Clinical Significance of Cognitive Performance by Hypertensive Patients

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SUMMARY Fifty-four subjects with uncomplicated essential hypertension and 54 normotensive subjects were compared with regard to a widely employed clinical index of cognitive dysfunction (the Average Impairment Rating) calculated from neuropsychological tests that discriminate between brain-damaged and neurologically normal persons. Hypertensive subjects exhibited lower mean scores on this index when education was ignored, but results were not the same for highly educated and less well educated groups. There were no differences between exceptionally well educated hypertensive and normotensive subjects, but in the less well educated group, hypertensive subjects performed more poorly than normotensive subjects. The percentages of hypertensive and normotensive subjects scoring in a cognitively impaired range on the Average Impairment Rating were low and did not differ for either education group. These data 1) indicate the important role of subtle differences in education level with respect to positive or negative findings for studies comparing hypertensive and normotensive subjects and 2) illustrate the important role of clinical neuropsychological indices of cognitive dysfunction when one wishes to make meaningful inferences regarding cerebral cortical function in hypertensive subjects. (Hypertension 9: 192-197, 1987)

KEY WORDS • hypertension • neuropsychology • education • cognitive function • Average Impairment Rating

REVIeWS of the literature indicate lower levels of cognitive, perceptual, and psychomotor performance for hypertensive than for normotensive groups.1-3 This has been true for subjects defined as mildly hypertensive4 or as uncomplicated, essential hypertensive5-7 and has been observed for tests that can be particularly sensitive to brain impairment when proper controls and testing procedures are employed (i.e., clinical neuropsychological tests).4,8,9 Psychological hypotheses advanced to explain poorer performance include altered cerebral metabolic processes, cerebral blood flow, and autoregulation or other physiological changes leading to, or resulting from, hypertension.10-16 There is no direct and conclusive evidence that any of these mechanisms represents a causal link between hypertension and test performance, and there are motivational, social, and emotional differences11-13 between hypertensive and normotensive persons that also might account for the differences observed.

Many investigators have interpreted neuropsychological test results as indicating cognitive impairment in hypertensive subjects and, by inference, cerebral cortical dysfunction.2,4,10,11-16 For example, Franceschi et al.8 raised the possibility that "[cerebral] cortical dysfunctions in the structures of the limbic system . . . and to the right hand temporoparietooccipital carrefour" were responsible for the lower level of cognitive performance for a mildly hypertensive group of patients. However, the data reported were limited to comparisons among means for hypertensive and normotensive groups. These data alone do not permit a characterization of any one hypertensive person, or hypertensive group as exhibiting clinically significant cognitive impairment. Data relevant to this term, when used in the clinical diagnostic sense, are the percent-
ages of hypertensive subjects as compared with normotensive subjects scoring in the impaired range on an index of impairment that has been validated by research involving patients with neurosurgically and neurologically defined central nervous system lesions or dysfunction. Data for this type of clinically relevant index have not been reported for uncomplicated essential hypertension. Thus, one major question raised in the present study was whether a higher proportion of persons with uncomplicated essential hypertension, as opposed to normotensive persons, achieve scores in the impaired range on a widely employed index of central nervous system impairment, the Average Impairment Rating (AIR).

Schultz et al. and Shapiro et al. have observed that moderately hypertensive patients do not exhibit mean performance levels that suggest interference with everyday work or leisure activities. Thus, we hypothesized that subjects with uncomplicated essential hypertension would exhibit lower mean levels of performance than normotensive subjects for the AIR but would not exhibit absolute levels of performance indicating cerebral cortical dysfunction.

A second question raised was whether results obtained would be the same for a highly educated group of hypertensive and normotensive subjects as compared with a less well educated group. Costa and Shock reported that a highly educated group of hypertensive and normotensive subjects (75% with college educations or above) differed on only a few of the numerous verbal and performance subtests on the Army Alpha Test. Given that investigators employing less well educated, but not poorly educated, subjects have consistently reported differences for a wide range of cognitive measures, we hypothesized an education level × blood pressure (BP) diagnostic group interaction with disproportionately greater performance differences between hypertensive and normotensive subjects in the less well educated groups.

