ORIGINAL ARTICLE

Sleep Disordered Breathing as Measured by SRBD-PSQ and Neurocognition in Children With Hypertension

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BACKGROUND
Cognitive test performance is decreased in hypertensive adults and children, a finding postulated to represent early target-organ damage to the brain. Hypertensive children are often obese, a comorbidity associated with sleep disordered breathing (SDB), itself associated with cognitive problems; potentially confounding the relation between hypertension (HTN) and neurocognition. Our objective was to determine the association between SDB as measured by a scale and questionnaire score and neurocognition among participants enrolled in an ongoing multicenter study of cognition in children with HTN.

METHODS
Subjects completed laboratory-based neurocognitive tests. Parents and subjects completed rating scales of executive function, mood, and behavior problems. Parents completed the Sleep-Related Breathing Disorder scale of the Pediatric Sleep Questionnaire (SRBD-PSQ).

RESULTS
To date, 38 HTN subjects and 34 control subjects have completed neurocognitive testing and the SRBD-PSQ. Median SRBD-PSQ scores were similar between groups but the HTN group had a higher percentage of subjects with SRBD-PSQ scores in the range suggestive of obstructive sleep apnea (26% vs. 6%, $P = 0.03$). Overall, higher SRBD-PSQ scores were not significantly associated with worse performance on laboratory-based measures of executive function and other cognitive domains but were significantly associated with worse scores on rating scales of executive function as well as mood and behavior problems.

CONCLUSIONS
A larger proportion of children with HTN had scores suggestive of SDB. The results underscore the importance of using a multi-method approach in the assessment of cognition and adjusting for potential confounding effects of SDB in studies of cognition in hypertensive children.

Keywords: blood pressure; cognition; executive function; hypertension; sleep apnea.

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Current estimates are that 4% of US children overall, and up to 10% of underrepresented minority children, have hypertension (HTN).[1] Furthermore, 10% of obese children are hypertensive, a remarkably high number given that nearly 20% of US adolescents are obese.[2] This striking prevalence of primary pediatric HTN has important public health implications for the long-term development of HTN-related morbidity in such children, including stroke, myocardial infarction, and kidney failure. It is clear that the origins of HTN-associated morbidity begin during childhood, as manifested by the common presence of left ventricular hypertrophy and increased carotid intima–media thickness in children with primary HTN.[3,4] There is emerging evidence that target organ damage to the brain may begin during childhood as well. Young adults with primary HTN demonstrate decreased performance on neurocognitive testing, a finding which has been proposed to represent an early manifestation of hypertensive target organ damage to the brain.[5–7] Similar to the adult findings, preliminary studies suggest that children with primary HTN score lower on measures of neurocognition compared with normotensive controls.[8–10]

With funding from the National Institutes of Health, we have established an ongoing prospective, multicenter study of neurocognition in children with primary HTN in order to more definitively evaluate the relation between cognition and HTN in children.[11] A potential confounding variable in the investigation of cognition and HTN is the presence of sleep disordered breathing (SDB). Children with primary HTN are often obese, and obesity, in turn, is often associated with

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SDB,[12] an entity itself associated with cognitive and behavioral problems.[13] Therefore, SDB potentially confounds the relation between HTN and cognition. While children with known obstructive sleep apnea (OSA) are excluded from the current study, the diagnosis of OSA is often unrecognized.[14] Thus, the extent to which SDB explains the association between HTN and cognitive deficits is unknown. The objectives of this study are (i) to determine the prevalence of SDB in our carefully selected study population and (ii) to examine the potential impact of SDB on the neurocognitive and behavioral measures being used in the current study of cognition in children with HTN.

