Neurocognitive Alterations in Hypertensive Children and Adolescents

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Hypertensive adults demonstrate performance deficits on neuropsychological testing compared with scores of normotensive controls. This article reviews emerging preliminary evidence that children with hypertension also manifest neurocognitive differences when compared with normotensive controls. Database and single-center studies suggest that children with hypertension manifest deficits on measures of neurocognition and have an increased prevalence of learning difficulties and that children with hypertension associated with obesity may be at increased risk for depression and anxiety. Studies suggesting blunted cerebrovascular reactivity in children with hypertension are also reviewed. *J Clin Hypertens (Greenwich).* 2012; 14:353–359.

Longitudinal studies suggest that hypertension from mid-life onward predicts the development of cognitive decline and dementia in the elderly.[1] However, subclinical changes in the brain may long precede the development of overt cognitive decline. For example, adult hypertension is associated with decreased performance on neurocognitive testing compared with that of matched normotensive controls. Compared with normotensive groups, adults with hypertension consistently demonstrate underperformance in cognitive domains of attention and working memory, executive function, and learning and recall of new information. There are less robust findings, although there is still some evidence for worse performance by hypertensive compared with normotensive groups in domains of visual perception, visuoconstructional abilities, psychomotor speed, and fine motor dexterity.[2–4] Where associations are found, there is evidence for a dose-response relationship between the extent of lower performance on tests of cognition and the gradient from high-normal ranges of blood pressure (BP) elevations and white-coat hypertension to sustained primary hypertension.[5,6]

While the performance deficits noted in hypertensives have been observed in individuals of all adult age groups, reports have shown a more pronounced difference in neuropsychological test performance between hypertensive and normotensive patients when young adults are studied compared with studies of middle-aged or older hypertensive adults.[7,8] In a study specifically designed to assess this observed interactive effect of age, Waldstein and colleagues[7] found that hypertensive young adults (23–40 years) scored significantly worse than young normotensive adults on tests of executive function and working memory. By contrast, middle-aged hypertensive (41–56 years) and normotensive participants were not distinguished by any measure.

Detailed review of the neurocognitive test performance deficits found in hypertensive adults are found in the more comprehensive reviews by Waldstein[2–4] and colleagues. Review of this area shows that performance deficits in tests of executive function and working memory (a component of executive function) feature prominently. Definitions of executive functions vary, but overall they are considered higher cognitive activities required to organize, implement, and evaluate purposeful, goal-directed behavior.[9,10] Theoretical components of executive function include problem-solving, set-shifting, planning, response inhibition, vigilance, and working memory.[9,10] Hypertensive adults, compared with normotensives, have performed worse on the Trail Making Test, a timed task of mental flexibility; the Halstead Category Test, a task of problem solving and concept formation; Maze Learning; and the Stroop color-word interference test, a test of the patient's ability to inhibit prepotent responses (eg, impulse control).[11–13]

Furthermore, there is evidence of a genetic predisposition to performance deficits on neurocognitive testing among hypertensive adults or those at risk for hypertension. Among young and middle-aged (range, 29–59 years) hypertensive adults, those with a positive family history of hypertension performed significantly worse on tasks of attention, mental flexibility, and speeded short-term memory than those without a family history of hypertension.[14] Task performance speed was also slower in another study of normotensive young adult offspring of hypertensive parents, compared with those without a family history of hypertension.[15,16]

STUDIES OF NEUROCOGNITIVE TEST PERFORMANCE IN CHILDREN WITH ELEVATED BP

Primary Hypertension

There is emerging, preliminary evidence that hypertensive children also manifest neurocognitive and