Subjects and Methods

The uncomplicated essential hypertensive and normotensive groups consisted of 54 subjects each (23 women and 31 men). All of the hypertensive subjects and 16 of the normotensive subjects were participating in a diagnostic clinic at SUNY Health Science Center in Syracuse, New York, as part of the hypertension pathogenesis studies of Streten et al. The remaining 38 normotensive subjects provided a detailed medical and drug history. All normotensive subjects were asymptomatic and met the same criteria for admission to the study as the hypertensive subjects, with the exception of BP values. Statistical comparisons of the two subgroups of normotensive subjects indicated no significant differences for BP values, age, education, or any of the dependent variables (all p > 0.10).

Thus, they were combined into a single normotensive group. Subjects were included in the hypertensive groups if 1) the referring physician’s initial diagnosis was confirmed at the clinic and 2) their mean arterial BP (diastolic BP + 1/3 pulse pressure) was 105 mm Hg or higher. This level corresponded to “cut-off values” of approximately 140 mm Hg systolic and 90 mm Hg diastolic pressures. The BP values were determined by automated and manual pressure cuff recordings. Normotensive subjects had no history of diagnosis or treatment of hypertension and exhibited sustained mean arterial BP values less than 100 mm Hg. Hypertensive subjects receiving medications were asked to cease taking them 21 days before reporting to the diagnostic clinic; thus, unmedicated BP values were obtained.

Subjects were excluded from the study if they exhibited angina pectoris, history of cardiovascular or cerebrovascular disease, transient ischemic attack, congestive heart failure, kidney dysfunction or transplant, retinopathy (type II or III eye ground changes), myocardial infarction, diabetes, neurological or psychological disorder, renal arterial stenosis, primary aldosteronism, hypercortisolism, pheochromocytoma, or improper use of medication, alcohol, or other drugs.

Data on age, education, occupation, and unmedicated BP values are shown in Table 1. Medications are described later. Hypertensive and normotensive subjects were matched for age and education and blocked into two groups: higher education (Hi-Ed), college graduate and above (16–22 years), and lower education (Lo-Ed), high school and some college (12–15 years). Mean occupation level differed significantly (p < 0.001), for the Hi-Ed and Lo-Ed groups as there were more professionals and executives in the former.
and more housepersons, clerics, and skilled laborers in the latter. There was an equal number of students (n = 3) in each group.

Test Materials and Measures

The AIR\textsuperscript{20} was used as an overall measure of performance for tests selected from the Halstead-Reitan neuropsychological battery.\textsuperscript{21,22} The predictive validities of the individual tests and the AIR are based on many studies involving neurologically normal persons and individuals with brain damage as established by neurosurgical and neurological evaluation.\textsuperscript{22-24}

The seven test scores employed in the construction of the AIR were among the best discriminators between brain-damaged and normal persons used in the development of the AIR\textsuperscript{20}: digit symbol; categories; tactile perception test (TPT) on total time, memory, and localization components; finger tapping (hand with poorest performance); and trail making (Trials B). The standardized testing procedures and order of administration were used.\textsuperscript{21,22} and thus, the Trials A test was given before the Trials B test, although the former was not used to calculate AIR. The individual tests measure a wide domain of cognitive, perceptual, and psychomotor functions and have been described in detail elsewhere.\textsuperscript{22-24} Very briefly, they include tests of discrimination; concept formation and learning (categories); speed, memory, and spatial localization components of a tactile sensory function (TPT — total time score, memory, and localization); simple motor behavior (finger tapping); visual scanning and performance of sequential activities as rapidly as possible (trail making B); and perceptual motor speed (digit symbol).