METHODS

The design of our ongoing study of cognition in HTN has been described in detail.[11] Briefly, both hypertensive and control subjects complete a baseline (pre-intervention) assessment consisting of laboratory evaluation, behavioral measures, and neurocognitive testing. The hypertensive subjects are then treated according to national consensus guidelines and local standards.[15] After a 12-month period, the same neurocognitive testing is repeated in both the hypertensive and control subjects. The overall goal is to recruit a total of 75 newly diagnosed, untreated hypertensive children aged 10–18 years old. All hypertensive subjects are required to have clinic blood pressure (BP) ≥ 95th percentile and sustained HTN confirmed by 24-hour ambulatory BP monitoring (ABPM).[16] For comparison, 75 normotensive, healthy 10- to 18-year old children are being recruited, and control subjects are required to have clinic BP < 95th percentile and normotension confirmed by ABPM.[16] The control group is frequency matched (not individually matched) to the hypertensive group for maternal education, sex, and proportion with obesity (body mass index (BMI) ≥ 95th percentile). Exclusion criteria include secondary HTN, medication for inattention, cognitive impairment, current antihypertensive medication, chronic disease, history of chelation for lead, and a previous sleep study diagnosis of OSA. The study was approved by each participating sites Institutional Review Board.

Neurocognitive test battery and behavior measures

Selected measures from baseline neurocognitive assessments were assessed in this analysis and included both behavior rating scales and performance-based laboratory measures. Laboratory measures of executive function included tests of attention regulation, problem solving and planning, and set shifting and working memory.[17–20] The battery also included laboratory measures of fine-motor dexterity, intellectual functioning, and verbal learning and memory.[21]

Behavior rating scales included parent and child ratings of executive function, mood, and behavior problems.[22–25] Therefore, the cognitive domain of executive function was assessed by both laboratory measures and rating scales. Laboratory measures of executive function are useful in assessing the capacity of the individual subject, whereas rating scales (questionnaires completed by the subject or parent) evaluate behavioral correlates of executive function in the context of real-life distractions and are therefore proposed to be more valid in the assessment of executive function in daily life.[26] Ratings scales and performance-based (i.e., laboratory) measures are felt to tap somewhat different dimensions of executive function, with both contributing important information to the clinical understanding of the child.[27] For these reasons, a multi-method approach that included both behavior ratings and laboratory-based measures was used for the assessment of the cognitive domain of executive function.

Table 1 lists all neurocognitive and behavioral rating scales by domain.

Measure of disordered sleep

Parents complete the validated 22-item Sleep-Related Breathing Disorder scale of the Pediatric Sleep Questionnaire (SRBD-PSQ).[14,28] The survey queries about snoring, daytime sleepiness, and inattention. It is commonly used to assess for OSA risk in pediatric research studies but is not meant to replace nocturnal polysomnography in the patient care setting or to render a clinical diagnosis of OSA. Higher scores represent worse disordered sleep, and scores > 0.33 are suggestive of high risk for a pediatric sleep-related breathing disorder.

Statistical analyses

Demographic data are expressed as mean ± SD or median and interquartile range, where appropriate. Two-tailed *t* test or the Wilcoxon rank sum test were used to examine demographic differences between the hypertensive and control groups for continuous variables and Fisher exact test was used for categorical variables. Obesity and morbid obesity were defined as BMI ≥ 95th and ≥99th percentile, respectively.

For the first study objective, the prevalence of elevated SDB in the study population overall was determined by calculating the proportion of subjects with a SRBD-PSQ score of ≥0.33. The differences in SDB between the HTN and control groups were examined by comparing group median SRBD-PSQ scores using the Wilcoxon rank sum test and by comparing the proportion of subjects in each group with a SRBD-PSQ score ≥ 0.33 using the Fisher exact test.

For the second study objective, the potential impact of SDB on the neurocognitive and behavioral measures was evaluated for all study subjects combined. Spearman correlation coefficients were used to examine correlations between SRBD-PSQ scores and neurocognitive and behavior measures. In addition, neurocognitive and behavior scores for subjects with SRBD-PSQ scores ≥ 0.33 (elevated SDB) were compared to those of subjects with SRBD-PSQ scores < 0.33 using 2-tailed *t* tests. Cohen's *d* effect sizes for this comparison were calculated to express the magnitude of the difference between the elevated SDB and nonelevated SDB groups. An effect size of 0.2 is considered small; 0.5, medium; and ≥0.8, large. We considered an effect size of medium or larger as clinically meaningful. *P* values < 0.05 were considered significant for all analyses. Statistical analysis was performed using SAS for Windows 9.1 (SAS Institute, Cary, NC).

