Pediatric Pulmonology 45:92–98 (2010)

Congenital Central Hypoventilation Syndrome: Neurocognitive Functioning in School Age Children

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Summary. Objective: Examine indices of neurocognitive functioning in children with *PHOX2B* mutation-confirmed neonatal onset congenital central hypoventilation syndrome (CCHS) and relate them to indices of *PHOX2B* genotype, demographics, and disease severity. Methods: Subjects were 20 patients with *PHOX2B* mutation-confirmed CCHS diagnosed as neonates who had undergone neurocognitive assessment in the course of clinical care at the Rush Children's Hospital CCHS Center between 1990 and 2006. Neurocognitive variables of interest included Full Scale IQ (FSIQ) and Wechsler-derived marker indices (subtests) of verbal comprehension (Vocabulary), visuoperceptual reasoning (Block Design), working memory (Digit Span), and clerical/processing speed (Coding). Results: Single sample *t*-tests revealed participants' general intelligence index (FSIQ; mean 84.9, SD 23.6) to be lower than the general population, though the range of FSIQ observed was broad. Visuoperceptual reasoning and clerical/visuographic speed marker indices were similarly depressed. These deficits were related to special education participation but not to *PHOX2B* genotype status or other demographic and clinical risk factors. Conclusions: *PHOX2B* mutation-confirmed CCHS confers risk for adverse neurocognitive outcome, though the range of functioning observed raises questions about factors that may contribute to neurocognitive variability. Visuoperceptual reasoning and clerical/visuographic speed appear particularly vulnerable. *PHOX2B* genotype and disease severity indicators were unrelated to neurocognitive indices, possibly due to our modest sample. Future research should employ comprehensive neurocognitive assessment emphasizing visuoperceptual ability, mental speed, attention, and information processing efficiency. Increased recognition and expedited diagnosis with *PHOX2B* testing should allow larger studies of the relationship between neurocognitive functioning, *PHOX2B* genotype/mutation, and disease severity and management. Pediatr. Pulmonol. © 2009 Wiley-Liss, Inc **Pediatr Pulmonol. 2010; 45:92–98.** © 2009 Wiley-Liss, Inc.

Key words: congenital central hypoventilation syndrome; autonomic nervous system; *PHOX2B*; intelligence; neuropsychology.

INTRODUCTION

Congenital central hypoventilation syndrome (CCHS) represents an increasingly recognized group of conditions characterized by respiratory and autonomic nervous system (ANS) dysregulation (ANSD),[1] or what has been recently termed respiratory and autonomic disorders of infancy, childhood, and adulthood (RADICA).[2] Though the hallmark of CCHS is alveolar hypoventilation with

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Additional Supporting Information may be found in the online version of this article.

These data were presented in part at the 2007 International Meeting of the American Thoracic Society, San Francisco, CA; the abstract appears in Am J Respir Crit Care Med 2007:175.

Grant sponsor: Chicago Community Foundation *PHOX2B* Patent Fund.

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Received 8 June 2009; Revised 23 October 2009; Accepted 23 October 2009.

DOI 10.1002/ppul.21170
Published online 3 December 2009 in Wiley InterScience (www.interscience.wiley.com).

insensitivity to resultant hypoxemia and hypercarbia, patients also have symptoms of ANSD including temperature dysregulation,[3] transient abrupt asystoles,[4] severe breath holding spells,[5] altered gut motility[6] and severe constipation,[3,7] pupillary abnormalities,[8] and decreased perception of pain[3] and anxiety.[9] A subset of children with CCHS also has Hirschsprung disease and/or tumors of neural crest origin. With awareness that the paired-like homeobox *PHOX2B* is the disease-defining gene for CCHS,[10–13] the availability of clinical testing since 2003, and the understanding that cases may be diagnosed from birth through adulthood,[12,14–16] more cases are being reported internationally.[2] Individuals with the CCHS phenotype are heterozygous for a polyalanine repeat expansion mutation (PARM) in the *PHOX2B* gene in ~90% of cases (genotypes 20/24 to 20/33; normal is 20/20), or for a non-PARM (NPARM) in the remaining ~10%[10–13,17,18] (missense, nonsense, and frameshift variants). *PHOX2B* genotype/CCHS phenotype analysis supports a relationship between the number of polyalanine repeats or the NPARM mutation and clinical phenotype severity.[2,11,12,17–19]

