Neurocognitive Function in Children with Primary Hypertension after Initiation of Antihypertensive Therapy

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Objective To determine the change in neurocognitive test performance in children with primary hypertension after initiation of antihypertensive therapy.

Study design Subjects with hypertension and normotensive control subjects had neurocognitive testing at baseline and again after 1 year, during which time the subjects with hypertension received antihypertensive therapy. Subjects completed tests of general intelligence, attention, memory, executive function, and processing speed, and parents completed rating scales of executive function.

Results Fifty-five subjects with hypertension and 66 normotensive control subjects underwent both baseline and 1-year assessments. Overall, the blood pressure (BP) of subjects with hypertension improved (24-hour systolic BP load: mean baseline vs 1 year, 58% vs 38%, $P < .001$). Primary multivariable analyses showed that the hypertension group improved in scores of subtests of the Rey Auditory Verbal Learning Test, Grooved Pegboard, and Delis-Kaplan Executive Function System Tower Test ($P < .05$). However, the control group also improved in the same measures with similar effects sizes. Secondary analyses by effectiveness of antihypertensive therapy showed that subjects with persistent ambulatory hypertension at 1 year (n = 17) did not improve in subtests of Rey Auditory Verbal Learning Test and had limited improvement in Grooved Pegboard.

Conclusions Overall, children with hypertension did not improve in neurocognitive test performance after 1 year of antihypertensive therapy, beyond that also seen in normotensive controls, suggesting improvements with age or practice effects because of repeated neurocognitive testing. However, the degree to which antihypertensive therapy improves BP may affect its impact upon neurocognitive function. *(J Pediatr 2017;■■:■■-■■).*

Young adults with hypertension have lower performance on neurocognitive testing compared with matched normotensive control subjects, a finding postulated to represent an early manifestation of hypertensive target organ damage to the brain.[1,2] Furthermore, hypertension in both adolescence and young adulthood has been associated with decreased neurocognitive test performance in mid-life, raising concern for a link between early hypertension and subsequent cognitive decline later in life.[3-5] Despite these observations, results of studies of the impact of hypertension treatment in adults on subsequent neurocognitive test performance have been mostly inconsistent and inconclusive.[6] As a consequence, a recent scientific statement from the American Heart Association on the impact of hypertension on cognitive function identified as a critical question whether treatment as early in life as possible, such as treatment in adolescence, would offer advantages for subsequent cognitive function.[7]

Studies focusing on the impact of childhood primary hypertension during youth itself have found that children with hypertension often demonstrate similar target organ damage findings as do adults, particularly left ventricular hypertrophy (LVH) and increased carotid intima-media thickness.[8,9] However, there have been only limited assessments of hypertensive target organ effects on the brains of children. We established a prospective, multicenter study of neurocognition in children with primary hypertension.[10] Our specific aims were 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

ACE	Angiotensin converting enzyme	DKEFS	Delis-Kaplan Executive Function System
ABPM	Ambulatory BP monitor	ES	Effect sizes
BMI	Body mass index	HTN-I	Hypertension improved
BP	Blood pressure	HTN-NI	Hypertension not improved
BRI	Behavior Regulation Index	LVH	Left ventricular hypertrophy
BRIEF	Behavior Rating Inventory of Executive Function	RAVLT	Rey Auditory Verbal Learning Test
Con-S	Controls with sustained normotension	SBP	Systolic BP
DBP	Diastolic BP		

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to evaluate the effect of 1 year of antihypertensive therapy on neurocognitive test performance. We recently reported results of the baseline comparison, showing that children with hypertension had worse performance on neurocognitive testing compared with that of the normotensive control subjects, particularly in the domains of attention, learning, and memory.[11] Here, we report the results of the effect of 1 year of antihypertensive therapy on neurocognitive test performance in the same cohort. We hypothesized that children with primary hypertension would show improvement in neurocognitive test performance after antihypertensive therapy; whereas the neurocognitive test performance of the normotensive control subjects would remain unchanged over the same time period.