Table 1. Neurocognitive and behavior measures

Performance-based measures[a]	
Domain	**Test name**
Attention/Response Inhibition	Conners' Continuous Performance Test-II (CPT-II)
Problem Solving/Planning	CogState Groton Maze Learning Task (GMLT)
	Delis-Kaplan Executive Function System (DKEFS), Tower Test
Set Shifting	CogState Set Shifting Task
Working Memory	Wechsler Intelligence Scale for Children-4th ed (WISC-IV), Spatial Span
	WISC-IV Digit Span
Fine Motor Dexterity	Grooved Pegboard Test
General Intellectual Ability	Wechsler Abbreviated Scales of Intelligence (WASI)
Verbal Learning & Memory	Rey Auditory Verbal Learning Test
Behavior rating scales[a,b]	
Sleep Disordered Breathing	Pediatric Sleep Questionnaire: Sleep-Related Breathing Disorder scale (SRBD-PSQ)
Executive Function	Behavior Rating Inventory of Executive Function—Parent Form[b]
	BRIEF—Self-Report (Child) Form[a]
General mood and behavior	Achenbach Child Behavior Checklist (CBCL)[b]
Depression	Child Depression Inventory[a]
Anxiety	Multidimensional Anxiety Scale for Children[a]

[a]Completed by child.
[b]Completed by parent.

RESULTS

Demographic characteristics

To date, 38 hypertensive (HTN) subjects and 34 control subjects have completed both the SRBD-PSQ and the baseline neurocognitive assessment, for a total of 72 subjects available for analysis. The HTN and control groups are similar in age, sex, maternal education level, percent obese, and significantly different in ambulatory BP, as expected by study design. Despite the similar proportion of obese subjects (BMI ≥ 95th percentile) between groups, the HTN group had a higher median BMI percentile and a higher proportion with morbid obesity (BMI ≥ 99th percentile) (Table 2).

Table 2. Demographic characteristics of the HTN and control groups

Characteristic	HTN	Control (N = 38)	*P* value (N = 34)
Age, years	15.0 ± 2.1	15.2 ± 1.9	0.67
Sex, % male	76.3	76.5	0.99
Maternal education ≤ high school, %	47.4	44.1	0.82
Minority,[a] %	47.4	35.3	0.34
BMI percentile[a]	99 (90 – 99)	97 (92 – 98)	0.05
Obesity, %	71	61.8	0.46
Morbid obesity, %	50	11.8	< 0.01
24-hour SBP load	55.1%	7.2%	< 0.01
24-hour DBP load	47.9%	5.3%	< 0.01

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HTN, hypertension; SBP, systolic blood pressure.
[a]Minority = AA race or Hispanic ethnicity.
[b]Median (interquartile range).

Prevalence of SDB in the study population

Twelve of the 72 subjects (17%) had an elevated SRBD-PSQ score of ≥0.33, suggesting high risk for OSA. All 12 subjects with an elevated SRBD-PSQ score had a BMI of at least the 95th percentile, and 9 (75%) had morbid obesity. The HTN group had a similar median SRBD-PSQ score compared with that of control subjects (0.18, interquartile range: 0.09–0.35 vs. 0.15; interquartile range: 0.05–0.27, $P = 0.27$). However, 26% of the HTN group had an elevated SRBD-PSQ score ≥ 0.33 compared with only 6% of the control group ($P = 0.03$, Figure 1).

Association between SDB and the neurocognitive and behavioral measures

Table 3 shows the correlations between SRBD-PSQ scores and scores on the neurocognitive battery and behavioral assessments. Overall, higher disordered sleep score was not significantly associated with worse performance on the laboratory measures of cognition. By contrast, higher SRBD-PSQ score was associated with significantly worse ratings of executive function, on both the parent and self Behavior Rating Inventory of Executive Function (BRIEF). In addition, higher SRBD-PSQ score was associated with worse internalizing and externalizing behavior on the parent-completed Child Behavior Checklist and worse ratings of depression on the subject-completed Child Depression Inventory.