Neurocognitive assessment of children with CCHS has identified varied impairments. Oren et al.[20] described six CCHS children with ''mild to moderate learning disabilities and developmental delays, especially in areas of fine motor and cognitive function,'' all of whom required individualized education programs. Marcus et al.[21] reported group means in the borderline deficient to very low average range from cognitive testing of nine CCHS children, with indices of achievement, mental processing, receptive vocabulary, and visuographic skills more than a standard deviation below the population mean; seven of nine were rated by parents as having developmentally immature attention and concentration skills and two of six school-age subjects had learning disabilities and received special education assistance. Silvestri et al.[22] previously reported clinical test results in a cohort of 17 CCHS infants and children indicating neurodevelopmental delay, especially on indices of visuospatial and visuographic ability, and academic difficulties in 78% of school-aged subjects.[22] Shortcomings of these three studies included (1) small sample sizes, (2) broad participant age ranges, (3) use of multiple assessment instruments with varying subscales and factor structures, (4) reporting in the pre-*PHOX2B* testing era, and (5) variable ventilatory needs among subjects. Nevertheless, they suggest that CNS processes underlying CCHS may also affect cognition. Furthermore, even seemingly healthy CCHS patients may be at-risk for adverse neurodevelopmental outcome due to repeated hypoxemia resulting from suboptimal ventilatory support, severe breath holding spells, vigorous exercise,[23–25] or transient abrupt asystoles.[18] Current data, therefore, suggest innate risk for neurocognitive delay in CCHS in addition to environmental susceptibility, though mechanisms of adverse outcome have not been elucidated.

The CCHS disease-defining *PHOX2B* gene encodes a highly conserved homeobox domain transcription factor[10] with early embryologic action promoting pan-neuronal differentiation in the ANS and a separate role repressing inhibitors of neurogenesis.[26–30] The implications of ANSD on neurodevelopment and neurocognitive functions in CCHS may be significant, given the critical role of the ANS in orienting responses underlying attention, learning, and conditioning.[31–33] It is reasonable to posit that ANSD may contribute to suboptimal learning and academic attainment, and appropriate to consider the relationship between CCHS-related mutations of the *PHOX2B* gene and neurocognitive outcome.

The current study examined the neurocognitive functioning of patients with neonatal onset CCHS within the psychometric framework of the Wechsler intelligence scales. We hypothesized that CCHS patients would fall below the population mean on an index of general intelligence. Based on previous studies, we posited that differences between CCHS patients and the general population would be most apparent on indices of visuospatial and visuographic ability from the Wechsler intelligence scales. Considering the role of the *PHOX2B* gene in CCHS and the embryologic origin of the ANS, and the role of the ANS in children's learning, we proposed the secondary hypothesis of a significant correlation between the number of polyalanine repeats in the *PHOX2B* expansion mutation of CCHS patients and their neurocognitive performance. Likewise, we posited that indices of environmental susceptibility related to postnatal hypoxemia would be related to neurocognitive outcome.

MATERIALS AND METHODS

Subjects

Candidates for participation were 33 patients with *PHOX2B* mutation-confirmed diagnoses of CCHS assigned in the neonatal period who had undergone routine neurocognitive assessment during their clinical care at Rush Children's Hospital CCHS Center between 1990 and 2006. Of 33 potential candidates, 23 had been administered a school-aged Wechsler intelligence scale. Participants were required to have taken one Wechsler scale providing a Full Scale IQ (FSIQ) index. The 20 children meeting this final criterion comprised the sample for this study. Fourteen of the 20 had taken more than one Wechsler over the interval studied, to a maximum of nine administrations. For subjects with more than one administration, mean values across all administrations were calculated for each study index. IRB approval was obtained for the retrospective chart review and data collection necessary to complete this investigation.

Among children in the current cohort, four had provided school-aged Wechsler intelligence data, three provided preschool-aged Wechsler intelligence data, and one provided infant assessment data in our 1992 publication.[5] Because the current study is limited to school-age Wechsler test results, only four children from our 1992 publication[5] provide data that overlap with the current research study.