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behavioral differences when compared with normotensive controls. Lande and colleagues first evaluated neurocognitive test performance of children with elevated BP in a cross-sectional analysis of 6- to 16-year-old participants in the Third Report of the National Health and Nutrition Examination Survey (NHANES III), a nationally representative sample of noninstitutionalized US children and adults.[17] As part of NHANES III, children were administered a limited battery of 4 neurocognitive tests, consisting of Block Design and Digit Span subtests of the Wechsler Intelligence Scale for Children, Revised (WISC-R) and the reading and arithmetic sections of the Wide Range Achievement Test, Revised (WRAT-R). Block Design is a measure of constructional skills and Digit Span is a measure of working memory and attention.[9] On bivariate analysis, children with elevated systolic BP (SBP; defined as ≥90th percentile) had lower average scores compared with normotensive children for Digital Span (7.9 vs 8.7, *P*=.03), Block Design (8.6 vs 9.5, *P*=.01), and mathematics (89.6 vs 93.8, *P*=.03). Elevated diastolic BP (DBP) was associated with lower average scores on Block Design only (9.5 vs 11, *P*=.01). Multivariate linear regression showed that elevated SBP remained independently associated with lower Digit Span scores (*P*=.03) after controlling for socioeconomic status, obesity, and other demographic factors. Furthermore, the decrease in Digit Span scores was more pronounced for children with SBP ≥95th percentile, suggesting a dose effect of BP on test scores.[17]

Lande and colleagues subsequently reported a prospective, single-center study comparing 32 children with newly diagnosed, untreated hypertension with 31 normotensive controls.[18] Hypertension was confirmed by 24-hour ambulatory BP monitoring (ABPM). Hypertensive and control patients were matched proportionally for characteristics potentially associated with performance on tests of cognition, including parental education, household income, obesity, race, and IQ. Parents completed the Behavior Rating Inventory of Executive Function (BRIEF), a rating scale that evaluates behavioral correlates of executive function in the context of the child's everyday life.[19] Executive functions may not be as amenable to laboratory-based performance measures as other cognitive domains since these tests are administered in a structured, quiet, one-on-one testing environment—a testing situation that does not always allow executive deficits to manifest. Thus, traditional neuropsychological testing may be augmented by specialized questionnaires such as the BRIEF test for the assessment of executive function by raters who have observed the child in everyday settings. The 86 BRIEF items are organized into theoretically developed and statistically validated factors reflecting constructs such as working memory and planning/organization; these, in turn, are organized into two higher-order factors: the Behavior Regulation Index (BRI) and the Metacognition Index (MI) and an overall score that summarizes all item responses, the Global Executive Composite (GEC).[19] Results are reported as sex- and age-normed T scores (mean=50; standard deviation=10) and higher scores indicate greater degrees of dysfunction. The study found that BRIEF scores were higher (worse executive function) for hypertensives compared with control patients (BRI: 51 vs 42.5, *P*=.014; MI: 51 vs 44, *P*=.031; GEC: 50 vs 43, *P*=.009). It is important to note that the differences between hypertensives and controls on the BRIEF test occurred within the normal limits of the rating scale. This finding is similar to that in adults, where significant differences on measures of executive function between hypertensives and normotensives are consistently seen, but few of those with hypertension are classified as cognitively impaired.

In the same study,[18] parents also completed the Achenbach Child Behavior Checklist (CBCL), another parent rating scale that measures internalizing and externalizing behavior problems.[20] Internalizing behaviors reflect mood disturbance, including anxiety and depression. Externalizing behaviors reflect conflict with others, including aggression. The CBCL reports internalizing and externalizing scales, each a composite of subscales containing items related to anxiety and depression and oppositional and aggressive behavior, respectively. As with the BRIEF examination, these are reported as sex- and age-normed T scores, with higher scores indicating greater behavioral problems. Hypertensive children were not different from normotensive controls with regard to externalizing behaviors, but hypertensives had more internalizing problems (internalizing scale, 53 vs 44.5, *P*<.02) with 37% falling within the clinically significant range vs 6% of control patients (*P*<.005). Internalizing score increased with increasing body mass index in hypertensive patients but not in normotensive controls. These findings indicated that clinically significant anxiety and depression may be common in children with obesity-associated hypertension. Unlike the BRIEF test, where executive function in hypertensive children was less well developed but not clinically impaired, the CBCL-based assessment of internalizing problems suggested that hypertensive children experienced a clinical impact of their mood symptoms.

