Prevalence of dementia subtypes in a developing country: a clinicopathological study

Lea T. Grinberg,[I,II] Ricardo Nitrini,[III] Claudia K. Suemoto,[IV] Renata Eloah de Lucena Ferretti-Rebustini,[V] Renata E. P. Leite,[I] Jose Marcelo Farfel,[IV] Erika Santos,[I] Mara Patricia Guilhermino de Andrade,[I,VI] Ana Tereza Di Lorenzo Alho,[I,VI] Maria do Carmo Lima,[I,VI] Katia C. Oliveira,[I] Edilaine Tampellini,[I,VI] Livia Polichiso,[I,VI] Glaucia B. Santos,[I,VI] Roberta Diehl Rodriguez,[I] Kenji Ueda,[VII] Carlos A. Pasqualucci,[I] Wilson Jacob-Filho[IV]

[I] Faculdade de Medicina da Universidade de São Paulo, Department of Pathology, Aging Brain Study Group, LIM-22, São Paulo/SP, Brazil. [II] University of California, Department of Neurology, San Francisco/CA, USA. [III] Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Department of Neurology, São Paulo/SP, Brazil [IV] Faculdade de Medicina da Universidade de São Paulo, Discipline of Geriatrics, São Paulo/SP, Brazil. [V] Universidade de São Paulo, Nursing School, São Paulo/SP, Brazil. [VI] Hospital Israelita Albert Einstein, São Paulo/SP, Brazil. [VII] Tokyo Institute of Psychiatry, Department of Neurochemistry, Setagaya-ku/Tokyo, Japan.

OBJECTIVES: To assess the distribution of dementia subtypes in Brazil using a population-based clinicopathological study.

METHOD: Brains from deceased individuals aged ≥50 years old were collected after the next of kin signed an informed consent form and provided information through standardized questionnaires. Post-mortem clinical diagnoses were established in consensus meetings, and only cases with moderate or severe dementia or without cognitive impairment were included in the analysis. Immunohistochemical neuropathological examinations were performed following the universally accepted guidelines. A diagnosis of Alzheimer's disease was made when there were at least both a moderate density of neuritic plaques (Consortium to Establish a Register for Alzheimer's disease B or C) and Braak stage III for neurofibrillary tangle distribution. For the diagnosis of vascular dementia, at least three zones or strategic areas had to be affected by infarcts, lacunae, or microinfarcts.

RESULTS: From 1,291 subjects, 113 cases were classified as having moderate or severe dementia, and 972 cases were free of cognitive impairment. The neuropathological diagnoses of the dementia sub-group were Alzheimer's disease (35.4%), vascular dementia (21.2%), Alzheimer's disease plus vascular dementia (13.3%), and other causes of dementia (30.1%). Small-vessel disease, which alone was not considered sufficient for a vascular dementia diagnosis, was present in 38.9% of all of the dementia cases and in 16.8% of the group without cognitive impairment (odds ratio = 2.91; 95% confidence interval, 1.53-5.51), adjusted for age, sex, and education.

CONCLUSIONS: The relatively high frequencies of vascular dementia and small-vessel disease in the dementia sub-group constitute relevant findings for public health initiatives because control of vascular risk factors could decrease the prevalence of dementia in developing countries.

KEYWORDS: Dementia; Alzheimer's Disease; Vascular Dementia; Cerebrovascular Disease; Post-Mortem Diagnosis; Prevalence.

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E-mail: rnitrini@uol.com.br

Tel.: 55 11 2661-7877

INTRODUCTION

Alzheimer's disease (AD) is considered to be the most frequent cause of dementia in Western countries (1), but recent studies have raised the hypothesis that vascular dementia (VaD), either pure or associated with AD, is at least as common as ''pure'' AD in developed countries (2,3).

It is known that almost two-thirds of individuals with dementia live in developing countries (4), where the risk factors for cerebrovascular disease, such as arterial

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hypertension, diabetes mellitus, and hyperlipidemia, are less adequately detected and treated (5). Therefore, it is reasonable to suppose that cerebrovascular disease plays a more decisive role in developing countries than in developed regions. Nevertheless, epidemiological studies performed in developing regions have shown AD to be the leading cause of dementia. In Latin America, population surveys have indicated AD as the cause of dementia in from 49.9% to 84.5% of cases, whereas VaD was diagnosed in only 8.5% to 26.5% of the cases (6). In a broader analysis of the prevalence of dementia in developing regions, 60% of the cases were attributed to AD and approximately 30% to VaD (7). However, none of these results were validated by autopsy.