Measures

Clinical/Risk Indices

Risk for postnatal hypoxemia was gauged by the child's history of pulmonary hypertension on echocardiogram, seizure activity on EEG or by witnessed seizures, or prolonged r–r interval $\geq$3 sec on Holter monitoring. Additional clinical data characterized the child's (1) level of ventilatory support, including indices of daytime and nocturnal ventilation, (2) use of a cardiac pacemaker, and (3) history of academic achievement and special education participation. Ethnicity was assigned based on parent report.

Neurocognitive Assessment

To assess the effectiveness of interim management and compliance, the model for routine care for patients in the CCHS Center specified a battery of neurocognitive tests,[22] with intellectual testing a core component of the evaluations. All tests were administered and scored by a senior psychologist (M.N.N.).

Over the time period of this study, three successive editions of the Wechsler Intelligence Scales for Children (WISC) and one edition of the Wechsler Adult Intelligence Scale (WAIS) were employed: the WISC-R (Revised),[34] WISC-III (3rd Edition),[35] WISC-IV (4th Edition),[36] and WAIS-III (3rd Edition).[37] Although the FSIQ index of overall intelligence is comparable across these scales, subdomain information from the Wechsler scales presents a challenge to statistical analysis because the factor structures of the test editions vary. Furthermore, some patients had been given two or more versions of the WISC and/or the WAIS over years of follow up, complicating analysis within an individual subject.

In order to combine data across the Wechsler intelligence scale versions, we selected subtests as ''markers'' for each of the four core subdomains defined in the most recent version of the Wechsler intelligence scales, the WISC-IV. The marker subtests and (italicized) subdomains are: Vocabulary (*verbal comprehension*), Block Design (*perceptual reasoning*), Digit Span (*working memory*), and Coding (*processing speed*). These subtests are common to all versions of the Wechsler and can be used as indicators of functional competence in the four intellectual subdomains. These indices and the subdomains they sample are described in Table 1. As previously indicated, the current analyses are particularly concerned with the performance of subjects upon Block Design and Coding as marker variables for abilities posited to be most vulnerable to the adverse effects of CCHS. FSIQ standard score indices have a mean of 100 and a standard deviation of 15. Subtest indices are presented as scaled scores, with a mean of 10 and a standard deviation of 3.

Data Analysis

Means and standard deviations were calculated for all neurocognitive indices and compared to population norms using single-sample *t*-tests. A repeated-measures analysis of variance was used to compare the four subdomain indices within the CCHS sample. Tukey post hoc analyses were employed following a significant *F*-test to detail differences among subdomain indices. Subgroups of the sample varying on gender, use of a cardiac pacemaker, seizure status, special education participation, and specific *PHOX2B* mutation were compared using *t*-tests on FSIQ and the subdomain indices. In all analyses, two-tailed tests were employed and a criterion of $P \leq 0.05$ applied to judge statistical significance.

TABLE 1— Description of Wechsler Intelligence Scale Study Indices

Study index (subtest)	Subtest description	Subdomain title	Subdomain description
Vocabulary	Subject provides oral definitions for words	Verbal comprehension	Fund of knowledge; ability to comprehend language and use it expressively
Block Design	Subject uses red and white blocks to reproduce sample block patterns	(Visuo)perceptual reasoning	Mechanical-spatial ability; visually mediated reasoning
Digit Span	Subject repeats digit sequences of varying lengths. Some are repeated exactly as given, others are repeated in reverse sequence	Working memory	Temporary retention and ability to manipulate verbal information in memory; auditory attention
Coding	Subject copies letter-like symbols as quickly as possible, matching them to printed numerals according to a sample code	Processing speed	Clerical speed and agility; fine motor dexterity; visual attention

RESULTS

Sample Characteristics

The sample comprised 11 girls and 9 boys of which 18 were Caucasian and 2 African-American in origin. Ages at Wechsler intelligence administrations ranged from 6 years, 5 months to 21 years, 5 months, with a mean of 12 years, 6 months, SD 44 months (median 11 years, 5 months).