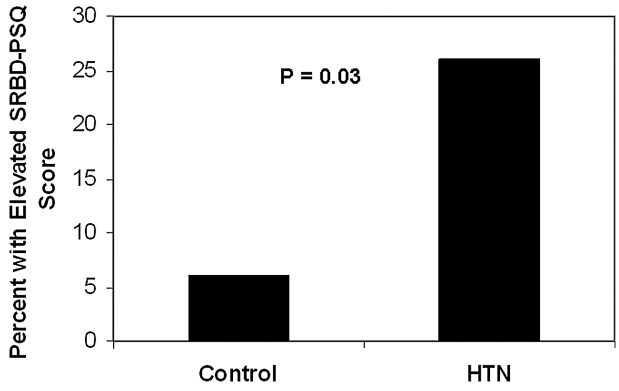

Figure 1. Proportion of subjects in the control and HTN groups with SRBD-PSQ score ≥ 0.33, suggestive of obstructive sleep apnea. Abbreviations: HTN, hypertension; SRBD-PSQ, Sleep-Related Breathing Disorder scale of the Pediatric Sleep Questionnaire.

Table 3. Neurocognitive test correlation with disordered sleep score

	All subjects (N = 72)	
Neurocognitive measure by cognitive domain	***r***	***P* value**
Laboratory measures		
Memory		
RAVLT Long Delayed Recall	−0.11	0.35
CogState GMLT Delayed Recall	0.08	0.48
Attention		
CPT-II Omission errors	−0.02	0.88
Spatial Span Forward	−0.05	0.66
Digit Span Forward	−0.05	0.65
Executive function		
CPT-II Omission errors	0.02	0.84
Spatial Span Forward	−0.08	0.52
Digit Span Forward	−0.13	0.28
DKEFS Tower total achievement	−0.01	0.92
CogState GMLT Total Error	0.19	0.12
CogState Set Shifting	0.09	0.47
Fine motor		
Grooved Pegboard, dominant	0.09	0.43
Questionnaires		
Parent BRIEF GEC	0.49	<0.01
Self BRIEF GEC	0.45	<0.01
MASC total	0.12	0.32
CDI total	0.41	<0.01
CBCL internalizing	0.45	<0.01
CBCL externalizing	0.45	<0.01

Abbreviations: BRIEF, Behavior Rating Inventory of Executive Function; CBCL, Child Behavior Checklist; CDI, Child Depression Inventory; CPT-II, Conners' Continuous Performance Test-II; DKEFS, Delis-Kaplan Executive Function System; GEC, Global Executive Composite; GMLT, Groton Maze Learning Test; MASC, Multidimensional Anxiety Scale for Children; RAVLT, Rey Auditory Verbal Learning Test.

To further evaluate the impact of SDB on the neurocognitive and behavioral measures being used in the current study of cognition in children with HTN, we also compared scores of subjects with elevated SDB to those of subjects without elevated SDB. Table 4 compares neurocognitive test performance and behavior measures for subjects felt to be at highest risk for SDB (SRBD-PSQ score ≥ 0.33) to those of subject with lower SRBD-PSQ score. Subjects with elevated SRBD-PSQ performed similar to those subjects without elevated SRBD-PSQ on the laboratory performance-based measures. By contrast, subjects with elevated SRBD-PSQ score obtained higher ratings (indicative of greater problems) on parent and self-ratings of executive function with large effect sizes of clinically meaningful magnitude of 0.94 and 1.37, respectively. Subjects with elevated SRBD-PSQ score also had higher scores (i.e., greater problems) on the Child Behavior Checklist and Child Depression Inventory.