Rigorous population-based clinicopathological studies have been very difficult to perform (8). The greatest weakness of these studies has been the use of biased samples, usually taken from memory clinics or other non-representative groups. Generally, this selection has resulted in participation being skewed toward subjects with severe dementia (8). No true population-based clinicopathological studies of dementia have been previously conducted in a developing country, where the factors that impact the clinical expression of dementia, such as the mean age at death and mean educational attainment, are different from those in developed countries. Here, we report the distribution of dementia subtypes in a developing country, evaluated in a population-based clinicopathological study, and we discuss the similarities and differences between these data and those derived from similar studies in developed countries.

SUBJECTS AND METHODS

Study subjects and clinical evaluation

This investigation was conducted at the Brain Bank of the Brazilian Aging Brain Study Group (BBBABSG), which is supplied by the São Paulo City Autopsy Service (SPAS). The SPAS performs approximately 13,000 autopsies per year. The methods used by the BBBABSG have been previously reported (9). In São Paulo, autopsy is compulsory for those deceased from presumed natural causes without death certificates. All the protocols were approved by the local ethics committee (285/04), and inclusion was conditional upon written consent from the next of kin (9). The BBBABSG collects brains from deceased individuals aged ≥50 years old, for whom an immediate brain examination was not required for completion of the death certificate. To be included in the BBBABSG, the cases had to have comprehensive clinical information from a reliable source. In brief, upon arrival at the SPAS, a knowledgeable informant in close contact with the subject was invited to participate in this study and to provide clinical and functional information about the deceased. The interview was conducted by a skilled team of gerontologists, trained in the application of a series of semi-structured questionnaires that covered major cognitive and functional domains (9).

The clinical diagnosis was made in a consensus meeting with the participation of gerontologists and of one neurologist with expertise in dementia, using all of the available information. At the brain bank, the diagnosis of dementia was based on DSM-IV criteria. Additionally, to increase specificity, only individuals with a Clinical Dementia Rating (CDR) >0.5 and an Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) score >3.41 (10) were included. The CDR is a five-point scale for classifying dementia severity, in which stage 0 corresponds to no cognitive decline, 0.5 indicates questionable dementia, and stages 1, 2, and 3 correspond to mild, moderate, and severe dementia, respectively (11). To determine the clinical dementia subtype, we used the NINCDS-ADRDA for the diagnosis of probable and possible AD (when not associated with cerebrovascular disease). The NINDS criteria were used for the diagnosis of possible VaD and for AD plus cerebrovascular disease. Other types of dementia were diagnosed using standard diagnostic criteria (9). In the control group, the individuals showed no signs of cognitive impairment (CDR 0 and IQCODE ≤3.41).

During the study period (April 2004 to March 2007), 23,473 autopsies of individuals aged ≥50 years old, who died from natural causes, were performed in the SPAS. These subjects had a mean age of 68.3 (±11.5) years old, and 56.7% were male. This sample represented 13.5% of the 173,635 deaths in this age group in the city of São Paulo. During the same period, 1,291 cases were added to the BBBABSG, with a mean age of 68.6 (±11.4) years old. Of these 1,291 cases, 56.0% were male. There were no differences between the ages or sexes of the cases included in the study and of the total group in whom autopsies were carried out (Student's t-test and chi square test, respectively, $p>0.05$).

The present study included all of the subjects with moderate or severe dementia (CDR≥2), plus the same number of paired control cases, matched for age and sex, who were electronically assigned from the control cases pool.

Tissue processing

The brain was removed from the skull, and both hemispheres were cut into 1-cm coronal slabs and examined macroscopically. From one hemisphere, 15 neurodegenerative disease-related structures, plus any other macroscopically lesioned areas on both hemispheres, were sampled for microscopic examination (9). All of the cases examined were submitted to neuropathological examination, according to standard protocols (9). Immunohistochemistry was performed using antibodies against β-amyloid (4G8; 1/5,000; Signet Laboratories, Dedhan, MA), phospho-tau (PHF-1; 1/1,000; gift of Peter Davies, New York, NY), and α-synuclein (EQV-1; 1/10,000; gift of Kenji Ueda, Tokyo, Japan). If frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP) was suspected, immunostaining for TDP-43 (1/500; ProteinTech, Chicago, IL) was performed. In cases with undefined neuropathological diagnoses after standard assessment, additional immunostaining for TDP-43 and ubiquitin was performed. All of the sections were submitted to antigenic retrieval in a steamer. The signals were detected using the Vectastain ABC Kit (Vector Laboratories, Burlingame, CA).

