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Cerebrovascular disease with and without stroke: Cognitive and clinical profiles

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ABSTRACT

Cerebrovascular disease (CVD) patients with and without stroke were compared using clinical and neurological criteria, Magnetic Resonance Imaging (MRI) and cognitive impairment including dementia. The sample comprised 143 CVD outpatients (86 males, 60.14%): Stroke (n=88), Non-Stroke (n=55). Neurological and MRI assessment, the Clinical Dementia Rating (CDR: Normal, Questionable, non-demented; and Mild, Moderate, demented); the Alzheimer's Disease Assessment Scale (ADAS-Cog), and the Trail Making Tests A (TMT-A) and B (TMT-B) were performed in all patients. Clinical, neurological and MRI results yielded statistically significant differences between patient groups ($0.0001<P<0.05$). Under Normal, Questionable and Mild CDR stages the Stroke group performed ADAS-Cog significantly worse ($P<0.0001$), showing non-significant differences in the Moderate stage. TMT time was always greater in the Stroke patients, while TMT errors resulted significantly greater in the Non-Stroke patient group ($0.0001<P<0.002$). The TMT-B/TMT-A ratio and the difference (B-A) were greater in the Non-Stroke patients ($0.0001<P<0.001$). At Moderate CDR the TMT's showed no differences. Stroke and Non-Stroke CVD patients behave differently concerning several clinical, neurological and MRI results. Cognitive tests differ between groups when impairment has not reached the Moderate stage; further evolution turns both groups undistinguishable. Functional and cognitive impairment present a convincing linear association.

KEYWORDS: cerebrovascular disease, stroke, non-stroke, silent brain infarct, incomplete white matter lesions, magnetic resonance images, cognitive impairment, dementia

INTRODUCTION

Cerebrovascular disease (CVD) causes high disability for daily living activities and high annual economic costs [1-4]. Stroke is the most common form of CVD in out- and in-patients. The main symptoms of stroke are *–inter alia–* the sudden onset of a focal neurological deficit, paralysis, sensory loss, visual deficits, dysphasia, dysphagia, dysarthria, urinary incontinence, gait and cognitive and behavior disorders.

Several reports indicate that CVD may also have an insidious onset and a slow progression [5-7]. Not only cognitive and behavioral deterioration develops gradually but also other symptoms such as gait disorders, urinary sphincter incontinence,

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dysarthria, and dysphagia [8-11]. Neurological manifestations occurring without stroke are associated with the presence of chronic hypoperfusion in deep areas and lacunars silent infarcts of the cerebral hemispheres. A claimed chronic progressive evolution of the CVD, Non-Stroke, has not been extensively studied in its clinical, cognitive and therapeutic aspects; consequently, no *consensus scholarum* has emerged to date.

Two types of lesions can be seen on magnetic resonance images (MRI) of Non-Stroke patients: silent complete infarctions (CI) and incomplete white matter lesions (IWML) [12, 13] reported as leukoaraiosis on CT images [14, 15]. Several abnormalities appear in the Non-Stroke patients, such as bilateral brain lesions, IWML, hypertension –the highest percentage in all CVD patients- as the main vascular risk factor (VRF), dysarthria, gait disorders of non-pyramidal type -also known as lower body parkinsonism-, and an evolution time of the chronic progressive form [6].

The hypotheses tested were: (i) Previous reports indicating several differences between the Stroke and Non-Stroke patients of CVD could be reproduced in this larger sample; both groups are expected to be associated with different clinical conditions, neurological and MRI features. (ii) The Alzheimer's Disease Assessment Scale (ADAS-Cog), the Trail Making Test A (TMT-A), and the Trail Making Test B (TMT-B) might differ between the Stroke and the Non-Stroke patients groups; implying more abnormal results in the Stroke patient group. (iii) As functional deterioration (CDR) increases, the differences between patient groups should tend to decrease.

