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NEUROPSYCHOLOGICAL PROFILE OF PATIENTS WITH PRIMARY SYSTEMIC HYPERTENSION

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Arterial hypertension represents a risk factor for cerebrovascular disease. It has been hypothesized that chronic hypertension may eventually result in small subcortical infarcts associated with some cognitive impairments.

One hundred fourteen patients with primary systemic hypertension (PSH) and 114 matched subjects were selected. PSH patients were further divided in four groups depending upon the hypertension severity. In addition to the medical and laboratory exams, a neuropsychological evaluation was administered. The NEUROPSI neuropsychological test battery was used.

An association between level of hypertension and cognitive impairment was observed. Most significant differences were observed in the following domains: Reading, executive functioning, constructional, and memory-recall. No differences were observed in orientation, memory-recognition, and language. Some neuropsychological functions appeared impaired even in the PSH group with the least risk factors.

Cognitive evaluation may be important in cases of PSH not only to determine early subtle cognitive changes, but also for follow-up purposes, and to assess the efficacy of different therapeutic procedures.

Keywords: Hypertension; Cognitive deficits; Vascular disease

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Primary systemic hypertension (PSH) represents one of the most important public health problems, both in industrialized and in developing countries (Harrison, 1991). PSH is characterized by a sustained increase in arterial blood pressure (systolic, diastolic, or both), equal or higher than 140/90 mm Hg. The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-V) (JNC-V, 1993) presents a classification of arterial blood pressure into six levels: (a) Normal: < 130 < 85; (b) Normal high: 130 - 139/85 89; (c) Hypertension Stage I: 140 159 90 - 99; (d) Hypertension Stage II: 160 - 179/100 109; (e) Hypertension Stage III: 180 209/110 -119; and (f) Hypertension Stage IV: > 210 > 120.

PSH represents one of the most impacting chronic diseases not only in Mexico, but also worldwide (Chavez, 1986; OPS, 1984). People over 65 are most affected. PSH is involved in 42% of the deaths associated with cerebrovascular disease, and in 27% of the decreases due to ischemic cardiopathies (Bustamante, 1991). The cause of hypertension is unknown in about 90% of the cases. In the rest, it may be associated with renal vascular hypertension or endocrine hypertension due to medication, toxics, environmental conditions, etc. (Chavez et al., 1995; Williams, 1988). It is assumed that age, alcohol abuse, familial aggregation, aging, genetics, obesity, and sensitivity to Na + represent predisposing factors to PSH. Age, sex, tobacco, seric cholesterol, and body weight may alter the prognosis (Harrison, 1991; Rubio, 1997). Patients with PSH die prematurely as a result of heart conditions, cerebrovascular disease, and renal insufficiency (Chavez et al., 1995).

Neurological effects are divided in two major groups: retinal and central nervous system (CNS) effects. Ophthalmologic examination provides direct information regarding the evolution of the disease (Biesenbach, 1994; Dahlof, Stenkula, & Hansson, 1992; Palatini, 1991). Keith and Wagener-Barker (1982) proposed a hypertensive retinopathy classification, including four different degrees of severity. Hypertensive retinopathy is considered an excellent correlate of PSH (Harrison, 1991; Chavez et al., 1995; Walsh, 1982). PSH has been classified as well according to the degree of damage upon different organs: (a) Stage I: no sign no organic alteration; (b) Stage II: hypertrophy of the left ventricle, proteinuria, mild increase in the seric creatinine (up to 2.0 mg/dL), radiologic signs of atherosclerotic plaques; and

(c) Stage III: symptoms and signs of organic damage to heart, brain, retina, kidney, and blood vessels. CNS effects include occipital headache, dizziness, vertigo, tinnitus, visual impairments, and syncope (Harrison, 1991). PSH is a risk factor for cerebrovascular disease, eventually leading to a vascular dementia (Aminoff, 1990; Liss & Gaviria, 1997; Puddu et al., 1996; Sokolow, 1990). Hypertension results in thickening of the perforating arterioles. Eventually, an atherosclerotic subcortical encephalopathy (Binswanger's disease) may be observed (Adams, Victor, & Ropper, 1997).

