controlled breathing rate; V, ventilator withdrawal. Behavioral State: W, wake; S, sleep, unspecified stage; R, rapid eye movement; N, non-rapid eye movement. Gas Mixtures: U, unspecified; A, ambient room air. Specific blends of $CO_2/O_2/N_2$ are shown. Results and Comments: f, respiratory frequency; V_T, end-tidal volume; P_{ETCO_2}, end-tidal partial pressure of CO_2; fMRI, functional magnetic resonance imaging; BOLD, blood-oxygen-level dependent; BP, blood pressure; CCHS, congenital central hypoventilation syndrome; LO-CCHS, late-onset CCHS; HRV, heart-rate variability; EMG, electromyography.

the disease-defining gene for CCHS (2, 57, 82, 102). *PHOX2B* encodes a highly conserved homeodomain transcription factor that plays a key role in mice ANS reflex circuit development (73, 74), such that *PHOX2B* determines cell fate as a sympathetic, parasympathetic, or enteric neuron. *PHOX2B*, located at 4p12, normally contains a 20-alanine repeat sequence (genotype 20/20) on *exon 3*. However, individuals with CCHS are heterozygous for a *PHOX2B* mutation, with the vast majority having a polyalanine repeat expansion mutation (PARM). As recently summarized (103, 104) (www.genereviews.org), the range for number of repeats in the *PHOX2B* polyalanine expansion on the affected allele in patients with CCHS is 24–33 (2, 4, 8, 9, 11, 24, 26, 41, 47, 48, 57, 70, 79, 82, 95, 96, 98, 102), accounting for 90–92% of CCHS cases. The remaining CCHS cases (8–10%) will have a *PHOX2B* missense, nonsense, or frameshift non-PARM (2, 5, 7, 9, 26, 27, 39, 49, 57, 65, 67, 69, 77, 82, 97–100, 102, 106). The specificity of these mutations to the disease phenotype is supported by the fact that no CCHS-related *PHOX2B* mutations were reported in ~2000 controls from the above-cited publications, or from a population study in Taiwan (41).

As of early 2010, laboratories in the United States and abroad have collectively diagnosed nearly 1,000 cases with *PHOX2B* mutation-confirmed CCHS (103, 105). Diagnosed in the absence of primary lung, cardiac, or neuromuscular disease or an identifiable brain stem lesion accounting for the phenotype, CCHS subjects lack an adaptive ventilatory and arousal responsiveness during sleep, as well as the perception of asphyxia during wakefulness. Consequently, they have diminished tidal volumes and monotonous respiratory rates awake and asleep (107), with more profound hypoventilation during sleep. Furthermore, CCHS is associated with other anatomic symptoms of ANSD, including Hirschsprung disease (HSCR) and neural crest tumors. Similarly, physiological symptoms of CCHS (like other ANSDs) can include diminished pupillary response, esophageal dysmotility, profound constipation even in the absence of HSCR, breath-holding spells, reduced basal body temperature, sporadic profuse diaphoresis, lack of perception to dyspnea, altered perception of anxiety, and lack of physiological responsiveness to the challenges of exercise and environmental stressors (23, 30, 55, 63, 71, 75, 84–87, 89, 93, 107–109). Collectively, these symptoms define the CCHS phenotype of this life-long disease. Individuals with CCHS typically require a tracheostomy and mechanical ventilation during sleep at a minimum, and, in more severe cases, mechanical ventilation or diaphragm pacing while awake. Taken together, an improved understanding of the *PHOX2B*-genotype/CCHS-phenotype correlation in terms of facial dysmorphology, ventilatory dependence, symptoms of autonomic dysregulation, cardiac asystoles, relation to age at presentation, HSCR, and neural crest tumors is emerging (9, 33, 57, 79, 92, 94, 98, 101, 102).