MATERIALS AND METHODS

Patients

One hundred and forty-nine consecutive outpatients with clinical manifestations and MRI diagnostic of CVD were recruited over a period of 12 months (November 2007 to October 2008), from the Neurology Services -Hospital Sirio-Libanés and FACENE-, Buenos Aires. Patients were prospectively studied in their persistent clinical, neurological and cognitive impairment. Only those with a clinical history of VRF and vascular lesions on MRI were included. Outpatients signed an informed consent for this study and were controlled for periods varying from 4 to 7 months. During the control period, all tests were performed twice, with a maximum interval of 2 months, and the means used. Along the recruiting period 6 patients were excluded because of various reasons: tumors, chronic infections, renal and heart failure. The total sample of 143 CVD patients (86 males, 60.14%) were divided accordingly to whether or not they have experienced one or more strokes, resulting in two groups: 88 Stroke (61.54%) and 55 Non-Stroke patients (38.46%).

Magnetic resonance images (MRI) were obtained on 1.5 Tesla MR Systems (Magnetron Siemens or Gyroscan Phillips). CI and IWML lesions can be seen on MRI of Stroke and Non-Stroke patients; CI refers to cavities formed by necrosis and reabsorption of ischemic brain lesion with destruction of axons, myelin and oligodendroglia in the white matter, glial cells and neurons in the gray matter [12]. On MRI, these cavities are bright on T2 and on fluid attenuated recovery (FLAIR) sequences and dark on T1 - weighted images. IWML are bright on T2 and FLAIR sequences, and inestimable on T1 - weighted images. The presence or absence of IWML and CI on MRI was determined in all patients.

Estimates of functional, cognitive and dementia impairment were obtained applying the Clinical Dementia Rating (CDR), the Barthel test, the ADAS-Cog scale, the TMT-A and TMT-B tests, and the Folstein's Mini-Mental State Examination (MMSE) [16-21]. The Evans's index was employed in the analysis of neuroimages, and depression was evaluated (Hamilton test) [22, 23]. Vascular dementia was defined according to the Consortium of Canadian Centers criteria [24]. The etiological subtypes of the CVD were assessed using the TOAST criteria [25].

The Non-Stroke patients of the CVD were previously defined as the slow appearance of clinical symptoms along a period of one month or more until reaching the maximum neurological deficit, including the Index of Gait and Equilibrium (IGE), the presence of pyramidal and non-pyramidal syndromes, and findings of silent infarctions [6, 26, 27].

Among the recorded drugs were aspirin (100 mg/day), clopidogrel (75 mg/day), atorvastatin or simvastatin (20 mg/day), enalapril (5-20 mg/day), athenolol (25-50 mg/day), dygoxine (0.25-0.5 mg/day) or warfarin (0.5-2 mg/day) in those patients with atrial fibrillation, and glibenclamide (5-10 mg/day) or metformin (500-750 mg/day) in diabetic patients.

Statistical analysis - clinical management - risk factors – clinical and neurological tests - neuroimages

Comparisons between clinical variables, risk factors, CVD subtypes, CDR, Barthel, MMSE, Hamilton, and IGE tests and the Evans's Index, differences in the time to maximum neurological deficiency, and neuroimagery results were assessed using the Chi-square (χ^2) statistic and a two-tailed Student's "t" test. Probability values (*P*) less than 0.05 were considered significant. Since the goal of MRI analysis was to compare type, localization and numbers of silent vascular lesions, data on their presence or absence was used rather than their details (*i.e.*, T1, T2, and Flair supra- and infratentorial).

Cognitive tests

The usual null hypotheses ($\mu_{i,j} = \mu_{l,k}$) were tested on ADAS-Cog using a univariate ANOVA model and on TMT-A and TMT-B a multivariate (MANOVA) model using Roy's largest characteristic root statistic [28]. For comparison, the means of the groups are presented in the usual form (*i.e.*, mean value ± standard deviation and mean value ± standard error).

Since all patients in the Moderate functional stage of CDR complete the TMT-A and TMT-B tests within the maximum time and errors assigned for the tasks (120 and 240 seconds, 12 and 24 errors) the statistical analysis of significance of differences in these variables was performed on the remaining three stages.

RESULTS

Outpatients were Caucasian with comparable age and education time. Demographic and baseline data are shown in Table 1.

In the Stroke group 70 patients (79.55%) had 1 stroke, 18 patients (20.45%) had recurrent strokes (11 patients with 2 strokes, 6 patients with 3 strokes, and 1 patient with 4 strokes).