In another recent report, Adams and colleagues[21] showed that children with hypertension are more likely to be diagnosed with a learning disability, suggesting that hypertensive children are at increased risk for academic difficulties. A total of 201 consecutive children aged 10 to 18 years referred for elevated BP were categorized as having either sustained hypertension (n=100) or prehypertension (n=101). The children with sustained hypertension were more likely than those with prehypertension to be receiving special education services at school for a learning disability (18% vs 9%, *P*<.001) and, in adjusted analysis, the odds of the diagnosis of learning disability was 4 times higher in hypertensive children. Furthermore, a higher proportion of children with sustained hypertension had attention deficit disorder (ADHD), defined as taking medication for inattention (27% vs 7%, *P*=.007). Stimulants prescribed for ADHD can increase BP,[22] a side effect that may have influenced the increased rate of ADHD in the group with sustained hypertension. However, ADHD and learning disability are highly comorbid.[23] While it is possible that some of the children with ADHD exhibited hypertension because they were receiving stimulants for treatment of ADHD, it also is possible that the increased prevalence of ADHD in the hypertensive group was in part a reflection of neurocognitive difficulties among children with hypertension.

Ditto and colleagues[24] further extended these studies by evaluating the neurocognitive test performance of children considered at risk for the development of hypertension but not currently hypertensive. The investigators administered a neurocognitive test battery to 88 normotensive 14-year-old boys participating in a longitudinal study of the development of aggression in males. Patients with both a parental history of hypertension and SBP in the high normal range had lower performance on a verbal learning factor score (including digit span tasks). In addition, patients with SBP in the high normal range had significantly lower performance on a spatial learning and memory factor score compared with patients with lower SBP. These findings suggest that, similar to findings in adults,[8,14,16] neurocognitive test performance deficits in children may be detectable even within the normal spectrum of BP and that there may be a genetic predisposition to such deficits.

These cross-sectional baseline studies do not allow inference about causality. Hypertension could lead to neurocognitive deficits, as an early manifestation of hypertensive target-organ damage to the brain. Alternatively, children with neurocognitive abnormalities could be more likely to develop hypertension, a disease which is known to be, in part, centrally mediated.[25]

Chronic Kidney Disease

Children with chronic kidney disease (CKD) are at risk for cognitive dysfunction and more than half have hypertension.[26] Lande and colleagues[27] recently investigated the potential contribution of elevated BP to decreased neurocognitive test performance in children with mild to moderate CKD. Patients in the Chronic Kidney Disease in Children (CKiD) project had both auscultatory BP and an extensive neurocognitive test battery. Of 383 patients, 132 (34%) had elevated BP, defined as SBP and/or DBP >90th percentile, regardless of whether the patient was taking antihypertensive medication. On bivariate analysis, patients with elevated BP had lower scores (worse performance) on the Performance IQ scale of the Wechsler Abbreviated Scales of Intelligence compared with patients with normal BP (92.4 vs 96.1, *P*=.03). In contrast, there was no difference between groups on measures of attention, verbal IQ, academic achievement, or parental ratings of executive function. On multivariate regression analysis, elevated BP remained independently associated with lower Performance IQ score, after adjusting for demographic and kidney disease–related variables. The authors concluded that children with mild to moderate CKD may have difficulties with visual-spatial organization and visuoconstructive abilities that are related, in part, to elevated BP.

