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Clinical and autonomic profile of patients with Alzheimer's disease and mixed dementia[☆]

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Objective: To analyze the clinical and autonomic profile of patients with Alzheimer's disease or mixed dementia (MD).

Methods: Fifty-four patients with indication for cholinesterase inhibitors use were evaluated through clinical examination, rest electrocardiogram, and spectral analysis of heart rate (HR) variability through digital Holter system recordings.

Results: Overall, 61.1% of patients were females and were, on average, 77.1 years of age, had 3.3 years of schooling, and scored 16.4 points on the Mini Mental State Examination. The gap between symptom onset and diagnosis was 26.2 months. Almost all patients (90.7%) presented at least one clinical comorbidity, and each patient took, on average, 3.7 drugs to control them. Thirty-one patients had some alteration on the electrocardiogram, and nine (16.6%) had orthostatic hypotension (OH). The latter was associated with the diagnosis of MD ($p = 0.001$), with lower values of low (LF) and high (HF) frequency components of the spectral analysis in the supine position ($p = 0.000$ and $p = 0.017$, respectively), and with lower values of LF in the orthostatic position ($p = 0.006$). Diagnosis of MD was associated with lower values of LF in both positions ($p = 0.003$ and $p = 0.007$).

Conclusion: This sample of patients had frequent comorbidities, which resulted in the prescription of multiple drugs. Signs of autonomic dysfunction resulting in OH were found mainly in those with MD.

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Perfil clínico e autonômico de pacientes com doença de Alzheimer e demência mista

R E S U M O

Palavras-chave:

Doença de Alzheimer
Sistema nervoso autônomo
Hipotensão ortostática

Objetivo: Analisar o perfil clínico e a atividade autonômica de pacientes com diagnóstico de doença de Alzheimer ou demência mista (DM).

Métodos: Foram avaliados 54 pacientes com indicação de uso de inibidores da colinesterase, por meio de exame clínico, eletrocardiograma de repouso e da análise espectral da variabilidade da frequência cardíaca (VFC).

Resultados: A casuística estudada, constituída por 61,1% de mulheres, apresentava média de 77,1 anos de idade, 3,3 anos de escolaridade, pontuação de 16,4 no miniteste do estado mental e intervalo médio de 26,2 meses entre o início dos sintomas e o diagnóstico. A quase totalidade (90,7%) apresentava comorbidades, com o uso, em média, de 3,7 drogas/paciente. Trinta e um (57,4%) pacientes apresentavam alterações eletrocardiográficas e nove (16,6%), hipotensão ortostática (HO). Esta apresentou associação com o diagnóstico de DM ($p = 0,001$) e com valores mais baixos dos componentes de baixa (BF) e de alta (AF) frequência da VFC na posição supina ($p = 0,000$ e $p = 0,017$), além de valores médios menores de BF em ortostatismo ($p = 0,006$). O diagnóstico de DM se associou a menores valores de BF nas duas posições ($p = 0,003$ e $p = 0,007$).

Conclusão: Na amostra estudada, a presença de comorbidades e o uso de vários fármacos foram frequentes. Foram observados sinais de disfunção autonômica, resultando em HO, principalmente nos pacientes com DM.

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Introduction

The term dementia refers to an acquired clinical syndrome characterized by a group of signs and symptoms expressed by memory difficulties, language disorders, behavioral alterations, and deficits in activities of daily living.¹ The most common causes are Alzheimer's disease (AD) – accounting for 60% to 70% of the cases² – vascular dementia (VD), and mixed dementia (MD), which is the combination of lesions resulting from the first two.³

The estimated overall prevalence of dementia is approximately 5% of those aged 65 or older,⁴ and a prevalence of 7.1% was found in a Brazilian study.⁵ It was estimated that, in 2005, there were approximately 24.3 million patients with dementia worldwide, a figure that could reach 81.1 million in 2040,⁶ and 114 million in 2050.⁷ The annual treatment costs range between U\$ 24.7 billion¹ and U\$ 83.9 billion⁸ in some countries, and personal costs (both for patients and for caregivers) and life years lost should also be taken into account.¹

The diagnosis is attained by associating the clinical assessment to cognitive function tests and the differential diagnosis with other conditions. The cognitive function assessment often consists of the Mini Mental State Examination (MMSE) and tests for specific cognitive domains (e.g., memory and executive functions), when indicated.⁹

Healthy elderly individuals, due to degenerative alterations characteristic of the aging process, have increased prevalence of falls and other forms of neurovascular instability. This picture becomes more pronounced in the elderly with dementia, as degenerative alterations are more prominent and there is greater impairment of the structures involved in the autonomic nervous system (ANS) control.¹⁰

One way to study the ANS activity is through spectral analysis of heart rate variability (HRV), in which the variation of the interval between successive heart beats originates high and low frequency (HF and LF) bands, reflecting activation of the sympathetic and parasympathetic branches, respectively, in addition to allowing for the study of sympathovagal balance, through their ratio¹¹ (LF/HF).