Associations with clinical variables

Clinical variables are presented in Table 1, together with the number of patients and percentages, Chi-square values and probabilities. Dysphasia resulted significantly associated with the Stroke patients, while urinary incontinence disorders and non-pyramidal gait with the Non-Stroke patients group.

Associations with VRF and subtypes of the CVD

VRF are presented in Table 1, and tested for association with both groups (Chi-square test). Hypertension resulted significantly associated with the Non-Stroke group, while hyperlipidemia and atrial fibrillation were associated with the Stroke group in both variables.

Concerning the vascular subtypes of the CVD, the Non-Stroke group was significantly associated with the small-vessel disease subtype. In contrast, the cardioembolism, the large-vessel disease and the indeterminate subtype were mainly associated with the Stroke group. Results are presented as histograms in Figure 1.

Neuroimages

All patients showed vascular lesions on MRI, most of them being supratentorial. CI and IWML lesions, their combinations and localization and Chi-square results are presented in Table 2.

Silent vascular infarctions resulted significantly associated with the Non-Stroke group: CI, IWML, the combination of CI and IWML, and bilateral infarctions. Pontine infarctions were also significantly associated with the Non-Stroke group: CI and IWML.

Neurological and cognitive tests

In the Stroke group the mean time of evolution was 1.60 days, while in the Non-Stroke group it was 364.91 days (Table 1). In Table 3 are presented the numerical values for the cognitive tests ADAS-Cog, TMT-A and TMT-B, and for the functional impairment CDR in both groups. The two-way ANOVA model fitted to the ADAS-Cog values resulted in significant differences

Table 1. Demographic and baseline data.

TOTAL PATIENTS = 143	Stroke group = 88 (61.54%)	Non-Stroke group = 55 (38.46%)		
Age (yr.) ± Standard Deviation			"*t*" (ν=141)	*P*
75.36 ± 3.33	75.96 ± 2.75	74.74 ± 3.90	2.175	0.029
Education (yr.) ± Standard Deviation				
13.22 ± 4.41	12.80 ± 3.80	13.89 ± 5.17	1.438	0.147
Gender				
86 M / 57 F (60.14 % M)	57 M / 31 F (64.77 % M)	29 M / 26 F (52.73 % M)	χ^2 (ν=1)	
			2.049	0.149

	Stroke group	Non-Stroke group		
RISK FACTORS	*n* patients (%)	*n* patients (%)	χ^2 (ν=1)	*P*
Hypertension	51 (57.95%)	43 (78.18%)	6.148	0.013
Hyperlipidemia	41 (46.59%)	10 (18.18%)	11.905	<0.0001
Diabetes	21 (23.86%)	9 (16.36%)	1.148	0.284
Smoking	22 (25.00%)	20 (36.36%)	2.107	0.142
Sedentarism	65 (73.86%)	40 (72.73%)	0.022	0.877
Obesity	18 (20.45%)	15 (27.27%)	0.886	0.349
Atrial fibrillation	25 (28.41%)	3 (5.45%)	11.326	<0.0001
CLINICAL VARIABLES				
Dementia	29 (32.95%)	22 (40.00%)	0.732	0.397
Dysphasia	30 (34.09%)	2 (3.64%)	18.072	<0.0001
Dysarthria	22 (25.00%)	14 (25.45%)	0.0037	0.949
Dysphagia	11 (12.50%)	5 (9.09%)	0.396	0.537
Depressive behavior	20 (22.72%)	8 (14.54%)	1.439	0.228
Urinary incontinence	23 (26.14%)	23 (41.82%)	3.815	0.048
Gait disorders	59 (67.05%)	43 (78.18%)	2.053	0.148
Non-pyramidal gait disorders	34 (38.64%)	50 (90.91%)	38.159	<0.0001
Acute myocardial infarctions	18 (20.45%)	9 (16.36%)	0.369	0.551

Table 1 continued..