Neuropathological analyses

Neuropathological examinations were performed in a blinded manner, and neuropathological diagnoses were made by two experienced neuropathologists following internationally accepted guidelines (9). The Consortium to Establish a Register for Alzheimer's disease (CERAD) criteria were used to classify the β-amyloid neuritic plaque burden as scarce, moderate, or frequent. The distribution of neurofibrillary tangles (NFTs) was classified according to the Braak and Braak staging system (9). The neuropathological

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Table 1 - Means of demographic data and scores on informant questionnaires.

	Total (N = 113)	Men (N = 42)	Women (N = 71)	*p*-value*	Controls (N = 113)	*p*-value **
Age of death (years)	78.3 (9.7)	75.1 (10.5)	80.7 (7.9)	0.002†	77.7 (8.8)	0.36†
Education (years of schooling)	3.1 (3.3)	3.3 (2.9)	2.6 (3.0)	0.246†	3.5 (3.0)	0.12†
Caucasians (%)	47 (66.2)	31 (73.8)	81 (72.3)	0.395#	78 (70.3)	0.44#
CDR (sum of boxes)	13.1 (4.6)	15.0 (2.8)	15.8 (2.4)	0.135†	0.08 (0.24)	<0.001†
IQCODE	4.3 (0.5)	4.5 (0.5)	4.6 (0.4)	0.275†	3.0 (0.05)	<0.001†
Number of individuals with CDR 2/3	42/71	19/23	23/48	0.227#	-	

*: comparison between sexes within the dementia group.
**: comparison between the dementia and control groups.
†t-test; #: chi-square test.
CDR: Clinical Dementia Rating.
IQCODE: Informant Questionnaire on Cognitive Decline of the Elderly.

diagnosis of AD was made in cases that showed at least Braak stage III and CERAD moderate (2). The usual neuropathological guidelines were used for other dementias and for Parkinson's disease (9).

Microvascular changes were analyzed semi-quantitatively using H&E staining in all of the sampled structures. The presence of diffuse small-vessel disease (SVD) in the white matter, of hippocampal sclerosis, and of lacunae, micro-infarcts, and infarcts were registered. Cerebral amyloid angiopathy (CAA) was verified using anti-β amyloid immunostaining. The diagnosis of VaD was made in cases with one large chronic infarct (>1 cm) or three lacunae in strategic areas (thalamus, frontocingular cortex, basal forebrain and caudate, medial temporal area, and angular gyrus) (12).

SVD was diagnosed when there was widespread and at least moderately severe SVD in three cortical regions. SVD included small-vessel arteriosclerosis/atherosclerosis, arteriolosclerosis, and lipohyalinosis (13). CAA was not included in the SVD group.

Cases were classified as positive for CAA when CAA was found diffusely in the parenchyma of at least three different cortical areas. In this study, SVD and pure CAA were not considered sufficient for the diagnosis of VaD because the literature remains unclear regarding vascular dementia diagnosis in cases with no obvious parenchymal lesions. Dementia cases in which SVD was the only finding were classified as ''undefined diagnosis''.

Statistical analyses

Relative frequencies of AD, VaD, and AD+VaD were measured as total numbers and were also divided by sex, age, and educational level. Age and years of schooling were divided into two groups: greater than or equal to the median and less than the median. The chi-square test or Fisher's exact test, when appropriate, was used for categorical variables. Student's t-test was used for quantitative variables. Logistic regression analysis was employed to evaluate the association of SVD with dementia, adjusted for age, sex, and schooling. SPSS (version 17; Statistical Package for the Social Sciences, Chicago, IL) was employed, and the value of significance was accepted as a *p*-value less than 0.05 in two-tailed tests.

RESULTS

Demographics and dementia subtypes

Dementia was diagnosed in 189 cases (14.6% of the 1,291 cases added to the BBBABSG collection over the collection period), of which 131 cases had a CDR score ≥2. Of these 131 cases, 113 were suitable and available for processing (113/131; 86.6%) and were included in the analyses. The mean age was 78.9 (±9.5) years old, and 37.2% were male. The dementia and control group demographics are shown in Table 1.