The standardized test procedures for calculating AIR scores from raw scores were employed.\textsuperscript{20} Raw test scores were transformed to a 6-point “rating equivalent” (RE) score: 0 to 1 (above average to average); 2 (mild impairment), and 3 to 5 (moderate to severe impairment). The RE scores were then combined into a single AIR score using the formula described in detail by Russell et al.\textsuperscript{20} In the present study, the AIR scores were used as a dependent variable and the percentages of hypertensive and normotensive subjects exceeding cutting scores separating normal from impaired performance also were determined. Russell et al.\textsuperscript{20} used a cutting score of 1.55 or more as an indication of brain impairment but encouraged modification of cutting scores for individual laboratories. Thus, we employed a more conservative definition of impaired performance in keeping with the mean age level of our sample (i.e., AIR ≥ 2.00).\textsuperscript{25}

Procedure

Testing was conducted individually by either a doctoral student or a Ph.D.-level psychologist (N.R.S.) trained thoroughly in administering the battery, blood pressure measurement, and medical interview procedures. The subjects’ medical history and drug history were obtained, and at least five recordings of BP, using the pressure cuff method, were taken before and after testing and during rest periods. Hypertensive subjects receiving medication at the time of testing exhibited a significant reduction in systolic and diastolic BP values relative to unmedicated values (p < 0.001) obtained at the clinic.

Informed consent was obtained before testing. The medical and behavioral studies were approved by the Institutional Review Boards for the Protection of Human Subjects of the SUNY Health Sciences Center in Syracuse (the testing site) and by the University of Maine.

Design

Preliminary Analyses

Thirty-one hypertensive subjects had been returned to the following medications at the time of testing: diuretic only (n = 8), β-blocker only (n = 4), vasodilator only (n = 1), α-blocker only (n = 1), combination of β-blocker and diuretic (n = 12), and α-blocker and diuretic (n = 5). Each of these subjects had a history of treatment (mean treatment time, 7.5 ± 7.44 [SD] years). However, preliminary tests comparing medicated with unmedicated groups at the time of testing indicated no differences (all p > 0.15) between medication groups or between medication × education interactions (p > 0.15) for any of the performance measures. Subjects with a history of receiving any antihypertensive medication (mean treatment time, 8.3 ± 8.32 [SD] years) before the clinic diagnostic procedure (n = 35) were compared with those with no history of taking antihypertensive medication. There were no main effects for medication as compared with nonmedication, nor were there any significant education × medication interactions for dependent variables (p > 0.15). Medicated and nonmedicated hypertensive subjects were combined into a single group for the final analyses.

The BP × sex × education and BP × sex interactions were nonsignificant for the AIR score (p > 0.25) and for all of the RE scores (all p > 0.26) with the exception of one BP × sex × education interaction (p < 0.01). For the Trails B score, hypertensive men in the Lo-Ed group performed more poorly than the hypertensive Lo-Ed women (p < 0.01) and all other diagnostic groups (p ≤ 0.05).

Final Design

A 2 (BP) × 2 (education level) design was employed. Analyses of variance were done for the major variable of interest, AIR scores, and for the RE scores making up the AIR score. Raw score findings (test scores before transformation to RE scores) are presented 1) for additional raw scores that were not employed in the AIR score and thus not transformed to an RE score and 2) if results for an RE score and its corresponding raw score were different. In all instances in which one or more univariate effects were significant, the overall multivariate analysis of variance was also significant. Age, sex, or age and sex together regressed (average within-cell regressions) significantly (all p < 0.05) on one or more of the dependent variables. Thus, sex and age together were used as covariates in analyses of covariance.
Results

Table 2 summarizes the AIR and the RE scores (scale = 0–5) for which statistically significant (p < 0.05) effects were obtained. It also shows the percentages of hypertensive and normotensive subjects obtaining AIR scores in the brain-impaired range using the cutting score of 2.00 or higher.

Average Impairment Rating Scores

When education groupings were ignored, hypertensive subjects exhibited significantly higher (poorer) AIR scores than normotensive subjects (p < 0.05), but the BP × education interaction was significant (p < 0.05). Specifically, differences between BP groups were nonsignificant (p > 0.05) for the Hi-Ed group. Mean level of performance was poorer (higher scores) for the hypertensive subjects than for the normotensive subjects in the Lo-Ed group. Contrasts between education levels within the hypertensive group indicated that Lo-Ed subjects performed more poorly for AIR scores (p < 0.001) than Hi-Ed subjects. Normotensive Hi- and Lo-Ed subjects showed no between-group differences.