Myocardial dilatation	4 (4.55%)	5 (9.09%)	1.186	0.276
Cardiac valvular lesion	4 (4.55%)	0	2.572	0.104
VASCULAR SUBTYPES			χ^2 (ν=3)	
Large-vessel disease	25 (28.41%)	4 (7.27%)		
Cardioembolism	19 (21.59%)	3 (5.45%)		
Small-vessel disease	15 (17.05%)	43 (78.18%)	52.481	<0.0001
Indeterminate	29 (32.95%)	5 (9.09%)		
NEUROLOGICAL AND COGNITIVE TESTS - TIME OF EVOLUTION			χ^2 (ν=3)	
CDR Test	0.722 ± 0.548*	0.946 ± 0.516*	3.395	0.335
			"*t*" (ν=141)	
Barthel test	54.716 ± 14.473*	66.000 ± 9.707*	4.992	<0.0001
Mini-Mental State Examination	23.852 ± 5.707*	23.100 ± 4.984*	0.799	0.431
Hamilton test	13.142 ± 9.685*	8.218 ± 7.478*	3.196	0.0018
IGE test	3.339 ± 2.613*	3.686 ± 2.199*	0.815	0.422
Mean time of evolution†	1.602 ± 0.960*	364.910 ± 203.370*	16.640	<0.0001

Percentages are reported with respect to the total *n* in each column. (yr.): years; M: Males, F: Females. χ^2: Chi square test value; ν: Degrees of freedom; *P*: Probability; "*t*": Student's test value. *: Mean value ± standard deviation. †: Time to maximum neurological deficiency is expressed in days.

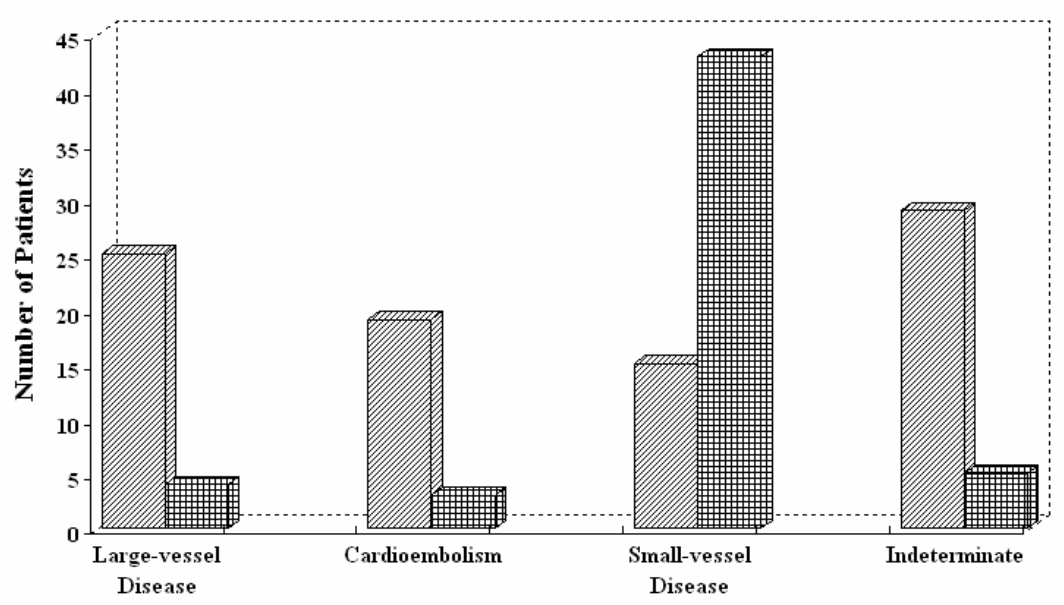

Figure 1. Vascular subtypes in the Stroke and the Non-Stroke groups. Data from Table 1. Streaky bars: Stroke group; railing bars: Non-Stroke group.

Table 2. Magnetic Resonance Images (MRI): Silent vascular lesions and Evans's Index values in symptomatic patients with and without stroke.

