

Neurocognitive Function in Children with Primary Hypertension

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Objective To compare neurocognitive test performance of children with primary hypertension with that of normotensive controls.

Study design Seventy-five children (10-18 years of age) with newly diagnosed, untreated hypertension and 75 frequency-matched normotensive controls had baseline neurocognitive testing as part of a prospective multi-center study of cognition in primary hypertension. Subjects completed tests of general intelligence, attention, memory, executive function, and processing speed. Parents completed rating scales of executive function and the Sleep-Related Breathing Disorder scale of the Pediatric Sleep Questionnaire (PSQ-SRBD).

Results Hypertension and control groups did not differ significantly in age, sex, maternal education, income, race, ethnicity, obesity, anxiety, depression, cholesterol, glucose, insulin, and C-reactive protein. Subjects with hypertension had greater PSQ-SRBD scores ($P = .04$) and triglycerides ($P = .037$). Multivariate analyses showed that hypertension was independently associated with worse performance on the Rey Auditory Verbal Learning Test (List A Trial 1, $P = .034$; List A Total, $P = .009$; Short delay recall, $P = .013$), CogState Groton Maze Learning Test delayed recall ($P = .002$), Grooved Pegboard dominant hand ($P = .045$), and Wechsler Abbreviated Scales of Intelligence Vocabulary ($P = .016$). Results indicated a significant interaction between disordered sleep (PSQ-SRBD score) and hypertension on ratings of executive function ($P = .04$), such that hypertension heightened the association between increased disordered sleep and worse executive function.

Conclusions Youth with primary hypertension demonstrated significantly lower performance on neurocognitive testing compared with normotensive controls, in particular, on measures of memory, attention, and executive functions. (*J Pediatr* 2016;■■:■■-■■).

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The prevalence of primary hypertension in children has increased significantly, a public health phenomenon that parallels the current childhood obesity epidemic. School screening studies show that the prevalence of hypertension is as high as 10% in children who are overweight, a remarkably high number given that nearly 20% of adolescents in the US are obese.^{1,2} Studies focusing on the impact of childhood primary hypertension during youth have found that youth with hypertension often demonstrate similar target organ damage findings as adults, including left ventricular hypertrophy (LVH), increased carotid intima-media thickness, and increased arterial stiffness.³⁻⁶

Although hypertension in young adults also has been associated with lower scores on tests of cognitive performance compared with scores in matched normotensive controls,⁷⁻⁹ there have been only very limited assessments of hypertensive target

ABPM	Ambulatory blood pressure monitoring
ADHD	Attention-deficit/hyperactivity disorder
BMI	Body mass index
BP	Blood pressure
BRI	Behavioral Regulation Index
BRIEF	Behavior Rating Inventory of Executive Function
CDI	Child Depression Inventory
CogState GMLT	CogState Groton Maze Learning Test
CRP	C-reactive protein
DKEFS	Delis-Kaplan Executive Function System
FSIQ	Full-Scale IQ
LVH	Left ventricular hypertrophy
MASC	Multidimensional Anxiety Scale for Children
PSQ-SRBD	Sleep-Related Breathing Disorder scale of the Pediatric Sleep Questionnaire
RAVLT	Rey Auditory Verbal Learning Test
SBP	Systolic blood pressure
WASI	Wechsler Abbreviated Scales of Intelligence

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Funded by the National Heart, Lung, and Blood Institute (R01HL098332 [to M.L.]). The authors declare no conflicts of interest.

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<http://dx.doi.org/10.1016/j.jpeds.2016.08.076>

organ effects on the brain in children. Instead, older descriptions were limited to gross neurologic events, such as facial palsy, seizure, and stroke, in children with malignant hypertension.¹⁰ Other studies provide emerging evidence that children with primary hypertension score lower on measures of neurocognition compared with normotensive controls, a pattern that is similar to young adults with hypertension.¹¹ These preliminary studies in children, however, have been limited mostly to database and single-center studies.¹²⁻¹⁴ Further study of neurocognition in children with hypertension is needed to determine both the short-term impact of childhood hypertension on the child's brain as well as long-term effects into adulthood and to assess the degree to which any effects can be minimized or reversed.