A decrease in intellectual functioning has been reported associated with PSH, including verbal memory deficits (Battersby et al., 1993), difficulties in concept formation (Elias, 1995), difficulties in shifting mental set, and decreased verbal fluency (Wilfe et al., 1990). Age and PSH severity represent major risk factors for cognitive deterioration (Freid et al., 1997). The impact of anti-hypertensive medications on cognitive functioning has been analyzed. No association between use of anti-hypertensive drugs and cognitive deterioration has been found (Leonetti & Salvatti, 1994; McCirvey, 1993; Prince, 1996, 1997).

The purpose of this research was to analyze the association between level of hypertension and performance in cognitive tests.

METHOD

Participants

One hundred fourteen normal (nonhypertensive group) and 114 arterial hypertension subjects (hypertensive group) were used in this study. Both samples were matched by age, sex, and education. Participants were Caucasians and "mestizos" (mixture of Caucasian and Indian). Subjects with psychiatric history based on DSM-IV criteria (American Psychiatric Association, 1994) including depression and alcohol or drug abuse or immunologic, endocrine, metabolic, and hepatic diseases were not included. Head and spinal injury patients were also not included. No thyroid testing was performed; participants, however, according to the clinical records and medical reports, did not present any thyroid dysfunction. Only nonsmokers were selected.

In addition to the characteristics listed above, nonhypertensive subjects were selected using the following criteria: no dementia according to DSM-IV criteria, no history of neurological disease, no history of renal disease (according to the clinical records), and active and functionally independent. Table 1 presents the general characteristics of the sample.

The following exams were performed on all the participants: (1) general medical examination; (2) optic fundus examination; (3) laboratory exams including total triglycerides, Na+, K−, Ca++, Cl−, glucose, creatinine, and urinalysis; (4) electrocardiogram; (5) chest X-ray; and (6) blood pressure. Table 2 presents the results of the laboratory exams.

These exams were performed by the staff general physician, cardiologist, and ophthalmologist of the hospital. The hypertensive group was taken from the outpatient Family Medicine Clinic No. 1.

TABLE 1 General characteristics of the sample

	Controls	*Group* 1	*Group* 2	*Group* 3	*Group* 4
N	114	32	31	23	28
Males	53	15	14	10	14
Females	61	17	17	13	14
Age: Mean	60.71	57.01	61.52	64.14	65.51
SD	14.24	13.82	12.87	15.32	12.51
Education: Mean	6.32	7.42	6.01	6.57	5.77
SD	4.81	6.32	4.21	4.39	3.84

TABLE 2 Results in the laboratory exams. Mean values and standard deviations (in parentheses)

Exam	*Controls* ($n = 114$)	*Groups* 1 ($n = 32$)	*Group* 2 ($n = 31$)	*Group* 3 ($n = 23$)	*Group* 4 ($n = 28$)
Electrolytes (MEq/L)					
Na^+	138(0.12)	140(1.5)	139.5(1.5)	140(1.5)	137(1.0)
K^+	4.2(1.0)	3.9(0.5)	4.0(0.5)	4.2(1.0)	3.8(0.5)
Ca^{++}	2.3(0.2)	2.4(0.2)	2.3(0.2)	2.4(0.1)	2.3(0.2)
Cl^-	98(1.0)	102(2.0)	97(1.0)	98(1.0)	100(2.0)
Sanguine chemistry					
Creatinine	1.2(0.3)	1.1(0.2)	0.9(0.3)	1.0(0.3)	0.9(0.2)
Urea	22(4.0)	28(3.5)	20(2.0)	25(1.5)	27(3.0)
Glucose	90(8.5)	105(4.0)	103(3.5)	108(2.0)	104(4.0)
Triglycerides (mg/dl)	130(18)	125(15)	115(20)	143(12)	132(16)
Cholesterol (mg/dl)	172(12)	180(8)	165(10)	160(8)	173(10)

Mexican Institute of Social Security, Colima (Colima, Mexico). They were attending this hospital for hypertension control. Nonhypertensive participants were selected in the same institution, but they were attending the hospital for different reasons (orthopedics, etc.).