	Total	Stroke group	Non-Stroke group	χ^2 (ν=1)	*P*
n patients	143	88	55		
n (%) patients with:					
Silent brain infarctions	76 (53.15%)	21 (23.86 %)	55 (100%)	78.791	<0.0001*
Complete infarctions (CI)	26 (11.18%)	7 (7.95%)	19 (34.55%)	16.087	<0.001*
Isolated IWML	14 (9.79%)	0	14 (23.45%)	24.831	<0.0001*
IWML+CI	42 (29.37%)	18 (20.45%)	24 (43.64%)	8.768	0.0032*
Bilateral infarctions	76 (53.15%)	31 (35.23%)	45 (81.82%)	29.505	<0.0001*
Pontine infarctions					
IWML	8 (5.59%)	1 (1.14%)	7 (12.73%)	8.610	0.0035*
CI	9 (6.29%)	0	9 (16.36%)	14.814	<0.001*
				"t" (ν=141)	*P*
Evans's Index		0.304 ± 0.018†	0.303 ±0.018†	0.022	0.980

Percentages are reported with respect to the total *n* in each column. χ^2: Chi square test value; ν: Degrees of freedom; *P*: Probability; "t": Student's test value. *: Significantly associated with the Non-Stroke group (Chi-square test); †: Mean value ± standard deviation.

The 76 patients with bilateral infarctions also presented a significant association between small-vessel disease subtype and Non-Stroke group: 35 of 45 (77.77%) Non-Stroke bilateral patients *versus* 10 of 31 (32.26%) Stroke bilateral patients (χ^2=17.001, *P*<0.001).

Table 3. Results of the ADAS-Cog, TMT-A and TMT-B tests in the Stroke and Non-Stroke groups.

CDR			ADAS-Cog	TMT-A Time	TMT-A Errors	TMT-B Time	TMT-B Errors
Stroke group							
0	Normal	(*n*=15)	13.66 ± 0.95	52.30 ± 4.83	1.37 ± 0.54	143.97 ± 7.28	6.93 ± 1.64
0.5	Questionable	(*n*=37)	17.52 ± 0.70	57.49 ± 2.12	6.51 ± 0.20	166.85 ± 6.22	12.93 ± 0.38
1	Mild	(*n*=27)	23.92 ± 0.59	109.70 ± 3.46	10.40 ± 0.23	222.67 ± 5.93	19.02 ± 0.44
2	Moderate	(*n*=9)	36.54 ± 1.32	120.00 ± 0	12.00 ± 0	240.00 ± 0	24.00 ± 0
Non-Stroke group							
1	Normal	(*n*=8)	6.75 ± 0.94	42.00 ± 3.86	5.13 ± 0.21	129.81 ± 5.29	11.13 ± 0.86
0.5	Questionable	(*n*=16)	9.68 ± 1.27	50.75 ± 3.44	9.17 ± 0.42	151.92 ± 7.04	14.83 ± 0.76
1	Mild	(*n*=23)	17.64 ± 1.41	86.94 ± 4.49	11.05 ± 0.24	203.64 ± 5.55	20.17 ± 0.57
2	Moderate	(*n*=8)	35.00 ± 0.74	120.00 ± 0	12.00 ± 0	240.00 ± 0	24.00 ± 0

Numerical values of the cognitive tests are expressed as Mean value ± Standard Error. CDR is the Clinical Dementia Rating. *n* is the number of patients in each CDR stage. ADAS-Cog results are numerical values of the test; TMT-A and TMT-B Time were expressed in seconds; TMT-A and TMT-B Errors were expressed as the number of errors.

between CVD patients groups (P<0.0001) and between CDR stages (P<0.0001). When Stroke and Non-Stroke groups were tested at the different CDR stages, in the Moderate CDR stage the difference was non-significant.

The two-way MANOVA model fitted to TMT-A and TMT-B data yielded significant overall differences for Times between CVD groups (P=0.0015) and between CDR stages (θ=0.57, S=2, M=-0.5, N=58.5, P<0.001). The overall differences for Errors resulted significant between CVD patients groups (P<0.0001) and between CDR stages (θ=0.85, S=2, M=-0.5, N=58.5, P<0.0001).