We have established a prospective, multicenter study of neurocognition in children with primary hypertension.¹⁵ Our specific aims are to compare the performance on neurocognitive testing of newly diagnosed subjects with untreated hypertension with that of the performance of matched normotensive controls at baseline and to evaluate the effect of 1-year of antihypertensive therapy on neurocognitive test performance. Here, we report the results of the baseline comparison of the neurocognitive test performance of subjects with hypertension and normotensive controls. Consistent with the emerging pediatric literature and the existing adult studies, we hypothesize that children with primary hypertension will show significantly lower neurocognitive functions when compared with a matched control group of normotensive, healthy peers, particularly in the area of executive functioning.

Methods

Participating recruitment sites included the University of Rochester, Emory University, Maimonides Medical Center, and the University of Texas Medical School at Houston. A total of 75 newly diagnosed children ages 10-18 years with untreated hypertension were enrolled through the Pediatric Hypertension Clinics at each site. All subjects with hypertension were required to have clinic blood pressure (BP) \geq 95th percentile⁶ and sustained hypertension confirmed by 24-hour ambulatory blood pressure monitoring (ABPM). For comparison, 75 normotensive, healthy 10- to 18-year-old children were enrolled from participating general pediatrics and family medicine practices. Control subjects were required to have clinic BP $<$ 95th percentile and normotension confirmed by ABPM. The control group was frequency matched to the group with hypertension for maternal education (less than high school, high school, college, beyond college), sex, and proportion with obesity (body mass index [BMI] \geq 95th percentile). Matching for maternal education and obesity was done because both factors are known to have potential influence on cognitive outcomes,^{16,17} and children with hypertension often are obese. Controls were matched to the subjects with hypertension for sex because subjects with hypertension recruited from patients referred for hypertension evaluation more frequently are male.¹⁸

Exclusion criteria included being on medication for attention-deficit/hyperactivity disorder (ADHD), the presence of a

pre-existing learning problem/disability (defined as having an Individual Educational Plan or Section 504 Plan at school), any disorder of cognitive impairment, history of chelation treatment for elevated lead level, history of chronic disease (known renal, cardiovascular, gastrointestinal tract, hepatic, endocrine, or rheumatologic disease), pregnancy or breastfeeding, previous sleep study diagnosis of obstructive sleep apnea, a diagnosis of secondary hypertension, and previous or current treatment with antihypertensive medication. Subjects with morbid obesity, a group more likely to have unrecognized obstructive sleep apnea, were not excluded. The study was approved by the institutional review board of each site, and parental permission obtained, as well as subject assent, when appropriate.

Neurocognitive Assessment

Measurements from the baseline neurocognitive assessment were analyzed in this report and included both laboratory performance-based measures and behavior rating scales. Laboratory measures of executive function included tests of problem solving/planning, set-shifting, response inhibition, vigilance, and working memory.

Behavior ratings of executive function included the Behavior Rating Inventory of Executive Function (BRIEF) completed by the parent. In addition to measures of executive function, the neurocognitive test battery included assessments of verbal learning and memory, attention, fine-motor dexterity, and general intellectual functioning. **Table I** lists the neurocognitive tests along with the primary variables for each test and the cognitive domain assessed.

In addition, mood symptoms were evaluated with the child self-report measures of the Multidimensional Anxiety Scale for Children (MASC) and the Child Depression Inventory (CDI). Lastly, because daytime sleepiness and sleep disorders are associated with cognitive dysfunction as well as obesity, parents completed the Sleep-Related Breathing Disorder scale of the Pediatric Sleep Questionnaire (PSQ-SRBD) as an estimate of disordered sleep.^{19,20} These rating scales were examined to determine the need for covarying these variables in the data analyses, because sleep and mood can influence neurocognitive function.

Other Measures and Procedures

All subjects underwent ABPM at baseline according to published American Heart Association guidelines via the Spacelabs 90217 oscillometric monitor (Spacelabs Healthcare, Snoqualmie, Washington).²¹ BP measurements were recorded every 20 minutes for the entire 24-hour period, and wake and sleep periods were determined by patient diary. A minimum of 40 total readings were required for the study to be considered valid without a minimum number of readings per hour requirement. BP load was defined as the percentage of readings above the 95th percentile for ambulatory norms in the 24-hour period. Subjects with hypertension were required to have sustained ambulatory hypertension, defined as mean wake or sleep systolic blood pressure (SBP) or diastolic BP \geq 95th percentile for ambulatory norms. A subject with hypertension also could be

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