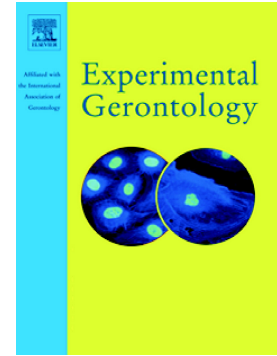


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A COMPARISON OF THE PREVALENCE OF ORTHOSTATIC HYPOTENSION BETWEEN OLDER PATIENTS WITH ALZHEIMER'S DISEASE, LEWY BODY DEMENTIA, AND WITHOUT DEMENTIA

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ABSTRACT (250/250)

Orthostatic hypotension (OH) is reported to be more prevalent particularly in patients with Dementia with Lewy bodies (DLB) because of the autonomic dysfunction, but prevalence of OH is not known in patients with Alzheimer Disease (AD). The aim of the present study was to determine whether OH can be used to distinguish DLB from AD. 38 patients with DLB, 88 patients with AD and 521 patients without dementia, underwent Comprehensive Geriatric Assessment. OH were evaluated for the 1st (OH1) and 3rd (OH3) minutes, taking the data in supine position as the basis, by Head-Up-Tilt Test. Prevalence of OH1 was 43.2% in AD, 44.7% in DLB and 17.9% in patients without dementia, and OH3 was 44.3% in AD, 47.4% in DLB and 17.9% in non-dementia group. The frequency of OH1 and OH3 was higher in the AD and DLB groups than in the patients without dementia ($p < 0.001$), but there was no significant difference between DLB and AD in terms of OH ($p > 0.05$). The percentage of asymptomatic patients with OH was 87.2% and 89.6% during 1st and 3rd minutes, respectively, and this percentage was similar in three groups ($p > 0.05$, for each). There was no significant difference between the two dementia groups in terms of comorbidities, drugs and laboratory values ($p > 0.05$). OH is more prevalent in patients with AD than controls and similar levels are observed in those with DLB. The prevalence of OH equally is greater with DLB or AD disease progression. Clinicians should be aware of OH and its related consequences in the management of the AD in older adults.

Keywords: Alzheimer's Disease, Dementia with Lewy bodies, Elderly, Orthostatic hypotension.

INTRODUCTION

Autonomic dysfunction is common in patients with dementia, and Orthostatic hypotension (OH) is the second most-common autonomic dysfunction after urinary dysfunction [1,2]. The prevalence of OH increases with age, and it indicates an increased risk of dementia and cognitive decline [3]. Additionally, OH cannot only cause several negative health consequences including cardiovascular events, falls, fractures, progression of dementia, and mortality in older adults [3,4], but it can be considered as a marker or risk factor of clinical frailty, as well[5,6]. On the other hand, cognitive impairment is a common health problem in older adults, and the number of people with dementia is increase predominantly owing to a global ageing population. Moreover, patients with dementia are at high risk of developing OH, and the relationship between OH and dementia may be a consequence of multiple mechanism one of which is the recurrent transient brain hypoperfusion hypothesis [7]. Although, potential association between OH and cognitive impairment has been evaluated in several studies, OH is reported to be prevalent in patients with Dementia with Lewy bodies (DLB) [7,8].

DLB is the second most common dementia, after Alzheimer's disease (AD), with a clinical prevalence of 15-42% of all dementia cases [9-11] and previous studies have demonstrated that prevalence of OH has been reported in 42-69% of patients with DLB [11,12]. Therefore, due to the high prevalence OH, it is accepted as one of the supportive clinical features of the disease together with other signs of autonomic dysfunction, such as constipation, and urinary incontinence [13]. Actually, autonomic dysfunctions are well-known, as a part of all the alfa-synucleinopathies including Multiple System Atrophy (MSA), DLB and Parkinson's Disease (PD), because of the presence of Lewy bodies in brain regions such as the locus coeruleus [14,15]. However, despite the fact that OH, as a sign of autonomic dysfunction, might also help in differential diagnosis among dementia subtypes, it should be kept in mind that autonomic dysfunction is common in all forms of dementia [2,14], and reported prevalence of OH is between 33-42% in patients with AD whereas it is between 13-14% in healthy controls [11,12]. In AD, it has been reported that both generalized deficit in cholinergic function and involvement of subcortical structures, implicated in autonomic nervous system regulation, in the disease course may be led to autonomic dysfunction [1,2].