Later-onset CCHS (LO-CCHS) is a more recently described subgroup of CCHS, defined as patients presenting outside of the newborn period with *PHOX2B* mutation-confirmed CCHS (3, 8, 18, 19, 54, 57, 69, 70, 79, 94, 96, 98, 101). Although fewer than 50 of these LO-CCHS cases have been reported so far, the population prevalence is likely to be much greater than that suggested by these studies, given the subtle phenotypic profile in many of these cases. LO-CCHS reflects the variable penetrance of the *PHOX2B* mutations with the fewest extra

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Table 2. *ROHHAD publications, including CO_2 challenge, in chronological order*

Citation	Ref. No.	*N*	Age at Onset	Age at Test	State & Challenge Method	Metrics	Results & Comments
Fishman, 1965	25	1	2.75 yr onset of obesity, 3.5 yr onset of respiratory symptoms	3.5 yr	Awake endogenous, exogenous O_2 (unspecified if awake or sleep)	Venous blood gas, $P_{ET}CO_2$	pH 7.21 with P_{CO_2} of 69 Torr. $P_{ET}CO_2$ was 8–10% of atmospheric pressure (normal 4.5%). Oxygen administration did not lower P_{CO_2}
Nattie, 1975	61	1	20 mo	30 mo	Awake endogenous (on presentation), sleep endogenous, awake exogenous CO_2, awake exogenous O_2	Whole body plethysmography; based on metabolic rate and box volume, the expected inspired. CO_2 concentration increased ~1% every 10 min	Pa_{CO_2} ≤60 Torr and hypoxia Pa_{O_2} 65 Torr. With sleep, P_{ACO_2} increased to 65–75 Torr. With exogenous CO_2 via sealed box, approx. no change in V_T and small increase in f and $\dot{V}_E$. Response diminished compared with normal (brisk increase in V_T and f). With 95% oxygen administration, P_{ACO_2} increased to 75 Torr (normal child remained normal at 35 Torr)
Moskowitz, 1976	59	1	7.4 yr	14.7 yr	Awake endogenous, sleep endogenous, awake exogenous: 5% CO_2 + 30% O_2, 7.7% CO_2 + 40% O_2	Arterial blood gas	Pa_{CO_2} 41 Torr. Apnea with sleep with lowest P_{AO_2} 41 Torr and highest P_{ACO_2} 57 Torr. Ventilatory response to inhaled CO_2 was in the low-normal range
				17 yr	Sleep endogenous, awake exogenous (repeated)		Apnea with sleep resulting in P_{AO_2} 29 Torr and Pa_{CO_2} 50 Torr. Exogenous challenge unchanged
Dunger, 1980	21	1	4.5 yr	13 yr	Endogenous (unspecified if awake or sleep), exogenous CO_2 (unspecified if awake or sleep)	Arterial blood gas, ventilatory response to CO_2 production assessed by rebreathing method	Pa_{CO_2} 60–70 Torr; unchanged after naloxone administration. No ventilatory response to $P_{ET}CO_2$ of 71 Torr
Frank, 1981	29	1	5 yr onset of weight gain, 6 yr onset of respiratory symptoms	6 yr	Sleep endogenous, sleep exogenous O_2	Arterial blood gas	Sleep P_{ACO_2} 60 Torr and had obstructive sleep apnea + hypnoneas with persistent hypopnea after tracheostomy placement. With supplemental oxygen, P_{ACO_2} increased to 100 Torr
DuRivage, 1985	22	2	4 yr onset of obesity, 7.5 yr onset of respiratory symptoms	7.5 yr	Sleep endogenous, exogenous (unspecified if awake or sleep)		P_{ACO_2} ~70 Torr and transcutaneous P_{O_2} 49 Torr. Depressed ventilatory response to hypercarbia and hypoxia (details unavailable)
			9 yr	14 yr	Sleep endogenous	Blood gases and polygraphic monitoring	Bradypnea (to 5 beats/min) while asleep with apnea of 33 s, P_{CO_2} 64 Torr, and hypoxemia P_{O_2} 46 Torr. "Adequate ventilation when awake"
Gurewitz, 1986	35	1	4 yr	16 yr	Sleep endogenous, awake exogenous CO_2	Neuromuscular responsiveness to CO_2 by mouth occlusion pressure method (normal 0.8–3.3 cmH_2O to P_{CO_2} 42.7–51.3 Torr)	With sleep, subject had central apnea and elevated apnea index. Depressed response to CO_2 by mouth occlusion (0.8–3.2 cmH_2O pressure in response to P_{CO_2} 48–61 Torr)
Proulx, 1993	76	1	4 yr	9 yr	Sleep endogenous, exogenous CO_2 (unspecified if awake or sleep)		With sleep, P_{CO_2} increased to 56 Torr. No ventilatory response to CO_2 (details unavailable)
North, 1993	62	1 of 2	2.3 yr	3.7 yr	Awake/sleep endogenous		Subject had a seizure, which led to respiratory failure; he subsequently "continued to hypoventilate and have apneic episodes" awake and asleep. He received a tracheostomy, but suffered sudden unexpected death a few weeks after weaned from ventilator