DISCUSSION

Hypertensive children are often obese, and obese children are at increased risk of OSA and upper airway resistance syndrome. OSA is characterized by upper airway obstruction with the cessation of ventilation despite respiratory effort. Upper airway resistance syndrome is characterized by partial obstruction of the upper airway causing arousals and sleep fragmentation without gas exchange abnormalities.[12] Children with SDB of either type are at increased risk of excessive daytime sleepiness, behavioral problems, inattention, and learning problems.[29] In the current ongoing National Institutes of Health–funded study of the effect of primary HTN on cognition in children, potential subjects with a previous sleep study diagnosis of OSA are excluded. However, this criterion is not expected to be adequate to prevent all subjects with SDB from entering the study, and performing nocturnal polysomnography on all potential subjects was felt to be impractical. Instead, the SRBD-PSQ is included in the battery of study assessments to allow for adjustment of results for the impact of SDB on cognition. In this analysis, we therefore set out to determine the prevalence of SDB in our study cohort to date and to determine the potential impact that SDB may have as a confounder in the investigation of the effect of primary HTN on cognition in this study population.

We found that SDB was common in the primary HTN group, with approximately one-quarter of the HTN subjects enrolled to date having elevated SRBD-PSQ scores in the range suggestive of OSA compared with less than 10% of the control group. There are 2 likely explanations for this difference between the HTN and control groups. First, studies in children suggest that OSA is associated with elevated BP, independent of obesity.[30] Therefore, subjects selected for elevated BP would be expected to have a higher prevalence of SDB compared with subjects selected for normotension. Second, studies have shown that the degree of SDB in children is proportional to the degree of obesity.[31,32] While the HTN and control groups were balanced in the proportion with obesity overall, the HTN group had a higher proportion with morbid obesity. The higher percentage of subjects with elevated SDB scores in the HTN group may be due, in part, to the higher proportion in that group with severe obesity. The lower proportion of subjects with morbid obesity

Table 4. Comparison of neurocognitive test scores of subjects with elevated SRBD score to that of subjects with non-elevated SRBD scores

Neurocognitive measure by cognitive domain	SRBD score elevated (N = 12)	SRBD score not elevated (N = 60)	Effect size	*P* value
Laboratory measures				
Memory				
RAVLT Long Delayed Recall	9.7 ± 2.6	10.2 ± 2.9	0.18	0.55
CogState GMLT Delayed Recall	6.9 ± 2.7	7.1 ± 5.2	0.05	0.91
Attention				
CPT-II Omission errors	48.9 ± 5.4	48.9 ± 7.3	0	0.99
Spatial Span Forward	9.25 ± 1.9	9.35 ± 3	0.04	0.91
Digit Span Forward	8.5 ± 2.3	8.6 ± 2.8	0.04	0.87
Executive function				
CPT-II Commission errors	53.7 ± 8	51.4 ± 9.8	0.26	0.46
Spatial Span Backward	10.2 ± 2.5	10.3 ± 2.3	0.04	0.86
Digit Span Backwards	8.7 ± 2.7	9.8 ± 2.6	0.41	0.19
DKEFS Tower total achievement	9.1 ± 2.2	9.4 ± 2.5	0.13	0.67
CogState GMLT Total Error	57.7 ± 18	54.5 ± 16.8	0.18	0.56
CogState Set Shifting Error	45.8 ± 20.2	36.3 ± 15.1	0.54	0.07
Fine motor				
Grooved Pegboard, dominant	82.6 ± 15.6	79.1 ± 14.1	0.24	0.45
Questionnaires				
Parent BRIEF GEC	56.8 ± 9.5	48.6 ± 8	0.94	0.03
Self BRIEF GEC	58.1 ± 9	45.5 ± 9.4	1.37	<0.01
MASC total	49.8 ± 10	44.9 ± 8	0.54	0.07
CDI total	52 ± 9.5	42.0 ± 6.9	1.22	<0.01
CBCL internalizing	55 ± 11.5	49.0 ± 8.5	0.6	0.04
CBCL externalizing	53.8 ± 10	46.0 ± 8.5	0.84	<0.01

Abbreviations: BRIEF, Behavior Rating Inventory of Executive Function; CBCL, Child Behavior Checklist; CDI, Child Depression Inventory; CPT-II, Conners' Continuous Performance Test-II; DKEFS, Delis-Kaplan Executive Function System; GEC, Global Executive Composite; GMLT, Groton Maze Learning Test; MASC, Multidimensional Anxiety Scale for Children; RAVLT, Rey Auditory Verbal Learning Test.

in the control group compared with the HTN group is likely a result of the exclusion of many severely obese children by the ambulatory BP criteria for normotension. Previous studies have shown that only a small minority of adolescents with severe obesity is normotensive by ABPM,[33] and that has been our experience during the ABPM screening process as well (data not shown).