Rating Equivalent Scores

The BP × education interactions were not significant (all p > 0.05), but planned contrasts within the Hi-Ed group indicated no statistically significant differences (all p > 0.05) between hypertensive and normotensive subjects for any of the RE scores. In contrast, analyses within the Lo-Ed group indicated lower levels of performance by hypertensive subjects for the categories test (p < 0.05), the TPT memory test (p < 0.01), and the TPT localization test (p < 0.05).

No differences for RE scores were observed for contrasts between Hi-Ed and Lo-Ed groups within the normotensive group, but in the hypertensive group, the Lo-Ed group performed more poorly on the categories test (p < 0.01), the TPT memory test (p < 0.05), and the Trails B test (p < 0.05).

Raw Scores

Raw score results were the same as those reported for the transformed scores (REs) with several important exceptions. When scores were averaged across education groups, hypertensive subjects performed more poorly (all p < 0.05) than normotensive subjects for the TPT memory (6.91 ± 0.23 vs 7.59 ± 0.20), TPT localization (4.01 ± 0.25 vs 4.85 ± 0.33), and finger tapping preferred hand test (49.58 ± 1.00 vs 52.28 ± 0.88).

Cutting Scores

Chi-square analyses with Yates’ correction revealed no differences (all p > 0.65) in the percentage of hypertensive and normotensive subjects who exceeded the cutting score for brain impairment for either education group or averaging over education (see Table 2). Further, none of the hypertensive or normotensive subjects reached a cutting score for brain impairment of 3.00. Thus, a large proportion of hypertensive and normotensive subjects scored within normal limits of performance, a finding that is consistent with the low mean values obtained for the RE scores and the modest differences between means for hypertensive and normotensive subjects.

All subjects with AIR scores of 2.00 or higher were examined for evidence of marked asymmetries in function for the right or left cerebral hemisphere and evidence of acute brain impairment. This examination was done by a neuropsychologist (M.F.E.) and a trained research assistant, both blind to the diagnosis. Based on the scoring criteria developed by Russell et al., three hypertensive subjects exhibited evidence of cognitive dysfunction weakly lateralized to the right cerebral hemisphere. However, two normotensive subjects also exhibited weakly lateralized effects, one to the right cerebral hemisphere and one to the left. None of the subjects met the criteria for acute damage. Further, the percentages of hypertensive and normotensive subjects scoring in the cognitively impaired range (≥2.00) did not differ for any of the RE scores.

Discussion

The major purposes of this study were to 1) test the hypothesis that differences in mean levels of performance between hypertensive and normotensive subjects would be diminished and involve fewer tests for highly educated as opposed to less well, but not poor-
ly, educated persons and 2) to determine whether subjects with uncomplicated essential hypertension could be characterized as suffering from clinically significant cognitive dysfunction.

Consistent with our hypotheses, differences between BP groups for the Hi-Ed subjects were not significant for the AIR or any of the individual RE scores. In contrast, hypertensive subjects in the Lo-Ed group exhibited higher (poorer) mean AIR scores and performed more poorly on the categories test, the TPT memory test, and the TPT localization test. Furthermore, differences between education groups for AIR and individual RE scores were only observed for the hypertensive subjects. Thus, discrepancies in findings among studies can result from relatively subtle differences in education level.

An important question is why mean differences in performance between hypertensive and normotensive subjects were not observed for Hi-Ed subjects. The tests are difficult, and performance limits were not reached by either hypertensive or normotensive subjects in the Hi-Ed group. Within the Lo-Ed group, the ratio of women to men (18:9) was higher for the normotensive than for the hypertensive (17:14). However, it is unlikely that a sex difference accounts for the results. There were no BP × sex or BP × sex × education interactions for the AIR scores or the three RE measures for which significant BP × education findings were obtained. Sex effects were observed when education and BP classifications were ignored, but women performed more poorly on the Categories test. Thus, the disproportionately larger presence of women in the normotensive group could not contribute to higher levels of performance for normotensive as compared with hypertensive subjects. Although sex differences did not affect education differences in the present experiment, middle-aged and older women tend to be less well educated than middle-aged and older men. Thus, education differences could account for sex × BP interactions reported in other studies.