Comparing the incidence of fall-related injuries in healthy elderly individuals and AD patients, an odds ratio of 6.4 was observed for these injuries in individuals with the disease.¹² A prevalence of neurovegetative instability was also observed in 57% of patients with AD, i.e., orthostatic hypotension (OH), vasovagal syncope, and carotid sinus hypersensitivity.¹³

Several studies have been performed to assess the ANS functioning in AD and, in general, although the results are not fully in agreement, they are consistent with the presence of autonomic dysfunction. Aharon-Peretz et al.¹⁴ demonstrated exacerbation of the sympathetic system with relative depression of the parasympathetic system, while Vitiello et al.¹⁵ found a deficit of blood pressure response to the orthostatic position test in patients with AD.

Another study demonstrated a decrease in parasympathetic function at rest and during deep breathing, as well as a preserved sympathetic response.¹⁰ Ferini-Strambi et al., studying HRV during sleep, found no change in vagal tone, but observed sympathetic dysfunction in over one third of patients with AD.¹⁶ Two studies from the same group of British researchers initially showed no difference between AD patients and control groups regarding the spectral analysis of HRV.¹⁷ Subsequently, using other tools in addition to HRV to assess dysautonomia, the authors found a greater decrease in blood pressure (BP) during orthostasis in AD patients when compared

to controls, concluding that, apart from a higher prevalence of OH, patients with AD have relatively preserved autonomic function.¹⁸

In the scientific literature analyzed, the only study performed in a Brazilian population to assess the matter demonstrated a decrease in parasympathetic influence and relative sympathetic exacerbation in a group of 22 patients with AD. An increase in LF/HF ratio was observed in the supine position, indicating the sympathetic predominance in sympathovagal balance.¹⁹

The first cholinesterase inhibitor (ChEI) was approved in Brazil for the treatment of AD in 1994; those most often used in the present were introduced in the market in 1998, 2000, and 2001.²⁰ Since these drugs have been introduced relatively recently in the market and are intended for use predominantly by the elderly – in whom the presence of comorbidities and polypharmacy is very common –, there is a great interest in studying the clinical profile and behavior of the ANS of the population to whom they are prescribed.

The present study aimed to analyze the clinical and ANS profile in patients with AD and MD who received an indication for ChEI use.

Methods

This was a prospective, observational, cross-sectional study of 54 patients diagnosed with AD or MD, who were treated at the outpatient clinics of Cognitive Neurology and Geriatrics from the Hospital das Clínicas of the Universidade Federal de Minas Gerais (UFMG), and who had received an indication for ChEI use.

Sample size calculation was conducted aiming to perform a longitudinal study to investigate the influence of ChEI on the autonomic profile in patients with AD or MD. For that purpose, the standard deviation of the high-frequency component of spectral analysis in the general population, the difference of at least 200 ms² to be detected, and a power of test of 90%, with a significance level of 5%, were used for a one-tailed test. Thus, an estimate of 34 patients was obtained and, considering a ratio of 50% possible discontinuity due to adverse effects of the drug, the value obtained was of a minimum of 50 patients.

Patients were included in the study after a diagnosis of probable mild to moderate AD, according to the NINCDS-ADRDA criteria,²¹ or AD with cerebrovascular disease (i.e., MD), according to the NINDS-AIREN criteria.²² For that purpose, the patients were submitted to extensive cognitive assessment that included the MMSE,^{23,24} functional evaluation through the Pfeffer questionnaire,^{25,26} the clock test,^{27,28} the picture memory test,²⁹ the CERAD word list,³⁰ biochemical tests (blood count, serum electrolytes, thyroid function, vitamin B12, among others), and neuroimaging (CT or MRI).