The ratio TMT-B/TMT-A was calculated for each patient resulting in the mean values: Normal CDR, 2.80 and 3.75 for Stroke and Non-Stroke patients respectively; Questionable CDR, 2.93 and 3.04; Mild CDR, 2.05 and 2.46. The two-way ANOVA yielded significant differences between CDR stages (P<0.0001), and between Stroke and Non-Stroke patients (P<0.001). The difference of scores (B-A) between groups resulted in the mean values: Normal CDR, 87.5 and 117.75 for the Stroke and Non-Stroke groups respectively; Questionable CDR, 103.66 and 101.17; Mild CDR, 112.75 and 117.04. Two-way ANOVA resulted at the edge of the statistical significance (P=0.07) in both differences, between CDR stages and between Stroke and Non-Stroke patients groups.

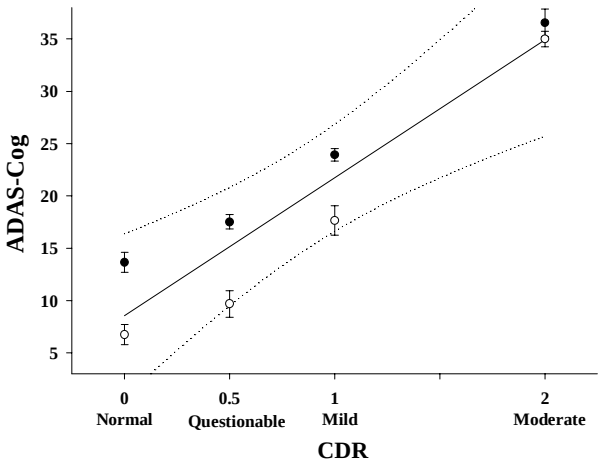

Figure 2. Impairment profiles of the ADAS-Cog variable in the studied deterioration stages. Data and statistics from Table 3. Mean values (*points*) and standard errors (*bars*), solid line is the linear regression (r=0.946) for all data plotted, dotted lines are the 99% confidence intervals. Stroke group: ●; Non-Stroke group: ○.

The plots of the variables ADAS-Cog, TMT-A and TMT-B against the CDR values are presented in Figures 2, 3 and 4. The values of the

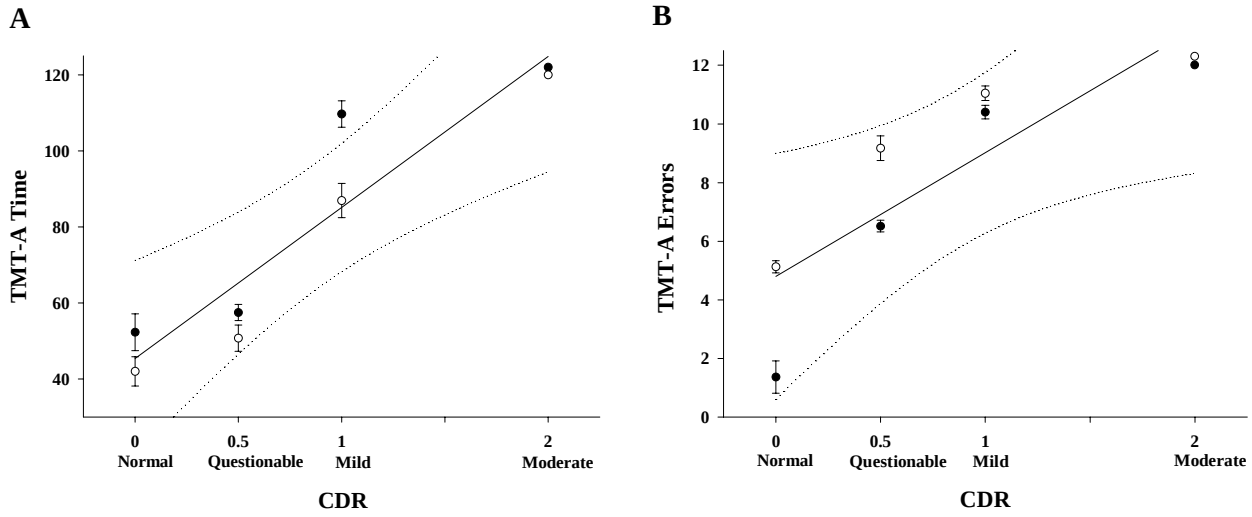

Figure 3. A: Impairment profiles of the TMT-A Time variable in the studied deterioration stages. Data, statistics (r=0.936; linear regression) and symbols as in Figure 2.