Based on previous studies in young adults and children, the negative effects of HTN on neurocognitive test performance are expected to be relatively subtle.[6,9] Therefore, it is important to understand the impact of potentially strong confounders that have the potential to overshadow the effects of HTN on cognition, despite the plan to adjust for confounding variables in the statistical models. Sleep-related breathing disorders represent such a potential confounder since they are associated with both HTN and obesity and are known to negatively impact cognitive function. The results of the current analysis show that high SDB scores were not significantly associated with worse performance on the laboratory-based cognitive measures employed in our ongoing study of neurocognition in primary HTN. This finding is reassuring in that it implies that emerging differences in laboratory neurocognitive test performance between hypertensive and normotensive subjects is not confounded by the higher proportion of HTN subjects with SDB.[34] By contrast, high SDB scores were associated with worse cognition as measured by parent and self-ratings of executive function. The finding that the group of subjects who had an elevated score of ≥0.33 on the SRBD-PSQ were predominantly the ones who had worse scores on the rating scales of executive function suggests that OSA likely accounted for much of this effect. In addition, elevated SDB scores were associated with parent and self-ratings of anxiety, depression, and even externalizing behaviors. Interestingly, an association between SDB and mood disturbances in children has been previously described.[13]

The reason for the difference in the impact of SDB on results for performance-based laboratory measures and that for the rating scales cannot be determined from the current analysis; however, some explanations can be reasonably postulated. Performance-based laboratory computer or paper-and-pencil

tests are administered in a structured, quiet, one-on-one testing environment, a setting where the cognitive effects of disordered sleep may not manifest and where cognitive performance is optimized. By contrast, when completing the BRIEF,[22] parents and subjects are asked to rate behaviors that reflect executive functioning in real-world settings over the preceding 6 months. The more chaotic nature of real-world settings compared with the laboratory testing environment may allow the manifestation of the cognitive effects of disordered sleep, especially over the longer time period of the assessment period. Rater bias may also be playing a role in the correlation between SRBD-PSQ scores and the parent and child ratings scales. That is, a rater who perceives poor functioning in the subject in 1 area may be prone to rate the subject as having worse functioning across cognitive and behavioral domains.[35]

The current analysis has several limitations. The diagnosis of SDB is assessed by parent questionnaire and not by the more definitive method of nocturnal polysomnography. There were no tests conducted to distinguish between OSA and central sleep apnea. In addition, the cross-sectional study design does not allow inference of causality between the presence of SDB and cognitive problems. In addition, the increased prevalence of elevated SDB in the HTN group in our cohort cannot be generalized to the whole population of children with primary HTN. Our HTN group had ABPM confirmed HTN and therefore may have more severely elevated BP than children diagnosed by office readings alone. Furthermore, the sample size was too small to allow comparison of cognition of the HTN and control groups, at this point in enrollment. Once full enrollment is achieved we will be able to evaluate the difference between groups in cognition with statistical adjustment for SBD.

These findings suggest that SDB is a significant problem in children with obesity-associated primary HTN, in that a larger proportion of children with HTN had scores suggestive of SDB. Children with primary HTN and SDB may be especially vulnerable to executive dysfunction in everyday settings. These findings underscore the importance of using a multi-method approach in the assessment of cognition and of adjusting for the potential confounding effects of SDB in studies investigating cognition as a possible manifestation of HTN target organ damage to the brain in children.

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DISCLOSURE

The authors declared no conflict of interest.

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