The *PHOX2B* Screening Test (Molecular Diagnostics Laboratory, Rush University Medical Center) revealed the following subject distribution by genotype: 20/25 (n = 2), 20/26 (n = 7), 20/27 (n = 7), 20/30 (n = 2), and 20/33 (n = 1). The *PHOX2B* Sequencing Test (Molecular Diagnostics Laboratory, Children's Memorial Hospital) also revealed a single case with a missense mutation, A428G.

Four subjects (20%) had a history of pulmonary hypertension and 14 (70%) had a history of seizure activity. Seventeen subjects (85%) received 24-hr ventilatory support whereas three (15%) received only nocturnal support. Daytime ventilation support for 15 subjects (75%) relied upon a diaphragm pacer; with two subjects (10%) requiring daytime support by tracheostomy and mechanical ventilator, and three subjects (15%) requiring no daytime support. During sleep, 17 subjects (85%) required tracheostomy-ventilator support, two subjects (10%) used a diaphragm pacer, and one (5%) used mask ventilation. Each of the patients studied had undergone clinical CT and/or MRI of the brain/brainstem. None of the imaging studies had findings that might be considered to represent hypoxic- and ischemic-related consequences. The academic risk status of the sample is illustrated by the fact that 12 of 19 subjects (63%) required some involvement in special education for academic reasons.

Neurocognitive Indices

Means and standard deviations for neurocognitive indices are presented in Table 2. Supplementary detail regarding the distribution of FSIQ scores for subjects with repeated evaluations is available on-line. Subgroup data are also presented in Table 3 for the following *PHOX2B* genotypes: 20/25, 20/26, 20/27, 20/30–20/33, and for the single case with a missense mutation. As Table 3 shows, the CCHS sample varied widely on all neurocognitive indices.

Single sample *t*-tests comparing CCHS patients against the standardization sample indicate significantly lower FSIQ, $t(19) = -2.87$, $P < 0.01$; Block Design, $t(18) = -3.54$, $P < 0.002$; and Coding, $t(18) = -2.64$, $P < 0.017$. A repeated measures analysis of variance comparing the subdomain indices was also significant, $F(3, 54) = 3.74$, $P < 0.016$, indicating that the mean subtest scores were not equivalent. Tukey post hoc comparisons revealed that the Block Design index was significantly lower than Vocabulary and Digit Span (which did not differ from one another), though Coding was intermediate and indistinguishable from the others.

Analysis of variance failed to show significant differences on neurocognitive indices among the *PHOX2B* genotype subgroups. Similarly, *t*-test comparisons of risk groups defined on the basis of seizure history and use of a cardiac pacemaker were not significant, nor were gender differences found. Due to disproportionate subgroup sizes, inferential analysis was not possible for risk indices related to sleep and wake ventilatory support. *t*-Test comparisons of CCHS subjects receiving special education versus those who do not were significant for FSIQ, $t(16) = -2.67$, $P < 0.017$; Block Design, $t(15) = -3.91$, $P < 0.001$; and Coding, $t(15) = -2.93$, $P < 0.010$.

DISCUSSION

In this analysis, we report indices of neurocognitive functioning in the largest sample to date of patients with *PHOX2B* mutation-confirmed neonatal onset CCHS. The range of general intellectual functioning demonstrated in the current sample was broad, extending from moderately deficient to superior. However, the CCHS group mean was distinctly lower than that of the general population, by a full standard deviation. If corroborated in future research, a downward IQ shift of this magnitude would increase the risk of mental handicap almost sevenfold, to include nearly 16% of the CCHS population. Within the current sample, five participants (25%) produced FSIQ indices in the deficient range (≤ -2 SD), supporting concerns about neurocognitive handicap in CCHS patients. Conversely, two participants (10%) produced superior ($\geq +2$ SD) FSIQ indices, demonstrating that functioning in CCHS is indeed varied.

As predicted, marker variables for the neurocognitive subdomains of visuoperceptual reasoning (Block Design)

TABLE 2—Overall Sample Means and Standard Deviations for Neurocognitive Test Indices

	N		FSIQ[1]	Vocabulary[2]	Block Design[2]	Digit Span[2]	Coding[2]
Total	20	Mean	84.88	8.33	6.85	8.96	7.60
		SD	23.56	4.76	3.87	4.87	3.95

[1]General population: mean = 100, standard deviation = 15.
[2]General population: mean = 10, standard deviation = 3.