B: Impairment profiles of the TMT-A Errors variable in the studied deterioration stages. Data, statistics, symbols and considerations (r=0.868; linear regression) as in Figure 2.

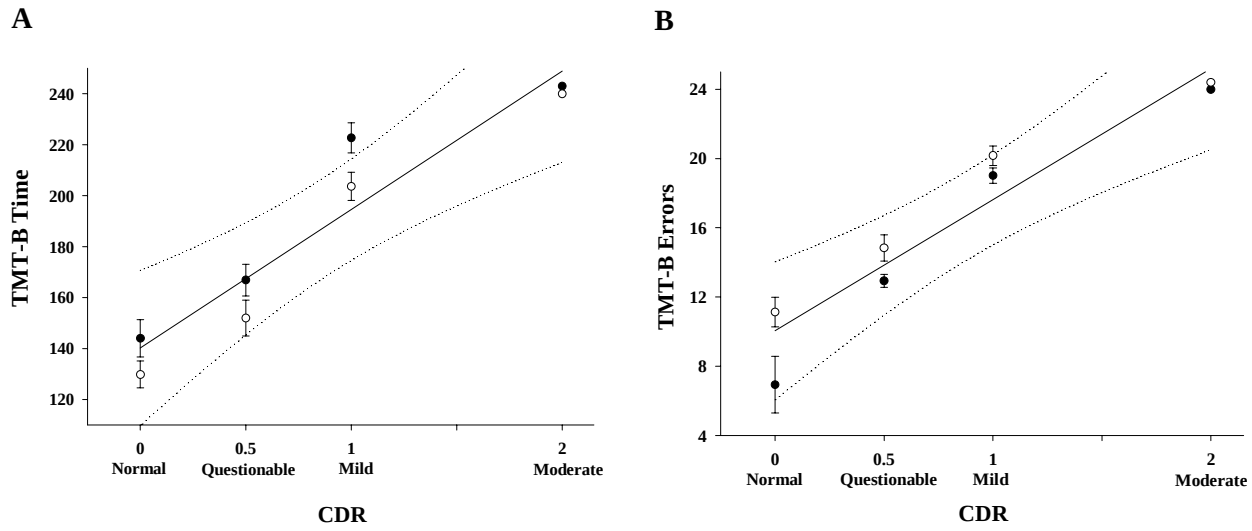

Figure 4. A: Impairment profiles of the TMT-B Time variable in the studied deterioration stages. Data, statistics (r=0.952; linear regression) and symbols as in Figure 2.

B: Impairment profiles of the TMT-B Errors variable in the studied deterioration stages. Data, statistics, symbols and considerations (r=0.957; linear regression) as in Figure 2.

determination coefficient were: a) ADAS-Cog *versus* CDR: Stroke group, r^2=0.996; Non-Stroke group, r^2=0.986; both groups (all data in the plot), r^2=0.946; b) TMT-A *versus* CDR (Time: r^2=0.917, r^2=0.982, and r^2=0.936, respectively; Errors: r^2=0.920, r^2=0.909, and r^2=0.868, respectively); c) TMT-B *versus* CDR (Time: r^2=0.948, r^2=0.978, and r^2=0.952, respectively; Errors: r^2=0.973, r^2=0.980, and r^2=0.957, respectively).

The relationships of cognitive tests with age and time of formal education yielded non-significant

determination coefficients ($0.0001<r^2<0.082$) either within groups and across the whole sample.

DISCUSSION

Demographic characteristics, MRI and VRF findings, somatic manifestations, and vascular etiology subtypes of this sample of patients are consistent with already published results [6], characterized *inter alia* by silent lacunars infarcts and IWML [29]. Correlation studies of MRI with neuropathology have shown myelin pallor, loss of oligodendroglia, axonal depopulation, and reactive gliosis and reduced brain vascular density in areas of IWML [15, 30]. Changes in white matter are accompanied by an increase in gait disorders [31]. Experimental studies of chronic ischemia in animals have also demonstrated increased extracellular fluid accumulation and reactive astrogliosis [32]. Present results show a Non-Stroke patient group as different from Stroke, but sharing common features in agreement with other results [33].