STUDIES OF ANTIHYPERTENSIVE THERAPY

If the performance deficits seen in patients with hypertension represent an early manifestation of target organ damage to the brain, then one might anticipate that such deficits would reverse, at least in part, with antihypertensive medication. However, results of adult studies on the effect of antihypertensive medication on cognition have been inconsistent in the existence and direction of drug effects.[28,29] Studies have been difficult to interpret due to methodological weaknesses, and most have focused on middle-aged and older adults, a group more prone to the potential confounding effects of advancing age. A previous study that focused specifically on young adults showed that hypertensive patients in whom treatment effectively lowered BP improved neurocognitive test performance toward the levels of normotensive control patients.[30] In a more recent study specifically designed to address previous methodological shortcomings in this area of investigation, Muldoon and colleagues[31] found that a short-term 6-week course of various antihypertensive agents (atenolol, metoprolol, methyldopa, thiazide, enalapril, or verapamil) slightly improved performance on tests of memory but also resulted in small decrements in psychomotor speed, without drug class differences.

Data on the effects of antihypertensive therapy on neurocognitive test performance in children are very limited. Lande and colleagues[32] reported on change in parent ratings of executive function in hypertensive children after 12 months of antihypertensive therapy (therapeutic lifestyle modification, angiotensin-converting enzyme [ACE] inhibition). The patients in this report were the participants from the prior study of baseline parental assessments described above,[18] whom subsequently returned for reassessment after 12 months. The sample size was small (hypertensives, n=22; controls, n=25) due to a relatively high dropout rate from baseline to 12 months. BP of the hypertensive patients improved significantly with antihypertensive therapy (SBP load baseline vs 12 months, 60% vs 25%, *P*<.001). Scores on the parent BRIEF assessment improved (baseline vs 12 months, BRI, 50.3 vs 46.2, *P*=.01; MI, 52.4 vs 46.3, *P*<0.01; GEC, 52.1 vs 46.1, *P*<.01). By contrast, BRIEF scores of the control patients did not change significantly in the 12-month period. Furthermore, hypertensive patients with baseline left ventricular hypertrophy or SBP load ≥50% were more likely to show improvement in executive function after antihypertensive therapy, suggesting that

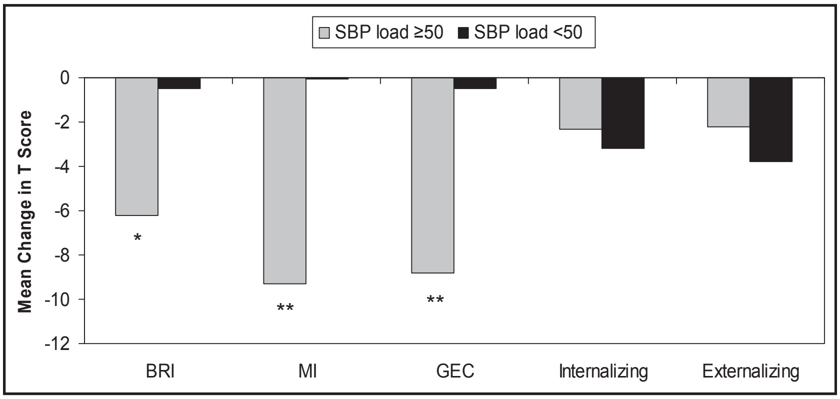

FIGURE. Mean change in Behavior Rating Inventory of Executive Function (BRIEF) and Achenbach Child Behavior Checklist (CBCL) summary scores from baseline to 12 months in hypertensive patients by initial 24-hour systolic blood pressure (SBP) load. A decrease in T scores (negative change) represents improvement. *$P<.05$, **$P<.005$; within-patient change, 12 months to baseline, adjusted for age, race, body mass index percentile, sex, and maternal education. BRIEF scores improved after 12 months of antihypertensive therapy in hypertensive patients with an initial SBP >50% but not in those with an SBP <50%. There was no difference in CBCL score change by SBP load. BRI indicates Behavior Regulation Index; MI, Metacognition Index; GEC, Global Executive Composite. Reprinted with permission.[32]

it was the patients most at risk for hypertensive target organ damage[33] who had improvement in cognition with BP-lowering (Figure). Neither hypertensive nor control patients had significant change in CBCL scores from baseline to 12 months, suggesting that the observed improvement in parent ratings of executive function on the BRIEF test in the patients with hypertension was not simply a false-positive finding caused by parents' nonspecific bias or expectation that their children improved with antihypertensive therapy. The results of this small, single-center study provide preliminary evidence that the neurocognitive deficits seen in children with primary hypertension may be, in part, reversible with antihypertensive therapy.

