CHEST

Congenital Central Hypoventilation Syndrome

Neurocognition Already Reduced in Preschool-Aged Children

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BACKGROUND: Congenital Central Hypoventilation Syndrome (CCHS) is a rare neurocristopathy characterized by severe hypoventilation and autonomic dysregulation, with typical presentation in the neonatal period, and deficient cognitive skills in school-aged patients. We hypothesized that younger (preschool) children with CCHS would also show neurocognitive delay and that CCHS-related physiologic factors would impact neurocognitive test results.

METHODS: We studied developmental (Bayley) test results collected during routine clinical care in 31 children (mean age 25.0 ± 8.5 months; range, 6-40 months) with *PHOX2B* mutation-confirmed CCHS by comparing them with the normative reference mean from the Bayley standardization sample; we also examined associations between Bayley scores and CCHS disease-related factors.

RESULTS: Preschool patients with CCHS fell significantly below the normative mean of 100 on Bayley indices of mental (mean, 83.35 ± 24.75) and motor (mean, 73.33 ± 20.48) development ($P < .001$ for both). Significantly lower Bayley mental and motor scores were associated with severe breath-holding spells, prolonged sinus pauses, and need for 24 h/d artificial ventilation. Lower Bayley motor scores were also associated with seizures. Bayley scores differed among children with the three most common polyalanine repeat expansion mutation genotypes (mental, $P = .001$; motor, $P = .006$), being essentially normal in children with the 20/25 genotype but significantly lower in the other genotype groups ($P < .05$).

CONCLUSIONS: These results confirm neurodevelopmental impairment of CCHS preschoolers, with severity related to physiologic compromise and *PHOX2B* genotype. These findings suggest that adverse effects begin early in the disease process, supporting the need for neurodevelopmental monitoring and intervention from early infancy.

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KEY WORDS: cognitive function; genetics; hypoventilation

ABBREVIATIONS: CCHS = Congenital Central Hypoventilation Syndrome; NPARMS = non-polyalanine repeat expansion mutations; PARMs = polyalanine repeat expansion mutations

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Congenital Central Hypoventilation Syndrome (CCHS) is a rare neurocristopathy characterized by severe hypoventilation and autonomic dysregulation, with typical presentation in the neonatal period. Initially described in 1970[1] and brought to public awareness in 1999,[2] *PHOX2B* was identified as the disease-defining gene for CCHS in 2003.[3-5] *PHOX2B* testing confirmation is now required for a diagnosis of CCHS,[6] expediting ascertainment, intervention, and anticipatory management.

Neurocognitive functioning has long been of great concern in CCHS because of the potential for repeated hypoxemia and hypercarbia in activities of daily living (including breath-holding spells and exertional physiologic compromise), even when mechanical ventilation is adequate for quiet activities. Past literature has indicated deficiencies of mental abilities in school-aged children with CCHS,[7-10] with Zelko et al[7] reporting a mean Wechsler intelligence more than 1 SD below the general population mean in a sample of 20 patients. Marcus et al[8] found 9 of 12 patients showed moderate to severe developmental delay and Oren et al[9] and Silvestri et al[10] described learning disabilities and developmental delay in smaller CCHS samples, identifying particular limitations of visuographic and visuoperceptual skills. Children with CCHS are, however, typically able to partake in age-appropriate classes and activities, albeit often with special education support. Though we and others have reported neurocognitive delay in CCHS children,[7-10] those reports have included limited sample sizes and focused upon school-aged children, often without *PHOX2B* genetic testing confirmation.

Neurocognitive testing (tests measuring intelligence, language, and motor skills) has been recommended in routine clinical care of all patients with CCHS (American Thoracic Society Statements in 1999[2] and 2010[6]) to identify developmental delays. It has also provided indications for targeted interventions for delays noted with advancing age.[6] Despite advances in diagnosis that allow early intervention, some physiologic factors specific to CCHS are often considered unavoidable,[11] yet they might impact neurocognitive performance. It is not known whether the observed deviations in neurocognitive performance are intrinsic to the CCHS genotype, due to diffuse central nervous system insult (eg, hypoxia) that is not necessarily specific to CCHS, or due to risk factors faced by children with the condition. The current study was undertaken to better understand the timing/onset of neurocognitive impairment and provide further insight into the nature of CCHS in regard to neurodevelopmental functioning. We hypothesized that younger (preschool) children (age, 6-42 months) with CCHS would show evidence of neurocognitive delay and that CCHS-related physiologic factors would impact neurocognitive test performance. We tested these hypotheses by comparing developmental assessment results in a sample of CCHS preschoolers against the normal reference value of 100 ± 15 of the Bayley Scales of Infant Development as defined in standardization, and by studying associations between CCHS-related factors and Bayley indices.

Materials and Methods

Participants

This study is a retrospective review of consecutively referred patients with *PHOX2B* mutation-confirmed CCHS aged 42 months or younger (preschool aged) who underwent developmental testing with a version of the Bayley Scales of Infant Development between 1993 and 2013 during routine clinical care by the Center for Autonomic Medicine in Pediatrics at two major teaching hospitals. All patients seen in the Center for Autonomic Medicine in Pediatrics program, with the exception of non-English-speaking children and one pre-2003 patient who did not complete *PHOX2B* mutation confirmation, were sampled. The comparison group was the (normative) standardization sample of the Bayley Scales of Infant Development.

Procedure

All subjects received at least one developmental evaluation by a licensed clinical psychologist while admitted for CCHS-related clinical care. All children were in good health at the time of testing. In cases in which more than one evaluation was performed on a child in the course of routine follow-up, the most recent evaluation under the age of 42 months was used. In one case in which a child received chemotherapy, prechemotherapy test results were included to eliminate confounding of test scores.

Developmental evaluations were conducted using two iterations of the Bayley Scales of Infant Development: the Bayley II[12] (administered to subjects tested before 2006) and the Bayley III[13] (administered to subjects tested in 2006 or later). Both versions of the Bayley are scaled to have a population mean of 100 and a SD of 15. Although developmental indices do not correspond directly

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