The following criteria were used to divide the hypertensive subjects into subgroups: (1) The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-V, 1993); (2) the Guidelines for the management of mild hypertension, from the WHO/ISH Meeting (Guidelines for the Management of Mild Hypertension. Memorandum, from WHO/ISH Meeting, 1993); and the classification of hypertensive retinopathy proposed by Keith and Wagener-Barker (1982). The hypertensive group was subdivided into four subgroups: (a) Group 1: No evidence of organic damage and arterial pressure 140 - 180/90 - 110; (b) Group 2: Retinopathy degree I, blood pressure 160 – 200/100 – 120; (c) Group 3: Retinopathy degree II, no clinical evidence of brain damage, and blood pressure 180 – 200/105 – 120; and (d) Group 4: Evidence of brain damage (according to the CT scans taken from the clinical records) with any degree of retinopathy, and blood pressure over 200/110.

The staff psychologist of the hospital administered the NEUROPSI neuropsychological test battery. He had been previously trained in the use of this testing instrument. He did not have knowledge of the subjects' classification.

Instrument

The NEUROPSI neuropsychological test battery was selected (Ostrosky, Ardila, & Rosselli, 1997). The NEUROPSI consists of simple and short items. By design, NEUROPSI represents a rather basic and simple neuropsychological test battery. It may be regarded as an extended Mini-Mental State Examination. Reliability has been calculated from .89 to 1.00. The NEUROPSI has been previously standardized and normalized in Spanish-speaking populations (1999).

The following sections are included in the NEUROPSI neuropsychological test battery:

1. Orientation. Maximum score = 6 points.
2. Attention and concentration (Maximum score = 27).

2.1. Digits backward, up to six digits. Maximum score = 6 points.
2.2. Visual detection. On a sheet which includes 16 different figures, each one repeated 16 times, the respondents are requested to cross out those figures identical to the one presented as a model. Maximum score = 16.
2.3. Serial 3 subtraction from 20 to 5 (Maximum score = 5).

3. Encoding (Maximum score = 18).

3.1. Verbal memory. Six common nouns corresponding to three different semantic categories are presented three times. The score is the average number of words repeated in the three trials (Maximum score = 6).
3.2. Copy of a semicomplex figure. A figure similar to the Rey Osterrieth Complex Figure, but much simpler, is presented to the subject. A specified scoring system is used, with a maximum score of 12 points.

4. Language (Maximum score = 26).

4.1. Naming. Eight different line drawing figures to be named are presented. Maximum score = 8.
4.2. Repetition. The subject is asked to repeat one monosyllabic word, one three-syllable word, one phrase with three words, and one seven-word sentence. Maximum score = 4.
4.3. Comprehension. On a sheet of paper two circles (small and large) and two squares (small and large) are drawn. Six commands, similar to those used in the Token Test, are given to the participant. Maximum score = 6.
4.4. Verbal fluency.

4.4.1. Semantic verbal fluency (animals). The total number of correct words in one minute is scored.
4.4.2. Phonological verbal fluency (words beginning with the letter F). The total number of correct words in one minute is scored.

5. Reading. Subjects are asked to read aloud a short paragraph (109 words). Three questions about the paragraph are orally presented. Maximum score = 3. Paralexias are noted.

6. Writing. This involves writing dictated a six-word sentence to dictation, and copying a different six-word sentence. Maximum score = 2.
7. Conceptual functions (maximum score = 10)
   - 7.1. Similarities. Three pairs of words are presented, and participants are asked to report the similarity. Maximum score = 6.
   - 7.2. Calculation abilities. Three simple arithmetic problems are presented. Maximum score = 3.
   - 7.3. Sequences. The participant is asked to continue a sequence of figures drawn on a paper: one circle, one cross, two circles, two crosses, three circles. Maximum score = 1.
8. Motor functions (maximum score = 8)
   - 8.1. Changing the position of the hand. Participants are asked to repeat three positions with the hand (right and left). A maximum score of 2 is used for each hand. Maximum score = 4.
   - 8.2. Alternating hand movements. To alternate the position of the hands (right hand closed, left hand open, and to switch). Maximum score = 2.
   - 8.3. Opposite reactions. If the examiner shows a finger, the subject must show a fist; if the examiner shows a fist, the subject must show a finger. Maximum score = 2.
9. Recall (maximum score = 30).
   - 9.1. Recall of verbal information. Recall of the six words presented in 3.1
     - 9.1.1. Spontaneous recall. Maximum recall = 6
     - 9.1.2. Cueing recall: Recall by categories. Maximum score = 6.
     - 9.1.3. Recognition. The examiner reads 14 different words, and the participant must tell which ones were previously presented. Maximum score = 6
   - 9.2. Recall of the semi-complex figure. Maximum score = 12