Cognitive tests

The ADAS-Cog explores global cognitive functions summarizing memory, orientation, language and praxis which are considered cortical functions [34, 35], while motor control and perceptual complexity are linked with subcortical functions. The CDR was applied to evaluate functional alterations of the daily living activities due to cognitive causes [16, 35, 36].

Cognitive impairment in Alzheimer's patients is mainly cortical and is well evaluated by the ADAS-Cog test. In CVD patients impairment results from subcortical damage [37] and is better evaluated by means of the TMT tests. Cognitive and functional decline may be assessed by means of neuropsychological tests, such as, the MMSE and the ADAS-Cog and are frequently associated with ischemic lesions in CVD patients [38].

Daily life activities are frequently impaired in the first weeks after stroke, but cannot be considered as an indication of deteriorated performance. The degree of cognitive impairment cannot be ascertained without neuropsychological assessment [34].

The present results of the ADAS-Cog test show significant differences between groups of CVD patients. Stroke patients presented larger values at the Normal, Questionable and Mild stages in comparison with the Non-Stroke group. Stroke patients with Moderate impairment showed non-significant differences when compared against the Non-Stroke counterparts (Figure 2).

TMT-A and TMT-B resulted significantly different between Stroke and Non-Stroke groups in the first three stages of the CDR. Additionally, patients in the Stroke group take significantly longer to complete the task as compared with those in the Non-Stroke group, but the number of errors is significantly lower (Figures 3 and 4). A possible explanation could be diminished information processing without loss of function. The significant differences between groups in the TMT-B/TMT-A ratio with mean values above 3, and in the B-A difference, is associated with impairment in the executive function in the Non-Stroke group [39, 40]. The performance in TMT measured by the ratio B/A provides an index of executive function. Cost for alternating switches was especially large for patients with B/A greater than 3 [40]; this study of TMT related with education and age has shown that the difference B-A is not linked with age in normal elderly subjects below 85 years old, and not linked with educational level above 6 years. However, the time to complete TMT-B is affected by educational level. Within the groups studied here no differences in TMT tests were found in relation with age or educational level. A tentative interpretation of present results might be based on the predominance of subcortical lesions in the Non-Stroke patients, thus affecting executive functions.

The MMSE and IGE tests and the Evans' index are close between groups, indicating that they are comparable regarding their dementia condition, gait disorders and ventricular enlargement. The significant associations between the Stroke group and functional impairment due to somatic causes - Barthel's test-, and depressive conditions - Hamilton test-, but in the normal range of test values, resulted as expected. However, it seems reasonable to advance the hypothesis that the differences between Stroke and Non-Stroke patients groups are due to the predominance of cortical over subcortical alterations as suggested

by the large difference in the probabilities associated with the statistical tests performed on ADAS-Cog and both TMT (*P* values of 10^{-12} against 10^{-7}).

The silent infarctions associated with the Non-Stroke group, frequently found on MRI of healthy and hypertensive subjects, suggest an increased risk of dementia and a more pronounced decline in motor and cognitive function [31, 33, 41-43]. In the vascular patients studied here the almost linear relationship between ADAS-Cog and both TMT against CDR (Figures 2, 3 and 4) suggest a *pari passu* evolution of cognitive and functional impairments.

ADAS-Cog test, designed for Alzheimer's disease, can also be used to assess vascular patients if a frontal cortical/subcortical tool is added. Stroke and Non-Stroke patients differ in some aspects, with a possible predominance of subcortical impairment in the Non-Stroke group. Since these patients are frequently found in everyday neurological practice they require further observations to identify their clinical, therapeutic and cognitive profiles.

CONCLUSIONS

In relation with the hypotheses tested, it might be concluded that: (i) In this larger sample of CVD patients those with non-stroke vascular lesions reproduce previous clinical and MRI results. (ii) The cognitive tests used differ between CVD groups when deterioration has not reached the advanced stages. (iii) In patients past the Mild stage of CDR the groups become undistinguishable, suggesting that the scale of the tests is unsuitable or that the potential diagnostic value of the tests is masked by the superimposed dementia condition.

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