Neuropathological diagnosis

Neuropathological examinations confirmed that 55 subjects (48.7% of the dementia group) met the criteria for AD (Table 2). ''Pure'' AD was found in 30 of the subjects, whereas 10 subjects had AD associated with other diseases: Lewy body disease (LBD; five cases); argyrophilic grain disease (AGD; four cases); and one case with Pick's disease. Another 15 cases met the neuropathological criteria for both AD and VaD (13.3%).

Thirty-nine cases fulfilled the criteria for VaD (34.5%). ''Pure'' VaD was diagnosed in 21 subjects. In three subjects, VaD was associated with other neurodegenerative diseases (AGD in two cases and dementia with tangles in one case). In the remaining 15 subjects, VaD was associated with AD, as described previously.

A diagnosis of definite AD was more frequent in women, whereas VaD was more frequent in men (Table 2). AD associated with VaD was equally represented in both sexes. VaD was more frequent in younger individuals, but AD associated with VaD was more prevalent in older individuals. Definitive AD showed the same frequency in both age groups. No difference in the relative frequencies of these diseases was found regarding years of schooling (Table 2).

Table 2 - Relative frequencies of Alzheimer' disease (AD), vascular dementia (VaD), and AD associated with VaD (AD+VaD) according to sex, age, and education.

	AD		VaD		AD+VaD	
Sex						
Male	7	*p* = 0.002	15	*p* = 0.007	5	*p* = 0.6
Female	33		9		10	
Age (years)						
<80	18	*p* = 0.6	18	*p* = 0.009	3	*p* = 0.024*
≥80	22		6		12	
Years of Schooling						
<3	20	*p* = 0.6	11	*p* = 0.9	8	*p* = 0.7
≥3	20		13		7	

*Fisher's exact test.

Other defined causes of dementia were found in 16 cases (14.1%). Nine of these cases had tauopathies (five had AGD, and the other cases had Pick's disease, progressive supranuclear palsy, dementia with tangles, and unclassifiable tauopathy). Five subjects had LBD (two also had AGD), and two had FTLD-TDP.

In 18 cases (15.9%), the diagnosis remained undefined following neuropathological examinations. Had widespread SVD been considered sufficient for a diagnosis of VaD, seven of them would have been classified as having VaD. This classification would have increased the prevalence of VaD from 34.5% to 40.7%. Another two cases had AD-related neuropathology, but it was not sufficient for a formal AD diagnosis. Of the remaining nine, review of the informants' reports disclosed that two of the individuals had been heavy drinkers and might therefore have developed alcohol-associated dementia, a condition that is difficult to diagnose neuropathologically. For the remaining seven cases, we could not identify other causes for the absence of neuropathological changes that would explain dementia.

Upon neuropathological examination of the control group, 73 (64.6%) individuals did not meet any criteria for neurodegenerative or cerebrovascular disease. The neuropathological criteria for AD were met in 19 cases (16.8%). Of these, 14 had ''pure'' AD, and three also showed VaD pathology. An additional four cases fulfilled the criteria for VaD. Thirteen individuals (11.5%) had AGD, three (2.6%) had LBD, and one (0.9%) had corticobasal degeneration.

SVD was present in 44 cases with dementia (38.9%), and these cases were associated with infarcts in 19 cases. SVD was present in 27.5% of the cases with the clinicopathological diagnoses of AD, 41.7% of the cases with VaD, 60.0% of the cases with AD plus VaD, 31.2% of the cases with other dementias, and 50.0% of the cases with undefined clinicopathological diagnoses. In the control group, 19 cases (16.8%) had SVD, which was associated with infarcts in four of these cases. Therefore, there was a significantly greater proportion of cases with dementia showing SVD, compared with the controls, even after adjustment for age, sex, and education (OR = 2.91 [95% CI, 1.53-5.51]; $p = 0.001$)

Clinicopathological correlations

The clinical and neuropathological diagnoses are depicted in Table 3.

The clinical diagnosis of AD (including cases with AD and VaD pathologies) had sensitivity of 70.9% and specificity of 44.8%. The clinical diagnosis of possible VaD (including cases with AD pathology) had sensitivity of 43.6% and specificity of 70.3%.