Both the research project and the informed consent were approved by the Research Ethics Committee of UFMG. Patients were invited to participate in the study when they were treated at the clinic, and the inclusion was performed consecutively. Patients with severe dementia and who were clinically unstable at the time of evaluation, in addition to those with conditions that might interfere with or prevent the interpretation of HRV,

such as atrial fibrillation, cardiac pacemaker rhythm, and use of antiarrhythmic drugs, except beta blockers, were excluded.

After acceptance to participate and signature of the informed consent by the patient or caregiver responsible (in case of patients with marked cognitive impairment), patients underwent clinical evaluation and a 12-lead electrocardiogram (ECG) assessment and digital monitoring by Holter system, in the morning.

The ECG was performed with a Philips equipment, model Pagewriter Trim III (Philips Medical Systems – USA) at a speed of 50 mm/s and an amplitude of 20 mm/mV. Holter monitoring was performed using a Cardioflash[®] digital multi-cardiographer, three-channel model (modified V1 and V5 and D3), version 1.0, in the supine and orthostatic position during a period of 15 and 10 minutes, respectively, for HRV analysis. The latter was performed using the DMI/Burdick Holter analysis program (ALTAIRPC v6.00B Holter System), evaluating the spectral analysis, i.e., assessing the frequency domain by Fourier transformation, allowing measurements of the LF, HF components, and LF/HF ratio. The evaluation of such components was made after strict manual editing of the records, with artifact elimination and arrhythmia correction. The results of the spectral analysis were expressed in milliseconds squared (ms²).

Data analysis was carried out using the Statistical Package for the Social Sciences (SPSS), 12.0 version. The results were expressed in numbers and proportion, in the case of discrete variables, and as measures of central tendency (mean and median) and dispersion for continuous variables. The Mann-Whitney and Chi-squared or Fisher's tests were used, when appropriate, to compare the differences between continuous and discrete variables, respectively. Spearman's coefficient was used to verify the correlations between variables. The level of rejection of the null hypothesis was set at 0.05.

Results

General sample characteristic

The mean age of patients was 77.1 ± 7.3 years (range 54-89), 33 (61.1% of the sample) were females and 21 males; mean level of schooling was 3.3 ± 2.4 years. Thirty-nine patients had probable AD and 15 had probable MD, whose mean score at the MMSE was 16.4 ± 5.0 points. There was a mean interval of 22.6 months between symptom onset and diagnosis. Family history of dementia was detected in 22 patients (40.7%).

Regarding comorbidities, only five patients (9.2%) had no clinical comorbidities and received psychotropic drugs only to control the behavioral changes related to dementia. Among the others, the most frequent comorbidities were hypertension (62.9%), depression (20.3%), diabetes mellitus (16.7%), osteoporosis (9.2%), prostatic hyperplasia (9.2%), epilepsy (7.4%), chronic obstructive pulmonary disease/asthma (7.4%), hypothyroidism (7.4%), and chronic renal failure (5.5%).

For the management of these comorbidities, patients received therapeutic regimen with other drugs, on average, 3.7 drugs each. Thirty-five patients (64%) used antihypertensive

Table 1 – Heart rate and blood pressure levels of the studied patients.

Variables	Mean	SD	Minimum value	Maximum value
HR (bpm)	70.4	11.8	48	108
Supine SBP (mmHg)	146.4	24.2	102	212
Supine DBP (mmHg)	80.0	9.2	58	102
Orthostatic SBP (mmHg)	145.5	23.6	106	214
Orthostatic DBP (mmHg)	79.0	12.4	46	108

bpm, beats per minute in the supine position; DBP, diastolic blood pressure; HR, heart rate; mmHg, millimeters of mercury; SBP, systolic blood pressure; SD, standard deviation.

drugs, of whom 13 received beta-blockers and 16 received angiotensin-converting enzyme inhibitors; hypoglycemic agents were used by seven patients, and psychotropic drugs – which included antidepressants, antipsychotics and especially benzodiazepines – were used by 32 patients (59%).

The therapeutic regimen of five patients consisted of only one drug, 33 used between two to four drugs, and 16 used more than four drugs, including two patients using eight drugs each.

Clinical examination and orthostatic hypotension test

Clinical examination showed that nine (16.6%) patients had OH, defined as a decrease of at least 20 mmHg in systolic blood pressure (SBP) and/or 10 mmHg in diastolic blood pressure (DBP) after three minutes in the orthostatic position.³¹ The clinical data of the study population are shown in Table 1.