CHALLENGES

The study of cognition in childhood hypertension presents unique challenges that are less problematic or not relevant in the study of other areas of hypertensive target organ damage. Obesity, a common comorbidity with hypertension, is associated with disordered sleep and obstructive sleep apnea, entities themselves associated with decreased performance on neurocognitive testing and academic difficulties.[34] Therefore, careful adjustment for the potential effects of obesity in studies of hypertension and cognition is important. Furthermore, the performance deficits reported in hypertensives tend to be relatively small and often occur within the normal range of the neurocognitive tests. Such findings may be overshadowed by patient characteristics that are known to more strongly influence performance on tests of cognition, such as parental education and socioeconomic status.[9] Therefore, studies of cognition in childhood hypertension need to control carefully for these confounding variables. In addition, factors associated with hypertension such as anxiety, depression,[35] and increased cardiovascular reactivity[36] may affect performance on tests of cognition.

Studies of the effect of antihypertensive medications on cognition often include a baseline neurocognitive assessment followed by a repeat assessment after a period of antihypertensive medication. However, practice effects are a common concern in longitudinal studies with repeated administration of the same or similar neuropsychological tests.[9] Prior exposure to tasks is associated with better subsequent performance on the same or similar tasks, by virtue of learned strategies and/or recall of task content (eg, a word list for a verbal learning test). Practice effects can be particularly prominent in tests of executive function, which commonly rely on the novelty of the task, a problem for studies of cognition in hypertension where tests of executive function are important. Attempts to mitigate practice effects include multiple versions of the same task with comparable reliability and validity (eg, alternate word lists for verbal learning tests), established standard waiting periods between test administrations to reduce recall and familiarity, estimating and adjusting for contemporary practice effects with a concurrent normotensive comparison group, and/or pre-established test-retest reliability values. Furthermore, studies investigating whether treatment for hypertension improves cognition may be influenced by direct central effects of an antihypertensive on the brain. For example, the brain has its own renin-angiotensin system[37] and studies in the elderly suggest that lipophilic ACE inhibitors are more likely to ameliorate cognitive decline than hydrophilic ACE inhibitors, an effect postulated to be due to better penetration of the blood-brain-barrier of the lipophilic drugs.[38]

Finally, patient motivation and engagement with neuropsychological testing is essential. Critical neurocognitive test data can be invalidated when patients are disinterested in the testing or are not well-rested on the day of examination, a particular challenge in studies involving adolescent participants.

POTENTIAL MECHANISMS: STUDIES OF CEREBROVASCULAR REACTIVITY

Since hypertension can affect small vessels, resulting in vascular remodeling and impairment of cerebral blood flow regulation, investigators have postulated the so-called vascular hypothesis of cognitive dysfunction in hypertension.[39] Cognitive processing elicits a regional distribution of blood flow, providing metabolic support to active neural areas. Interference with this redistribution of blood flow or decreased ability to enhance cerebral blood flow in response to increased neuronal activity might underlie the cognitive deficits of hypertensive individuals.[39] However, the possibility that the brain is affected before the blood vessels has also been suggested as an alternative hypothesis.[40]

Cerebrovascular reactivity (CVR) reflects the capacity of cerebral blood vessels to dilate and may be an important marker for brain vascular reserve. Several analyses using different reactivity stimuli (ie, carbon dioxide, hyperventilation) and different measures of cerebral blood flow (ie, transcranial Doppler [TCD], functional magnetic resonance imaging) have attempted to characterize the physiological association between hypertension and CVR, mostly in adults.[41,42]