Costa and Shock have hypothesized that very well educated hypertensive subjects may delay, or prevent, behavioral manifestations of the adverse effects of hypertension by exercising cognitive functions within the context of academic, professional, and managerial occupations. This hypothesis is consistent with the observation that age-related decline in intellectual performance is observed later in life and, to a lesser extent, in well educated persons. Thus, education may affect the extent to which a test can be sensitive to subtle differences in cerebral blood flow, cerebral anatomy, and other characteristics that distinguish individuals with uncomplicated essential hypertension from normotensive persons.

Hypertensive subjects exhibit higher levels of reactive (state) anxiety and greater endocrine and psychophysiological reactivity to stressful situations than do normotensive subjects. Highly educated persons may be less stressed by test material than less well educated subjects. Studies might profitably explore the hypothesis that BP × education interactions reflect group differences in situational anxiety or stress-related endocrine reactivity. Shapiro et al. suggest that anxiety, or other differences in mood state or personality, between hypertensive and normotensive subjects may result from a recognition of poorer levels of performance by hypertensive persons. It is also possible that anxiety or other emotional reactions to the test materials may contribute to poorer performance. The direction of the relationships among performance and mood state variables has not yet been determined.

Effects of medication do not account for these results. No significant education × medication (on-off) interactions or medication main effects were observed. Recently, Miller et al. have reported improvements in performance for several neuropsychological measures over a 15-month test-retest period for hypertensive subjects who were carefully medicated during the test-retest interim, but not for normotensive subjects or nonmedicated hypertensive subjects. In the present study, however, the poorer performing hypertensive subjects in the Lo-Ed group had only a slightly lower proportion of hypertensive subjects who were not and had never been medicated (39%) than did the Hi-Ed group (43%). Failure to find differences between medicated and nonmedicated hypertensive subjects should not be interpreted as contradictory to the findings of Miller et al. Medicated subjects in the present study had a more varied history in terms of length of treatment and kinds of medications employed, and the study was not designed specifically to examine the effects of antihypertensive treatment on performance. However, recent data from our laboratory indicate that hypertensive subjects medicated carefully for 5 to 6 years show no changes in cognitive performance.

Our findings illustrate the importance of employing clinical indices of cognitive dysfunction if one wishes to make inferences regarding cerebral cortical dysfunction. Clinically relevant analyses of AIR scores provided no evidence that would permit characterization of our sample of subjects with uncomplicated essential hypertension as cognitively impaired or, by inference, as suffering cerebral cortical dysfunction of clinical significance. Mean differences, though significant, were very modest, and the majority of scores for hypertensive and normotensive subjects were well within the normal range. Further, the percentages of hypertensive subjects as compared with normotensive subjects performing in the cognitively impaired range were low and did not differ.

These findings are consistent with conclusions by Shapiro et al., Miller et al.,  and Schultz et al. that patients with uncomplicated mild hypertension may be expected to perform everyday recreational, avocational, and employment activities in an adequate manner. Yet a question remains as to why mean levels of performance are poorer for hypertensive subjects. Shapiro et al. and Miller et al. raised the possibility that differences between BP groups in their study may have been due to mild cognitive deficits resulting from the disease process itself or from mechanisms related to the disease. Given heterogeneity in the genesis, diag-
nosis, and treatment of essential hypertension, some hypertensive persons may be more affected cognitively than others, thus lowering mean levels of performance for hypertensive groups. Given the subtle nature of physiological and anatomical changes related to hypertension, it might also be expected that the behavioral manifestations of the disease will be mild, particularly for effectively treated hypertensive persons. The present study does not rule out the possibility of mild deficits with physiological, anatomical, or other bases. It does indicate that persons with uncomplicated essential hypertension do not exhibit clinically significant cognitive impairment.

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