When analyzing the association between the presence of OH and clinical variables such as gender, age, anthropometric data, time since dementia diagnosis, family history of dementia, and type of dementia, a significant association was observed only with the latter. Among patients with OH, seven patients (46.6%) had MD and two patients (5.4%) had AD ($p = 0.001$). After applying Spearman's correlation coefficient, the value 0.50 was obtained ($p = 0.000$) between these two variables.

Electrocardiogram

The ECG showed sinus rhythm in 50 patients; two were in atrial fibrillation, one had low atrial rhythm, and another patient had atrial flutter with a 4:1 atrioventricular conduction. Mean heart rate (HR) was 68.9 ± 14.4 bpm, ranging from 34 to 123 bpm. The electrocardiographic tracings of 23 patients showed no significant alterations, while the remaining 31 patients had electrocardiographic alterations, which are summarized in Table 2.

Autonomic nervous system

Table 3 shows the values found when evaluating the ANS of 50 patients in sinus rhythm through spectral analysis, in the supine and standing positions. This table also shows

Table 2 – Electrocardiographic abnormalities detected.

ECG alteration	Number of patients
Left ventricular hypertrophy (Sokolow-Lyon index)	9
Left anterior-superior division block	7
Isolated ventricular extrasystoles	6
Nonspecific ventricular repolarization	5
First-degree atrioventricular block	5
Isolated atrial extrasystoles	5
Repolarization with pressure overload	3
Electrically inactive area	3
Anterolateral subepicardial ischemia	2
Complete left bundle branch block	2
Incomplete left bundle branch block	1
Complete right bundle branch block	1
Left atrial overload	1
Coupled atrial extrasystoles	1
Junctional extrasystole	1

ECG, electrocardiogram.

the statistical treatment using the Wilcoxon test, comparing the values of LF and HF components and their association with change in position. Logarithmic conversion was also performed, maintaining the same p-values.

There was no association between the spectral analysis components and gender. However, there was an association between this spectral analysis and the two types of dementia. MD patients had a lower mean LF component in the supine position compared to AD patients (137.2 ms^2 vs. 385.1 ms^2 , $p = 0.003$), as well as lower mean LF component in the orthostatic position (124.8 ms^2 vs. 426.7 ms^2 , $p = 0.007$). Regarding the HF component in the orthostatic position, the difference was borderline significant ($p = 0.055$).

The spectral analysis between patients without and with OH showed lower values of the LF (360.3 ms^2 and 26 ms^2 , respectively, $p = 0.000$) and HF ($1,206.7 \text{ ms}^2$ and 72.6 ms^2 , $p = 0.017$) components in the supine position in the second group. There was also mean lower LF component in the orthostatic position in that group (383.0 ms^2 vs. 57.1 ms^2 , $p = 0.006$), with no significant difference in LF/HF ratio in both positions.

Discussion

Based on the results obtained, it appears that the studied sample was representative of the population for whom ChEI is routinely indicated, with a slightly higher prevalence of women (61.1%), as observed in a systematic review of Latin American population studies.³² This figure is almost identical to that found in a Spanish study, whose population of 1,940 patients was composed by 62% of women.³³ The same study found a mean age of 77 years, which is the same observed in the present sample.

The mean score in the MMSE was within the range recommended for ChEI prescription,³⁴ but it was slightly lower than that found in a study by Froelich et al.³⁵ (19.7 points), possibly due to the lower educational level of the present

Table 3 – Spectral analysis of the autonomic nervous system of the patients in the supine and orthostatic positions.

Supine position (mean ± SD)		Orthostatic position (mean ± SD)		p
LF (ms ²)	319.3 ± 398.2	LF (ms ²)	339.5 ± 514.8	0.758
HF (ms ²)	1067.8 ± 3754.4	HF (ms ²)	388.0 ± 1146.7	0.055
LF/HF	1.8 ± 2.1	LF/HF	3.2 ± 2.9	0.024
Recording time (min)	4.6 ± 0.6	Recording time (min)	4.4 ± 0.9	

HF, high-frequency component; LF, low-frequency component of heart rate variability; SD, standard deviation.

population. In the same German population study, the mean duration of symptoms until the start of therapy was 15.8 months, significantly lower than that found in the present study (26.2 months). This is probably due to the difficulty in having access to appropriate treatment in the Brazilian public health system and to the lack of knowledge of the population about dementia symptoms and the existence of treatment.