TABLE 3— Means, Standard Deviations, and Ranges for Neurocognitive Test Indices by Genotype Subgroup

PHOX2B genotype subgroup	N		FSIQ[1]	Vocabulary[2]	Block Design[2]	Digit Span[2]	Coding[2]
20/25	2	Mean	86.3	9.0	6.3	8.3	9.8
		SD	3.2	0.7	1.1	2.5	3.9
		Range	84.0–88.5	8.5–9.5	5.5–7.0	6.5–10.0	7.0–12.5
20/26	7	Mean	78.6	6.9	5.8	7.5	6.6
		SD	32.1	5.6	5.1	6.4	5.5
		Range	40.7–132.0	1.0–15.0	1.0–15.0	1.0–16.0	1.0–17.0
20/27	7	Mean	86.4	8.6	7.2	8.9	7.6
		SD	15.3	4.7	2.5	4.3	2.9
		Range	58.8–100.4	1.7–13.2	3.3–10.2	1.8–13.4	4.5–12.1
20/30–20/33	3	Mean	79.7	7.8	6.5	11.1	7.2
		SD	15.4	2.8	3.5	3.3	1.8
		Range	62.0–89.2	4.5–9.8	2.5–9.0	7.6–14.0	5.5–9.0
A428G	1		131	17	14	15	12

[1]General population: mean = 100, standard deviation = 15.
[2]General population: mean = 10, standard deviation = 3.

and clerical/visuographic speed (Coding) were significantly below the normative mean, whereas indices of verbal comprehension (Vocabulary) and working memory (Digit Span) were not. Indeed, the subdomain of visuoperceptual reasoning appears to be more challenging to CCHS patients than verbal comprehension and working memory. These findings suggest that tasks measuring visuoperceptual ability and clerical/visuographic speed may be particularly sensitive to the neurocognitive effects of CCHS, regardless of whether they are mediated by neurogenetic or secondary factors such as postnatal hypoxic- and ischemic events. Verbal comprehension and working memory skills, in contrast, appear to be relatively less affected by CCHS and environmental susceptibility factors. Likewise, the current data link CCHS neurocognitive deficits with special educational involvement, suggesting that they have ecological validity in that they are related to ''real world'' academic difficulties. One consideration with these results is the possibility that ocular abnormalities may have contributed to the current findings. Though untreated myopia could impact Block Design and Coding performance, nearly all of the children in our cohort wore corrective lenses and all tests were performed at close range. Thus, we do not anticipate that the presence of or the need for visual correction would be a factor in the reported findings.

We did not identify significant associations between neurocognitive indices and *PHOX2B* genotype in this sample. This may have been partly due to its size, as few patients identified with 20/25, 20/30, and 20/33 *PHOX2B* genotypes were old enough to have had the neurocognitive testing necessary for this study. Similarly, our modest sample did not allow us to conduct analyses of the relationships between neurocognitive indices and the disease risk parameters of pulmonary hypertension, daytime ventilatory support, and nocturnal ventilatory support. Relationships with gender, seizure history, and use of a cardiac pacemaker were examined among CCHS participants but not found to be significant. However, without continuous at-home documented monitoring with pulse oximetry, the role of intermittent hypoxemia as a potential cause of cognitive delays could be missed or at least under-appreciated.

These findings suggest that PARMs in *PHOX2B* (regardless of size) may predispose to cognitive impairment, supporting existing literature on the role of the ANS in learning. In fact, data already support the premise that ANSD may impact neurocognitive performance. Welton et al.[38] demonstrated below average intellectual and fine-motor performance in patients with familial dysautonomia (FD), another disease characterized by respiratory and ANSD.[38,39] Specifically, on the WISC-R, FD patients demonstrated significantly lower Performance than Verbal IQs. Whether the effect of *PHOX2B* mutations on cognition is the direct result of *PHOX2B* protein dysfunction on CNS development or whether it is mediated through acquired CNS damage (e.g., due to chronic intermittent brain hypoxia or altered cerebral perfusion due to swings in oxygenation and carbon dioxide) remains unknown and is an important topic for future research.