The effects of hypertension on CVR in children have been studied by TCD, a noninvasive procedure, to assess changes in cerebral blood flow in response to different stimuli. Settakis and colleagues studied 113 hypertensive (mean age, 16.4 years) and 58 normotensive (mean age, 15.8 years) adolescents at rest and after 30 seconds of breath-holding, as a vasodilatory stimulus,[43] and at rest and after 60 seconds of voluntary hyperventilation, as a vasocontrictory stimulus.[44] Hypertension was defined by the average of many casual BP measurements on different occasions. The middle cerebral artery was insonated through the temporal window on both sides. Hypertensive patients showed decreased vasodilatory and vasoconstrictory ability of the cerebral arterioles, consistent with decreased CVR among hypertensives compared with healthy controls.

Pall and colleagues divided patients according to ambulatory BP findings. Seventy-three patients with hypertension (mean age 16.5 years) and 47 with white-coat hypertension (mean age 16.3 years) were compared with 59 normotensive controls (mean age, 15.8 years). CVR was assessed by TCD breath-holding test and expressed in percent change to the resting cerebral blood flow velocity value.[45] These investigators found that reactivity to carbon dioxide (CO_2) was diminished in both white-coat hypertension and hypertension patients, compared with controls, also suggesting involvement of the cerebral arterioles.

Wong and colleagues studied 56 children and adolescents (mean age, 15.3 years) with hypertension, prehypertension, or white-coat hypertension (diagnosed by ambulatory pressure monitoring), compared with controls, by TCD examinations of the middle cerebral artery while rebreathing CO_2. Time-averaged maximum mean cerebral blood flow velocity and end-tidal CO_2 were used to quantify CRV reactivity during hypercapnia. The authors found that young patients with untreated hypertension had significantly lower hypercapneic reactivity than normotensive controls.[46]

In summary, preliminary studies showed a blunted reactivity response to hypercapnia, indicating a deranged vasodilatory reactivity in untreated hypertensive children and adolescents. These studies have many limitations, especially the small number of patients. Whether these effects of hypertension on the cerebral vessels are cause and effect is unknown as it may just be an epiphenomenon. Further studies are needed to elucidate the findings.

Hypertension, Cognition, and CVR

In children, there are no published studies addressing the effects of elevated BP on both CVR and cognition. Alterations in cerebral blood flow and possible neurocognitive deficits have been described in other diseases such as in sickle cell disease[47] and with mild-disordered breathing.[48] Investigators have suggested that the neurocognitive deficits described in children and adolescents with hypertension may be secondary to abnormal CRV.[46] Ongoing research will help clarify the relationship among elevated BP, abnormal CRV, and neurocognitive deficits in children and adolescents.

IMPLICATIONS

Executive function skills are normally still developing through the adolescent and young adult years.[49] In addition, structural and functional magnetic resonance imaging studies demonstrate continued maturation of the frontal area of the brain, a region felt to be important in executive functioning, through adolescence and into young adulthood.[50] These observations imply that adolescents and young adults may be vulnerable to potential effects of hypertension on executive function.

The practical implications of the potential neurocognitive deficits associated with hypertension in childhood is not clear, although one might speculate that the presence of such deficits would be problematic in the cognitively challenging environment of school, especially as executive demands increase over successive school years. It is even less clear whether there would be any implications for longer-term cognitive reserve and ultimate cognitive decline in later life.

CONCLUSIONS

Together, the above studies provide preliminary evidence that children with hypertension may (1) manifest deficits on measures of neurocognition, (2) have an increased prevalence of learning difficulties, and (3) have altered cerebrovascular reactivity. Children with hypertension associated with obesity may be at increased risk for depression and anxiety compared with their normotensive and/or nonoverweight peers. The results on neurocognitive testing are consistent with findings in young hypertensive adults, where performance deficits on measures of executive function and working memory feature prominently. Larger longitudinal studies using more extensive neurocognitive measures of executive function, before and after antihypertensive therapy, and using further neuroimaging techniques are needed to confirm the presence of a hypertension-cognitive link in children.

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