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Table 2.—*Continued*

Citation	Ref. No.	*N*	Age at Onset	Age at Test	State & Challenge Method	Metrics	Results & Comments
Ouvrier, 1995	68	1	3.5 yr	3.5 yr	Sleep endogenous	Polysomnography	Central hypoventilation with frequent apneic episodes (details unavailable). After 5 mo, he died of respiratory failure
Del Carmen Sanchez, 1996	17	1 of 2	2.5 yr	3 yr	Awake/sleep endogenous	Monitoring in pediatric intensive care unit	Central sleep apnea; $P_{A_{CO_2}}$ >80 Torr and Sa_{O_2} <70%. With wakefulness, normal $P_{A_{CO_2}}$ and $P_{A_{O_2}}$
Katz, 2000	43	1	2 yr onset of obesity, 3.5 yr onset of respiratory symptoms	8 yr	Awake endogenous, sleep endogenous, awake exogenous O_2, awake exogenous CO_2	Rebreathing technique	Awake, $P_{ET_{CO_2}}$ 65 Torr and Sa_{O_2} of 98%. With sleep, $P_{ET_{CO_2}}$ increased to 76 Torr and Sa_{O_2} decreased to 81%. With supplemental oxygen, $P_{ET_{CO_2}}$ increased by ~10 Torr. No response to CO_2 (graph in reference demonstrates increase $P_{ET_{CO_2}}$ to 75 Torr without increase in $\dot{V}_E$)
Sirvent, 2002	88	1 of 2	18 mo	3.3 yr			Central and obstructive sleep apnea (details unavailable)
Gothi, 2005	31	1	8 yr	10 yr	Awake endogenous, sleep endogenous	Arterial blood gas, polysomnography	When awake, $P_{A_{CO_2}}$ 36 Torr and $P_{A_{O_2}}$ of 72 Torr. With sleep, the subject had hypopnea (no apnea) with $P_{A_{CO_2}}$ 48–59 Torr and $P_{A_{O_2}}$ 58–78 Torr
Ize-Ludlow, 2007	42	23	Median age: hypothalamic dysfunction 3 yr hypoventilation 6.17 yr		Comprehensive physiological testing for 9 patients; awake endogenous: tachypnea (34 ± 13 beats/min), $P_{ET_{CO_2}}$ 56 ± 7 Torr, SpO_2 89 ± 6%; sleep endogenous: increased $P_{ET_{CO_2}}$ 62 ± 13 Torr, no change in f or V_T; 4 of 9 patients had 24-h mechanical ventilator support	Comprehensive medical record review of 15 subjects of whom 9 subjects had comprehensive physiological testing	Alveolar hypoventilation in 15 patients; obstructive sleep apnea in 5 patients (33%); tracheostomy and mechanical ventilator (24-h/day) in 7 cases (47%) and mask ventilation (night only) in 8 cases (53%). Patients who required 24-h/day ventilation had earlier onset of respiratory manifestations, with median onset at 3.8 yr for 24-h/day vent group, compared with 7.8 yr for nighttime-only ventilation group (P = .03). Genetic testing negative for *PHOX2B, TRKB, BDNF*
Bougneres, 2008	10	6	Age range: obesity 1.5–4.3 yr, hypoventilation: 4.3–8.5 yr				No details of respiratory evaluation
De Pontual, 2008	16	12 of 13	0.7–9 yr		Method unknown but for 7 cases tested, response to CO_2 was abnormal (details unavailable)		Excluded subject with onset at birth. 6 of 12 patients required full-time artificial ventilation; 7/13 required ventilatory support during sleep only. Included 6 subjects also reported in Bougneres paper. Genetic testing negative for *PHOX2B, ASCL1, NECDIN*. Reported 5 autoimmune predisposing alleles on evaluation of HLA-DQ complex
Rand, 2009	78	25	2–7 yr		Challenges not conducted; aim was genetics evaluation		Genetic testing negative for *PHOX2B, HTR_{1A}, OTP*