It is interesting to compare the current results with neuropsychological findings in pediatric obstructive sleep apnea (OSA), because children with OSA are also vulnerable to recurrent episodes of nocturnal hypoxia. In a recent review, Halbower and Mahone[40] found the most commonly reported neurocognitive correlates of OSA to involve attention, executive skills, learning, and memory. Findings of depressed intelligence, language, and processing speed were less frequent, and deficits of visuoperceptual skills were seldom reported. Although our findings of depressed IQ and clerical/visuographic slowing bear

some similarity to OSA, our data raise the possibility that visuoperceptual deficits are more characteristic of CCHS, regardless of whether they are related to its genetic substrate (i.e., *PHOX2B* genotype) or secondary hypoxia.

The current study has a number of limitations. It did not allow comparison with a demographically matched control group of individuals unaffected by CCHS. By controlling for factors such as socioeconomic status, a carefully selected comparison group of peers or siblings would make it possible to gain a clearer sense of the neurocognitive deficits that are attributable to CCHS. Our modest sample provided limited opportunity to study the relationship between CCHS genotype and neurocognitive outcome, and reduced the statistical power of our analyses. Specifically, our sample size and data dispersion limited analyses of the impact of disease-related risk factors such as pulmonary hypertension, daytime ventilatory support, and nocturnal ventilatory support. Intrinsic limitations of clinical retrospective data also made it difficult for us to quantify the level of hypoxic episodes actually experienced by our patients. Although the hypoxic risk variables we chose (e.g., seizures, ventilatory support, cor pulmonale, asystoles) should identify subjects more likely to have had a hypoxic event(s), one cannot be certain of this, and increased care given to patients with seizures, cardiac issues, or continuous ventilation needs may have an ameliorative effect on neurodevelopmental outcome. Finally, although the Wechsler intelligence framework was helpful in allowing us to combine data drawn from clinical assessments over many years using different instruments, all domains of neurocognitive functioning were not sampled in our analyses.

Future research efforts should sample a broader range of functional domains, with a greater emphasis upon fluid mental abilities such as attention, executive skills, memory, and information processing speed. Such assessments should allow a more finely detailed picture to emerge of the deficits experienced by CCHS individuals. Other important topics of research in CCHS will include quality of life and psychosocial adjustment. Prospective, longitudinal approaches that integrate state-of-the-art technologies for autonomic and physiologic monitoring and real-time psychometric assessment will provide the best opportunity to understand neurocognitive deficits in CCHS within a developmental framework. Future studies will also need to consider home care protocols in greater detail for a better understanding of the effect of socioeconomic and respiratory regulation factors on neurocognitive outcome in the presence of a *PHOX2B* mutation.

Even with the limitations of the current investigation, our data have clear implications for clinical practice. It behooves clinicians, parents, and caregivers to recognize that there may be many sources for the variability identified in this cohort. Modifiable sources would include age at diagnosis, tracheostomy, and initiation of appropriate ventilatory management; guidance in home ventilatory management; avoidance of cerebral hypoperfusion due to intentional hyperventilation or inadvertent hypoxemia; and aggressive educational intervention. Non-modifiable sources might include *PHOX2B* genotype or mutation and heritable components of intellect and neurocognitive functioning. It remains to be determined, for example, if an active child with a 20/25 genotype and adequate spontaneous waking ventilation is less vulnerable physiologically than a less active ventilator-dependent child with a 20/33 genotype or NPARM. Likewise, it remains to be determined if a child who requires 24 hr/day ventilation might actually demonstrate superior performance because a caregiver is present continuously and ventilation is optimal at all times. Taken collectively, it is likely that the inclusion of patients from the ''early days'' of CCHS management introduces too many confounding variables (e.g., delay of diagnosis) to allow clear differentiation of the factors that contribute to neurocognitive outcome. A prospective family study of a cohort diagnosed and treated in the first days of life will offer a better opportunity to discern the role of *PHOX2B* genotype and other treatment and environmental factors in determining neurocognitive outcome in these seemingly vulnerable children with CCHS.

ACKNOWLEDGMENTS

The authors would like to thank those physicians who have referred their patients to our Center for study, the families of these patients, and the children with CCHS. We also thank Joanne Wuu, M.S. for her statistical assistance and Geno DeMarchi B.S. for his early involvement in this project.

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