In total, 26 different scores are obtained. The maximum total score is 130. Administration time was 25 to 30 minutes. In order to assure

standardized procedures a detailed "Instruction Manual" for both administration and scoring was developed.

RESULTS

No significant differences in age ($t = 0.888$; $df. = 1, 227$; $p = .554$) and educational level ($t = 0.815$; $df. = 1, 227$; $p = .775$) were found between the nonhypertensive and hypertensive group.

Table 3 presents the means and standard deviation in the different NEUROPSI subtests. In general, highest scores were observed in the nonhypertensive group, whereas minimal scores were found in hypertensive Group 4. In some subtests, differences were extreme, whereas in other subtests, differences were minimal and even nonexisting.

Several ANOVAs with Bonferroni correction were calculated. Significance level was set at $p < .05$. Significant differences among groups were observed in 18 subtests. No differences were found in six subtests. *F*-value was highest in the following subtests: Reading, Similarities, Copy of a Semi-Complex Figure, Recall Semi-Complex Figure, and Changing Hand Position (right hand). No differences were observed in Orientation (place and person), Recognition of Words, Naming, Repetition, and Sequences. In some subtests, significant differences were observed between the nonhypertensive group and Group 1: Phonological Verbal Fluency, Motor Functions Left Hand, and Similarities. In some subtests, differences were only found between the nonhypertensive subjects and Group 4: 20 minus 3, Recall of Words- Cueing, and Writing (both conditions: Dictation and Copy) (see Table 3).

An index of forgetfulness was calculated using the following formula: (Immediate memory - Recall/Immediate memory) × 100. These indexes are presented in Table 4. Forgetfulness of the words varies from 19.16% in the nonhypertensive group up to 64.55% in the hypertensive Group 4. When using the Cueing condition nonhypertensive participants obtained a performance of 96.80%, whereas Group 4 performance was 70.09%. In the Recognition condition, however, all the groups had a rather similar performance, close to 100%. Forgetfulness of the Semi-Complex Figure varied between 13.45% and 40.87% in the extreme groups.

TABLE 3 Means and standard deviations (in parentheses) found in the different neuropsychological tests in the control and hypertensive groups