The percentage of patients who reported a positive family history for dementia was quite similar to that found by Zintl et al., whose study demonstrated that 39.5% of the 210 assessed patients had such history.³⁶

Another important finding is related to the high prevalence of medical comorbidities, mainly hypertension, depression, diabetes mellitus, and hypothyroidism. These findings are consistent with those observed in a German population study in which 90% of the population had a clinical comorbidity, with a high prevalence of cardiovascular disorders in 53%, mental disorders in 27%, and endocrine-metabolic disorders in 27%.³⁵ Among the population studied by the latter authors,³³ 86% used other drugs (57% cardiovascular drugs and 40% psychotropic drugs), and these values are consistent with the present findings. The number of drugs used for the treatment of comorbidities was slightly lower than that observed in other studies, whose results vary from 5.1 to 5.8 drugs/patient.^{37,38}

Nevertheless, it is emphasized that the routine use of other drugs in treatment regimens, which in the population studied comprised the use of up to eight drugs, raises the question of potential drug interaction dangers.³⁹

The ECG showed the presence of significant alterations in some patients, which is consistent with the findings of a clinical trial with rivastigmine.⁴⁰ Some of these alterations are considered as relative contraindications to the use of ChEI (such as atrioventricular block and complete bundle-branch block). For this reason, some specialists consider it prudent to request an electrocardiogram before prescribing the anticholinesterase therapy.^{1,41,42}

The OH prevalence found in this population is consistent with those found in the studies by Ballard et al. and by Mehrabian et al., in which 14% of patients with dementia had OH.^{13,43} The finding of an association between MD and OH can be justified by the fact that these patients have, in addition to vasomotor center lesions resulting from AD, additional impairment of vascular origin. This is consistent with studies that showed a higher prevalence of autonomic dysfunction¹⁸ and OH^{43,44} in VD compared to AD. Thus, although there were no studies in the literature that specifically evaluated MD in this regard, it is possible to infer that the vascular origin component of cognitive impairment is accompanied by ANS

impairment. Accordingly, it has been shown that cognitive impairment and BP alterations mutually influence each other, i.e., neurodegenerative dementia processes lead to BP instability and alterations in cerebral perfusion can worsen brain lesions, consequently leading to cognitive impairment.⁴³

There was a significant association between the presence of OH and lower values of LF and HF components in the spectral analysis in the supine position, and of LF in the orthostatic position. This may represent a causal association between ANS imbalance and prevalence of neurovascular instability of up to six times higher in patients with dementia,¹³ as well as an increased risk of falls.⁴⁴

The ANS behavior during postural change showed no alteration in the isolated components with the orthostatic position, as observed in healthy subjects. There was a slight increase in LF and decrease in HF, both with no statistical significance, but a significant increase in LF/HF ratio, indicating the sympathetic predominance necessary to maintain BP on active orthostatic stress.

These results are consistent with others reported in literature that show only borderline alterations in the ANS of dementia patients,^{18,19} in this case, represented by non-significant alterations in the individual components of HRV with the maintenance of sympathetic predominance in the orthostatic position.

The main limitation of the present study was the relatively small sample size and the sample heterogeneity that, although fitting the purpose of representing the population attended to at the daily clinical practice, makes it difficult to draw more specific conclusions. There was no information regarding ion measurements and renal function, which may result in ECG changes, but all patients were stable from the clinical standpoint at the time of their assessment.

Conclusion

The profile of the patients in this study showed a predominance of the female gender, low educational level, and frequent presence of comorbidities, resulting in the concomitant use of several drugs. There was a long interval between symptom onset and diagnosis of dementia. An autonomic dysfunction picture was observed, resulting in orthostatic hypotension, mainly in patients with MD.

These findings indicate the need to strive for earlier diagnosis and provide more explicit and accessible information to ensure proper understanding of the treatment. Additionally, greater caution is necessary when prescribing drugs that act on

the ANS and the use of ChEI, in order to minimize undesirable drug interactions and decrease the risk of falls.

The study was approved by the Ethics Committee of UFMG on September 19, 2008, under No. 401/08.

Conflicts of interest

Paulo Caramelli received financial support from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG); he is a member of the Editorial Board of the scientific journals (with no grant) *Arquivos de Neuro-Psiquiatria*, *Dementia & Neuropsychologia*, *Journal of Alzheimer's Disease*, and *Revista da Associação Médica Brasileira*; he has given lectures for the following pharmaceutical companies: Janssen-Cilag, Moksha8, Novartis, Pfizer, and was a consultant for Janssen-Cilag.

The other authors declare to have no conflicts of interest.

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