DISCUSSION

In our study, the percentage of individuals with a definite neuropathological diagnosis of AD, including AD associated with other diseases (except for VaD), was the lowest (35.4% of subjects with moderate to severe dementia) compared with other clinicopathological studies, in which the AD prevalence ranged from 41.6% to 65% (8,12,14-19). In contrast, the prevalence of pathologically confirmed VaD (21.2%) and VaD associated with AD (13.3%) in our study was at the higher end of other reported rates, which ranged from 2.4% to 23.7% and from 4.1% to 21.6%, respectively (8,12,14-19). Several factors could have contributed to these differences, such as the use of different pathological criteria, case-selection bias, and genetic and environmental differences between the populations.

The neuropathological criteria we used might have decreased the sensitivity and increased the specificity of AD diagnosis. Several other studies have adopted criteria based solely on the presence of amyloid plaques, such as the Khachaturian criteria, which show very high sensitivity and low specificity (20), or the CERAD criteria alone. There is evidence that the presence of neocortical NFTs is more closely correlated with cognitive decline than the amyloid plaque burden or distribution (21). This correlation was also verified in the present study and in two other population-based studies (22,23), in which the rates of neuropathological AD in the non-demented groups were 9.6%, 7.4% (23), and 21.9% (22), respectively, using the CERAD criteria plus Braak stage, compared with 12.5%, 33.0% (23), and 54.8% (22), respectively, using the CERAD criteria alone.

No generally accepted neuropathological criteria for VaD have been established thus far, and each center has adopted its own criteria. Even the nature of the cerebrovascular lesions believed to cause cognitive decline varies considerably (13,23). In addition, it is now clear that the amount of brain destruction required to cause dementia is smaller than was previously appreciated (13,25). We used conservative criteria because only cases with large chronic infarcts or lacunar or microinfarcts in strategic areas were diagnosed with VaD. Had isolated, but widespread, SVD been considered part of our criteria, the proportion of VaD diagnosed in our series would have been even greater.

The proportion of individuals with LBD (4.4%), including Parkinson's disease and dementia with Lewy bodies, was similar to that in some studies (12,15), although much higher rates (more than 20%) have also been reported.

The high prevalence of VaD or AD plus VaD found in the present study might reflect the limited access of the study population to basic healthcare, particularly for arterial hypertension and hypercholesterolemia, as well as poor

Table 3 - Clinical and neuropathological diagnoses of the dementia group (n = 113).

Clinical diagnoses	Neuropathological diagnosis					Total
	AD	VaD	AD plus VaD	Other dementias	Undefined	
AD	24	9	9	4	6	52 (46.0%)
VaD	5	5	3	5	2	20 (17.7%)
AD plus CVD	3	6	3	1	6	19 (16.8%)
Other dementias	4	1	0	3	1	9 (7.9%)
Undefined	4	3	0	3	3	13 (11.5%)
Total	40 (35.4%)	24 (21.2%)	15 (13.3%)	16 (14.2%)	18 (15.9%)	113 (100.0%)

AD: Alzheimer's disease; CVD: cerebrovascular disease; VaD: vascular dementia.

control of other risk factors for cerebrovascular disease and vascular cognitive impairment (25). However, low educational level was not associated with a higher frequency of VaD in this study, although we found that VaD was more frequent in men. Additionally, in the younger individuals, AD was more frequent in women, and AD associated with VaD was more frequent in older individuals.

In addition, other factors might have contributed to the high proportion of VaD. The Brazilian population is highly mixed genetically, mainly due to historical waves of immigration from Africa, Europe, and Asia. In a recent genetic study, performed using a random sample of 202 BBBABSG cases, 102 (55.4%) had significant African ancestry, and it was also shown that African ancestry might be protective against AD neuropathology (26).

From a clinical standpoint, we detected relatively high sensitivity and low specificity for the clinical diagnosis of AD. High sensitivity and low specificity in the clinical diagnosis of AD with the NINCDS-ADRDA criteria was reported in a study that involved 31 US academic medical centers (15). In contrast, we found low sensitivity and relatively high specificity for the diagnosis of VaD (either ''pure'' or associated with other diseases). Low sensitivity of the clinical criteria for VaD has been found in similar population-based studies (27,28), particularly those using the NINDS-AIREN criteria, the same criteria adopted in the present study. These findings support the hypothesis that the true frequency of VaD is greater than usually detected clinically. In contrast, we and others have adopted conservative neuropathological criteria for VaD (27), and this choice could have contributed to the low sensitivity of the clinical criteria.