Test ($n = 114$)	*Controls* ($n = 32$)	*Groups* 1 ($n = 31$)	*Group* 2 ($n = 23$)	*Group* 3 ($n = 28$)	*Group* 4	*F*	*p*	*Differences*
Orientation								
Time	2.82(0.52)	2.84(0.89)	2.86(0.81)	2.57(0.78)	2.27(0.66)	2.79	.03	ctl vs G4
Place	2.00(0.00)	1.90(0.22)	2.00(0.00)	2.00(0.00)	1.88(0.32)	2.42	.15	none
Person	0.98(0.12)	1.00(0.00)	1.00(0.00)	1.00(0.00)	0.94(0.23)	0.67	.60	none
Attention								
Digits backwards	3.45(0.99)	3.52(0.90)	2.65(0.71)	3.57(0.97)	2.33(0.84)	8.18	.01	ctl,G1 vs G3, G3 vs G4
Visual detection	11.07(3.6)	11.26(4.67)	8.95(3.94)	9.28(4.88)	6.00(3.97)	6.84	.01	ctl,G1 vs G4
20 minus 3	4.42(1.04)	3.78(1.58)	3.86(1.21)	4.28(0.48)	3.00(1.57)	5.34	.01	ctl vs G4
Coding								
Verbal memory	4.77(0.83)	4.57(0.50)	4.30(0.76)	4.00(1.29)	3.61(1.03)	7.74	.01	ctl, G1 vs G4
Copy figure	10.20(2.00)	9.21(1.84)	8.06(1.87)	8.50(2.61)	6.69(2.58)	12.78	.01	ctl vs G2, G3, G1 vs G4
Language								
Naming	7.63(0.73)	7.84(0.37)	7.86(0.45)	7.85(0.37)	7.83(0.51)	1.09	.36	none
Repetition	4.00(0.00)	4.00(0.00)	4.00(0.00)	4.00(0.00)	3.77(0.42)	0.38	.91	none
Comprehension	5.10(1.02)	4.94(0.84)	4.56(0.84)	4.28(0.75)	3.94(1.25)	5.68	.01	ctl, G1 vs G4
Fluency: Semantic	16.50(4.98)	12.89(3.68)	15.17(4.91)	14.14(4.41)	11.16(3.80)	6.02	.01	ctl, G1, G2, G G4
Phonologic	9.82(4.97)	6.05(5.82)	6.43(4.69)	4.14(3.93)	3.77(3.29)	8.14	.01	ctl vs G2, G3,
Reading	2.26(0.92)	1.68(1.10)	1.43(1.30)	0.85(0.89)	0.38(0.60)	15.01	.01	ctl vs G3, G4; G1, G2 vs G4
Writing: Dictat	0.91(0.28)	0.84(0.37)	0.60(0.49)	0.57(0.53)	0.55(0.51)	5.19	.01	ctl vs G4
Copy	0.92(0.26)	0.78(0.41)	0.60(0.49)	0.57(0.53)	0.55(0.51)	5.59	.01	ctl vs G4
Conceptual functions								
Similarities	4.54(1.53)	3.009(2.66)	2.69(2.53)	1.42(2.29)	1.16(1.72)	14.11	.01	ctl vs G1, G2, G3, G4
Calculation	2.19(0.96)	1.73(0.73)	1.43(0.89)	1.42(0.53)	1.44(1.09)	4.73	.01	ctl vs G3, G4
Sequences	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)	0	1.00	none

TABLE 3 (Continued)

Test (*n* = 114)	*Controls* (*n* = 32)	*Groups* 1 (*n* = 31)	*Group* 2 (*n* = 23)	*Group* 3 (*n* = 28)	*Group* 4	*F*	*p*	*Differences*
Motor functions								
Left-hand	1.66(0.51)	1.36(0.49)	1.34(0.48)	1.14(0.89)	0.94(0.80)	6.54	.01	ctl vs G1, G2, G3, G4
Right-hand	1.55(0.55)	1.84(0.37)	1.47(0.51)	1.14(0.89)	0.72(0.75)	10.41	.01	ctl, G1, G2, G3, G4
Alternating	1.35(0.56)	1.26(0.80)	1.08(0.84)	0.85(0.89)	0.50(0.78)	5.72	.01	ctl, G1 vs G4
Opposite reactions	1.86(0.34)	1.78(0.41)	1.69(0.47)	1.85(0.37)	1.33(0.68)	5.58	.01	ctl, G1, G2, G3, G4
Recall								
Words	3.79(1.92)	3.05(2.17)	2.21(2.04)	1.57(2.14)	1.38(1.91)	7.46	.01	ctl vs G2, G3,
Cueing	4.52(1.55)	4.31(1.45)	3.08(1.67)	3.28(1.88)	3.00(1.94)	5.71	.01	ctl vs G4
Recognition	5.57(0.77)	5.52(0.69)	5.13(0.63)	5.42(0.68)	5.50(1.09)	0.26	.23	none
Figure	8.79(2.64)	7.15(2.08)	6.95(1.75)	6.92(2.26)	4.38(2.85)	12.36	.01	ctl, G1, G2 vs crl vs G3

TABLE 4 Index of forgetfulness in different memory subtests: Percentage of the information forgot between the immediate and delayed condition. Means and standard deviations (in parentheses) are presented