ROHHAD, rapid onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation; $P_{ET_{O_2}}$, end-tidal partial pressure of O_2; SpO_2, oxygen saturation from pulse oximetry; Pa_{O_2}, arterial partial pressure of O_2; Pa_{CO_2}, arterial partial pressure of CO_2; $P_{A_{CO_2}}$, alveolar partial pressure of CO_2; $P_{A_{O_2}}$, alveolar partial pressure of O_2; $\dot{V}_E$, minute ventilation; Sa_{O_2}, arterial saturation of O_2; *TRKB*, tropomyosin-related kinase B; *BDNF*, brain-derived neurotrophic factor; *ASCL1*, achaete-scute complex 1; *NECDIN*, neurally differentiated embryonal carcinoma-derived protein; HLA-DQ, human leukocyte antigen-DQ; HTR_{1A}, 5-hydroxytryptamine (serotonin) receptor 1A; *OTP*, orthopedia.

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alanines (genotypes 20/24 and 20/25, or rarely a non-PARM) that, at times, may require an environmental cofactor to elicit the profound hypoventilation and/or respiratory arrest (i.e., sedation, anesthesia, anticonvulsants, severe respiratory illness, treated obstructive sleep apnea; or the homozygous condition; Ref. 95).

Mode of inheritance, mosaicism, and clinical testing. The existence of mosaicism in a subset of parents of CCHS probands (98, 102), and an autosomal dominant inheritance pattern from probands (98, 102) and mosaic parents (102) have stimulated improved educational efforts regarding reproductive risks. The *PHOX2B* Screening Test (102), a clinically available accurate method for detecting and sizing the repeat sequence associated with the polyalanine tract expansion (patented; proceeds support CCHS research), is now widely used for prenatal diagnosis, family testing to ascertain mosaicism and disease, and diagnosis of individuals with relevant symptoms. In the event of negative Screening Test results, but strong indications of the clinical phenotype, *PHOX2B* sequencing is recommended as a sequel test (103).

Specifics regarding carbon dioxide chemoreception and CCHS. Table 1 summarizes relevant publications describing individuals with CCHS who underwent hypercarbic challenges, either from exogenous manipulation of breathing gases, or from spontaneously arising hypercarbia/hypoxemia events during wakefulness, sleep, or ventilator withdrawal (case studies with insufficiently detailed challenges are excluded). Several observations can be made from these summaries: sample sizes are small; experimental and analytic methods are variable; adequate age, sex, and ethnicity-matched control subjects are infrequent; there is inconsistent documentation of a *PHOX2B* mutation (to confirm the diagnosis of CCHS); most are studies of cases with the mildest phenotypes; and there is a paucity of analysis stratified by *PHOX2B* genotype. Even among those studies published after 2003, the year that *PHOX2B* was determined to be the disease-defining gene for CCHS, authors have published research without inclusion of the *PHOX2B* testing results (38, 45, 46, 50–53), included patients with non-CCHS diagnoses in grouped data analysis (40), and not analyzed phenotype data by *PHOX2B* genotype. To better understand the role of specific genotypes in the development and function of carbon dioxide chemoreception, it behooves reviewers to be better informed regarding the limitations of studies not including this critical information, as continued publication of such studies can only delay our understanding of how *PHOX2B* mutations determine the CCHS phenotype and related functional deficits in the control of breathing.