Methods

The participants in this study were the subjects with hypertension and control subjects from our initial report who subsequently returned for reassessment after 12 months. During the 1-year interval between study visits, the subjects with hypertension received standard of care antihypertensive therapy as detailed below. Control subjects were not seen between the initial assessment and the 1-year visit. Hypertension and control subjects completed the same neurocognitive assessment at baseline and again at 1 year. The study methods have been previously described in detail.[10]

Participating recruitment sites included the University of Rochester, Emory University, Maimonides Medical Center, and the McGovern Medical School at UTHealth. Newly diagnosed children ages 10-18 years with untreated hypertension were enrolled through the Pediatric Hypertension Clinics at each site. For comparison, normotensive, healthy 10- to 18-year-old children were enrolled from participating general pediatrics and family medicine primary care practices. Our initial report compared 75 subjects with hypertension and 75 control subjects who were frequency matched for sex, proportion with obesity (body mass index [BMI] ≥95th percentile), and maternal education. Race and ethnicity were not formally matched, but the results were adjusted for these characteristics in the multivariate analyses. At baseline, each subject with hypertension had a history of office hypertension that was confirmed with 24-hour ambulatory blood pressure (BP) monitoring (ABPM) by the presence of mean awake systolic BP (SBP) and/or awake diastolic BP (DBP), mean sleep BP, or both ≥95th percentile.[12] Subjects with hypertension were also included if the mean ambulatory BP was <95th percentile, but the subject had both BP load >25% (ambulatory prehypertension) and LVH on echocardiogram. Only 3 subjects with hypertension were included by these alternate criteria; therefore, their results were combined with the other subjects with hypertension in the current analysis. Normotensive control subjects were required to have office normotension, confirmed by mean awake and sleep SBP and DBP <95th percentile and 24-hour SBP and DBP load <25% on ABPM.[12] Both subjects with hypertension and control subjects underwent repeat ABPM at the 1-year visit to assess the adequacy of the hypertension treatment in the subjects with hypertension and to confirm the persistence of normotension in the control subjects. All subjects with hypertension underwent a complete 2-dimensional echocardiogram at the baseline visit that was read centrally at the University of Rochester. LVH was defined as a left ventricular mass index ≥95th percentile.[13] Echocardiogram and ABPM procedures have been described in our earlier report.[11] All subjects had baseline central laboratory evaluations, including fasting lipid profile, insulin level, glucose, and C-reactive protein. Homeostatic model assessment for insulin resistance was calculated as glucose × insulin/405.

Exclusion criteria were as follows: being on medication for attention deficit/hyperactivity disorder, having 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. The study was approved by the institutional review board at each site, and parental permission was obtained (as well as subject assent when age-appropriate).

Hypertension and control subjects underwent the same neurocognitive assessment at baseline and at the 1-year follow-up visit, a study design that allowed the assessment of change in test performance in the hypertensive subjects after 1 year of antihypertensive therapy. The neurocognitive assessment in the control subjects was repeated at 1 year to detect any improvement in test performance because of increasing age or because of the practice effect, the propensity for scores to improve by virtue of learned strategies, or recall of task content from repeated test administration.[14] As previously described, the neurocognitive assessment included both laboratory performance-based measures and behavior rating scales.[10] The laboratory tests included measures of executive function (measures of problem solving/planning, set-shifting, response inhibition, vigilance, and working memory), verbal learning and memory, attention, fine-motor dexterity, and general intellectual functioning. Behavior ratings of executive function included the Behavior Rating Inventory of Executive Function (BRIEF) completed by the parent. **Table I** lists the neurocognitive measures, along with the primary subtests for each test and the cognitive domain assessed. Mood symptoms were also evaluated with the child self-report measures of the Multidimensional Anxiety Scale for Children, and the Child Depression Inventory. Lastly, parents completed the Sleep-Related Breathing Disorder Scale of the Pediatric Sleep Questionnaire as an estimate of disordered sleep, a common comorbidity in obese children and a potential confounder of neurocognitive test performance.[15,16]

This study was not a clinical trial, but instead an observational study of neurocognitive changes that occur during usual standard of care. We did not randomize subjects to different treatments. Instead the subjects with hypertension were treated according to local standards and national consensus guide-

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