Subtest	*Controls* ($n = 114$)	*Groups* 1 ($n - 32$)	*Group* 2 ($n - 31$)	*Group* 3 ($n = 23$)	*Group* 4 ($n = 28$)
Recall: Words	19.16 (39.61)	32.10 (48.08)	50.86 (43.53)	62.42 (48.73)	64.55 (45.59)
Cueing	3.20 (27.95)	4.21 (35.01)	21.28 (30.21)	21.71 (36.42)	29.91 (43.32)
Recognition	0.42 (0.12)	0.45 (0.21)	0.60 (0.29)	1.02 (1.21)	1.04 (1.41)
Semi-complex figure	13.45 (20.33)	16.11 (19.04)	13.86 (14.34)	19.59 (12.05)	40.87 (40.81)

DISCUSSION

This study has several important limitations: (a) the impact of some potentially confounding variables (e.g., obesity, life conditions, etc.) was not analyzed; (b) sex differences were not considered; (c) even though participants were matched according to age and education, differences in age and education among the four nonhypertensive subgroups can represent potentially confounding variables; and (c) only a brief neuropsychological test battery was used.

Our results, however, point to a cognitive deterioration associated with arterial hypertension. Impaired neuropsychological domains include attention (Digits—Backward, Visual Detection, 20 minus 3), visuoconstructive abilities (Copy of a Semi-Complex Figure), verbal fluency, language comprehension, reading and writing, motor functions, executive function, and memory. This covers virtually all the cognitive domains that are included in the NEUROPSI. Difficulties were found in all the four hypertensive groups, though they were particularly evident in the hypertensive Group 4. An association between neuropsychological test performance and arterial hypertension severity was evident. Our results support previous studies reporting some cognitive impairment associated with hypertension (Wilfe et al., 1990).

Multiple small infarct areas may represent the neuroanatomical correlate of the cognitive defects observed in PSH patients. Stuss and Cummings (1990; Cummings, 1993) described six different subtypes of

vascular dementia. Specific cognitive profile depends on the localization, amount, and extension of ischemic lesions. At autopsy, PSH patients frequently may present small lacunar infarcts in subcortical areas including the basal ganglia. Periventricular area is also particularly susceptible to vascular accidents as a result of the significant amount of arterioles without collateral circulation. Small 2-to-3 mm infarcts are not usually detected using standard radiological techniques. This means that hypertension may be associated with small infarcts difficult to recognize using CAT scans or MRI. They usually do not result in overt clinical manifestations, but subtle changes in motor activity and cognition may be recognized. It is interesting to note that our PSH patients presented a significantly decreased performance in the "Changing the position of the hand" subtest. Subtle motor dysfunction may be assumed.

Cognitive abnormalities in our hypertensive subjects were not restricted to a single specific cognitive domain. We found defects in attention, visuoconstructive abilities, verbal fluency, language comprehension, reading and writing, motor functions, executive function, and memory. In consequence, it can be conjectured that vascular abnormalities associated with hypertension are not restricted to specific cortical areas, but may involve rather different cortical regions resulting in extended cognitive defects, and eventually leading to dementia.

Also noteworthy is that in some neuropsychological tests we failed to find significant differences between hypertensive and nonhypertensive groups: Orientation (place and person), Recognition of Words, Naming, Repetition, and Sequences. Nonetheless, Orientation in time was significantly abnormal in the last hypertensive subgroup, and Spontaneous Recall of Words was significantly abnormal in the last three hypertensive subgroups. In fact, Orientation (particularly in person, but also in space) and memory using a recognition strategy are relatively resistant abilities in cases of dementia (Cummings & Benson, 1992). By the same token, naming when using high frequency words (as in the NEUROPSI) and language repetition can be relatively well preserved in cases of cognitive deterioration. The NEUROPSI Sequences subtest is a rather simple test, and a ceiling effect was evident: All the subjects in all groups obtained a perfect score.

In conclusion, neuropsychological evaluation may be useful in cases of PSH, not only to determine early subtle cognitive changes, but also

for follow-up purposes, and to assess the efficiency of different therapeutic procedures.

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