Specifics regarding carbon dioxide chemoreception and PHOX2B in the animal model. The earliest viable animal studies were from heterozygous *phox2b*$^{-/+}$ knockout models. Despite interesting and suggestive results, with mutants showing a transient respiratory phenotype in the first days of life (15), observations from this model were difficult to interpret in the context of the human disorder. In humans, by far the most prevalent disease-associated genotype is the polyalanine repeat expansion mutation, which, together with pedigree evidence, strongly suggests a toxic gain of function rather than a haploinsufficiency-caused loss of function (as in the heterozygous mouse model). Subsequent models, especially the knock-in mouse with the 20/27 *phox2b* genotype, have more specific applicability to the human condition because they reproduce the disease-associated genotype more faithfully (20). Interestingly, these mutants show site-specific loss of neurons in a medullary region, known alternately as the retrotrapezoid nucleus (36) and the parafacial respiratory group (20, 64), which has been suggested as an important site for integration/relay of chemosensory drive to respiratory rhythm and pattern-generating circuits (90). However, this mouse is very short-lived and has not yet been evaluated for the presence of several phenotypic features associated with the genotype in humans, such as HSCR, cardiac asystoles, and symptoms of autonomic dysregulation. Other sophisticated animal studies have improved the understanding of the role of *PHOX2B* in carbon dioxide chemoreception (1, 91), but they do not have clear applicability to the human condition, where the ideal model system would be ethically prohibitive.

Interpretation of known carbon dioxide chemoreception in CCHS and the PHOX2B animal models. CCHS offers a unique opportunity to assess carbon dioxide responsiveness as a component of clinical management, as long as needs and safety of patients are the number one priority. Collaboration between basic scientists and physician-scientists will undoubtedly lead to a more clear understanding of mechanisms and manifestations of carbon dioxide chemoreception, central and peripheral segregation of function, the importance of feedback and feedforward effects, and the role of the human analogs of the retrotrapezoid nucleus/parafacial respiratory group. In addition to cultivating an appreciation for mechanisms that can be elucidated even in simple experimental models, clinicians can learn from basic scientists to increase the sophistication and subtlety of their quantitative analyses of physiological waveforms. Similarly, basic scientists can benefit from understanding the natural history of disease and treatment in all of its confounding variety. This knowledge can motivate studies based on animal models that reproduce as much of the CCHS clinical profile as possible. Such clinically informed animal studies will not only improve the therapeutic relevance of basic research, they may help decipher such issues as the difference between neonatal and adult age at diagnosis, or the role of neural plasticity in the presentation of the mildest phenotypes (and 20/24 and 20/25 genotypes).

ROHHAD

Background. ROHHAD is a rare and complex pediatric disorder for which rapid onset of obesity is a harbinger of potentially fatal central hypoventilation and variably shown to include symptoms of autonomic dysfunction, endocrine dysfunction, and tumors of neural crest origin (10, 16, 42, 43). ROHHAD was first described as late-onset central hypoventilation with hypothalamic dysfunction by Fishman in 1965 (25), with later clarification as a distinct disorder in 2000 with a review of 10 cases in the literature (43). With the discovery of the genetic source for CCHS in 2003 and with only 15 published late-onset central hypoventilation with hypothalamic dysfunction cases through 2004, Ize-Ludlow et al. (42) reported on systematic analysis of comprehensive medical records from 23 subjects, described the phenotypic profile, confirmed the absence of a *PHOX2B* mutation, and demonstrated a clear distinction from CCHS. Because identification of these children is challenging, but extremely important due to the devastating consequences of hypoventilation and auto-

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nomic dysregulation, the acronym "ROHHAD" was developed to help facilitate early diagnosis (42). Now, a total of 75 cases have been described in the literature using these criteria: *1*) onset of rapid-onset obesity and alveolar hypoventilation after the age of 1.5 yr; *2*) evidence of hypothalamic dysfunction, as defined by one or more of the following findings: rapid-onset obesity, hyperprolactinemia, central hypothyroidism, disordered water balance, failed growth hormone stimulation test, corticotrophin deficiency, or delayed/precocious puberty; and *3*) absence of *PHOX2B* mutation in cases reported after 2003.