Interestingly, SVD was detected more frequently in cases with dementia than in the control group, even after adjustment for age of death, sex, and education. It is also noteworthy that SVD was frequently present in cases of dementia with undefined pathological diagnoses, suggesting that SVD might have been the neurobiological basis of the cognitive loss. Microvascular injury, with no clear parenchymal destruction, worsens cognition if present in strategic regions (13). Indeed, in some brain samples from individuals with dementia, microvascular injury has been as common as Alzheimer-type pathology (8,13). Although most of the published population-based clinicopathological studies have not provided information on microvascular injuries, evidence has shown that the burden of cerebral amyloid angiopathy, a common finding in AD, is correlated with white matter changes, suggesting that both processes could share pathophysiological mechanisms (29).

More than one-third of our control group met the criteria for neurodegenerative disease. The cause might have been the high number of control subjects with argyrophilic grain disease. Although these conditions seem to be rather protective, or at least benign, in most of the cases (30), they are still considered part of the neurodegenerative disease spectrum (31). Neuropathological diagnoses were made blinded to clinical status. The frequencies of AD and VaD in the control group were similar to those reported in the literature (32,33).

One limitation of the present study was the means of sample procurement because death caused by cardiovascular conditions was significantly more frequent in individuals who died after the age of 50 years old and who underwent autopsy, compared with those who did undergo an autopsy (data unpublished). This difference most likely occurred because death caused by an acute event, such as cardiac arrest, was more likely to require an autopsy. This over-representation of cardiovascular conditions might have increased the frequency of cerebrovascular lesions in both groups (those with dementia and the controls), but it should be emphasized that cerebrovascular lesions and SVD were much more frequent in the group with dementia. In contrast, individuals with acute stroke were excluded from our study because cases with macroscopically detectable acute brain infarctions, hemorrhages, or trauma could not be included in the BBBABSG, as an immediate examination was required for the completion of the death certificate. This fact might have decreased the frequency of VaD in our sample. Unfortunately, shortcomings in case selection have been found in all the population-based studies on dementia. For instance, 48% of the first 209 subjects submitted to autopsy in the CFAS study had dementia, a much higher proportion than the general population in this age group (24), whereas the Honolulu study only recruited subjects of Japanese ethnicity (34).

The absence of ante mortem examination of the cases included in the present study was an obvious limitation. We attempted to compensate for this limitation by using a semi-structured protocol with several questionnaires and the CDR scale, which were applied by trained interviewers to informants who were close to the deceased study subjects (9). The CDR scale is mostly an informant-based questionnaire, and a former study reported that informant CDR scores showed good agreement with clinician CDR scores (35). In addition to these precautions, we only included cases with moderate or severe dementia (CDR≥2) to reduce the possibility of a misdiagnosis of dementia. In a previous study (36), we prospectively compared the sensitivity and specificity of our protocol applied to informants of living patients with the diagnosis established in our memory clinic, where the same patients were submitted to full assessments. The sensitivity was 86.6%, and the specificity was 84.4% for the diagnosis of dementia, but both reached 100% for cases with CDR≥2. For the diagnosis of normal cognition, the sensitivity was 65.3%, whereas the specificity was 93.7%.

In conclusion, we postulate that the lack of appropriate control of risk factors for circulatory diseases, combined with the genetic particularities of our population, might have been the main causes of the high prevalence of VaD, AD plus VaD, and SVD in this sample. These factors might also apply for other developing countries and even for developed countries with high frequencies of VaD, particularly in which the clinical control of vascular risk factors is inadequate. Our findings are readily applicable to public health initiatives because this high frequency of vascular pathology could be preventable, and it represents a valuable therapeutic target for postponing the onset of dementia, thus decreasing its prevalence.

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AUTHOR CONTRIBUTIONS

Grinberg LT and Nitrini R contributed equally to this study. Grinberg LT contributed to the study design, pathological examination, and writing of the manuscript. Nitrini R contributed to the study design, clinical diagnosis, and writing of the manuscript. Suemoto CK contributed to the study design, clinical data collection, and writing of the manuscript. Ferretti RE contributed to the study design, clinical data collection, clinical diagnosis, and writing of the manuscript. Leite RE and Farfel JM contributed to the study design, clinical data collection, and writing of the manuscript. Santos E, Lima MC, Tampellini KC, Polichiso L, and Santos GB contributed to the clinical data collection. Andrade M, Rodriguez-Diehl R, and Ueda K contributed to the pathological examination. Alho AT contributed to the clinical data collection and immunohistochemistry. Pasqualucci CA and Jacob-Filho W contributed to the study design and writing of the manuscript.

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