A remarkable feature of ROHHAD is the apparent normality of the first 1.5–7 yr of life in these cases, marked by sudden onset of hypothalamic dysfunction, typically with the onset of rapid weight gain and obesity early in life, followed by more apparent autonomic dysregulation and alveolar hypoventilation that manifests after an acute viral illness and (in a subset of cases) a cardiorespiratory arrest or neural crest tumor. There is wide variation in age at onset of autonomic dysfunction, as well as in the interval between the onset of hypothalamic dysfunction and subsequent hypoventilation. Although many of these children can be supported with nocturnal mask ventilation, a subset requires 24 h/day supported mechanical ventilation via a tracheostomy. If not identified and adequately treated, the hypoventilation can be fatal, or induce potential morbidity. The available data have allowed improved characterization of ROHHAD, including the earliest presenting symptoms and typical time course, and reinforce the high incidence of cardiorespiratory arrests in this syndrome (10, 16, 29, 42, 43, 62, 68, 76).

Although some features of the CCHS phenotype are seen in patients with ROHHAD, the latter demonstrate an even wider spectrum of systems involved, suggesting a defect in a more proximal or different genetic pathway involved in ANS differentiation or development. Candidate gene analysis has only recently been undertaken (see Table 2), and discovery of gene-disease association has yet to be successful (16, 42, 78). Although less well known than CCHS, ROHHAD is a potentially related condition of autonomic dysregulation/RADICA that affects seemingly normal children. Consequently, ROHHAD may provide clues regarding maturational issues related to ANSD and respiratory control.

Specifics regarding carbon dioxide chemoreception and ROHHAD. Although first described in 1965, it is immediately apparent from review of Table 2 that several years of productive research were lost to confusion in details of the phenotype and a need for clear diagnostic distinction from CCHS. Furthermore, with the introduction of *PHOX2B* testing and the acronym ROHHAD describing the phenotype in the order of symptom manifestation, there has been a dramatic increase in reported cases in the literature. Despite excellent case reports, and growing cohorts, a thorough quantitative assessment of carbon dioxide chemoreception in these patients has yet to be published. Just as with CCHS, it is immediately apparent that extant studies include small sample sizes, variable methods of study, a lack of adequately matched control subjects, and inconsistent documentation of the ROHHAD phenotype.

Interpretation of known carbon dioxide chemoreception in ROHHAD. ROHHAD subjects clearly demonstrate an abnormal response to both endogenous and exogenous carbon dioxide challenge. The variability in severity of response, along with the mechanism by which control of breathing is affected, has yet to be comprehensively evaluated. As with CCHS, ROHHAD offers a unique opportunity to disentangle carbon dioxide responsiveness from other regulatory systems. With growing awareness of the phenotype, and the ability to eliminate CCHS from the differential diagnosis with *PHOX2B* testing, a more homogeneous cohort of patients with ROHHAD will emerge, allowing more focused investigation of genetic (or perhaps epigenetic) and environmental causes.

OVERALL SUMMARY

The future of understanding the role of carbon dioxide chemoreception in RADICA lies with the collaboration of basic scientists with physician-scientists. CCHS has already proven to be a fruitful area for such a cooperative effort, elucidating essential mechanisms of respiratory control while improving patient care, and ROHHAD represents a similar opportunity. Individuals with these disorders allow us to learn about control of breathing in health as well as disease, thereby allowing for these special needs patients to further our understanding of the basic science underlying carbon dioxide chemoreception and its relationship to the ANS. However, such success depends on completion of careful protocols, targeting specific questions, and application in large cohorts of cases and matched controls, with a clear hypothesis driving the analysis. For example, the finding of neural crest tumors in a subset of CCHS and ROHHAD cases and the concern for a possible paraneoplastic basis in ROHHAD may lead to a more basic understanding of the neural crest origin in RADICA. A centralized database of ROHHAD patients would be invaluable in elucidating the cause of this syndrome, improve identification and treatment of these children, and may provide key insights into the normal physiology of some of the most basic vital neurological functions. Such characterization will also likely guide future candidate gene analysis. Within RADICA, CCHS and ROHHAD exhibit the most prominent respiratory control deficits, which, if inadequately treated, can lead to serious morbidity and even mortality in these patients. Thus a profound humanitarian purpose coincides with a compelling set of fundamental research questions, providing what promises to be an ideal environment for progress in both realms.

DISCLOSURES

No conflicts of interest are declared by the author(s).

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