Until now, although the importance of OH for dementia practice is well known, there are no previous prospective studies of OH comparing the most common dementia subtypes in the

elderly, AD and DLB. For this reason, this study aimed to evaluate the presence and frequency of OH, measured by Head up Tilt Table (HUT), in elderly patients with AD or DLB and without dementia.

PATIENTS AND METHODS

Study design

A total of 647 older adults, who were admitted to one geriatric clinic between January 2016 and June 2018, were included in this prospective observational study. Comprehensive Geriatric Assessment (CGA) including HUT was performed in those geriatric patients after obtaining their informed written consents.

Inclusion Criteria

Patients all over 65 years old who were admitted to the department of geriatrics for any reason and who had no exclusion criteria were included in this study.

Exclusion Criteria

Patients with severe anemia (<10 g/dL), severe metabolic acidosis, electrolyte imbalance, severe kidney or heart failure, hypotensive or septic shock, coma, gastrointestinal bleeding, severe mitral valve or aortic valve stenosis, tachycardia, severe proximal cerebral artery stenosis, severe coronary artery disease, prior stroke or myocardial infarction in the past 7 days, lower extremity fractures, all of which are contraindications of HUT, were excluded [1]. In addition, patients with dementia except those with probable DLB or AD were also excluded. 647 patients were available for study analysis.

Orthostatic Blood Pressure Measurement

HUT Test was performed for the diagnosis of OH. The test was performed in the morning after the patients received their daily medications and patients were told not to smoke, drink caffeine, or exercise within 30 min prior to the test. HUT was performed by tilt Table (Gemesan1 Tilt TableG-71, Turkey). Monitoring over the course of HUT was applied by Biolight® BIOM69 (Australia) with a reusable adult arm cuff. After allowing the patients to rest in a silent room with temperature of 20–24 °C for at least 10 min in a supine position, the tilt Table was rapidly and fluently raised up to an angle of 60–80°. The data of monitoring at the 1st (HUT1) and 3rd minutes (HUT3) were recorded. The diagnosis of OH was made in the

event of 20 mmHg and higher decrease in systolic pressure and/or 10 mmHg and higher decrease in diastolic pressure during transition from the supine position to at least 60° head-up position during HUT [16,17]. According to this definition, orthostatic blood pressure at the 1st and 3rd minutes were evaluated taking the data of supine position as the basis.

Diagnosis of Alzheimer's Disease (AD) and Dementia with Lewy Body (DLB)

AD (probable) was diagnosed with National Institute on Aging-Alzheimer's Association workgroup's criteria [18] and DLB (36 of probable and 2 of possible) was diagnosed with Fourth consensus report of the DLB Consortium [13]. The assessment of dementia stages was classified according to the Clinical Dementia Rating (CDR) and all patients underwent cranial imaging.

Ethical issues

The study was conducted in conformity with the Declaration of Helsinki and was approved by the ethics committee of the School of Medicine, Dokuz Eylul University in Izmir, Turkey. All participating subjects gave their written informed consent.

Comprehensive Geriatric Assessment (CGA) [19]

Demographic characteristics (age, gender, and years of education) were recorded. Patients were questioned in terms of recurrent falls (≥ 1 falls/year) and balance impairment within the past year. Patients were interrogated for comorbidities. Laboratory data, which was performed routinely in geriatric population, was obtained. All participants were queried regarding the use of medication that could lead to OH. These medications include drugs that block angiotensin, calcium channel blockers, beta blockers, alpha blockers, diuretics, nitrates, antidepressants and antipsychotics. Basic and Instrumental Activities of Daily Living (ADL) were assessed by Barthel Index and Lawton-Brody Scale, respectively. Nutritional status was assessed using the Mini-Nutritional Assessment (MNA) score. Cognitive status was evaluated by Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (Scale).

Statistical Analysis

The participants were divided into three groups: AD, DLB and non-Dementia groups. All statistical analyzes were performed to compare three groups. Continuous variables were assessed as means and standard deviations and evaluated by Kolmogorov-Smirnov test for normal distribution. Normally distributed continuous variables were analyzed by paired sample t-test. In case of non-normal distribution, continuous variables were evaluated by

Mann Whitney U test. Differences between categorical variables were evaluated by Chi-square and Fisher's exact Chi-square tests. A probability <0.05 was considered as significant. All statistical analyses were carried out using SPSS 22.0 (SPSS Inc.). Binary logistic regression analysis was performed to assess covariate factors between binary groups (AD and no dementia group, DLB and no dementia group). The sample sizes were calculated as 72 for AD and 25 for DLB to ensure that the minimum required size necessary for comparing prevalence of OH was within 95% confidence interval and 5% within marginal failure. Additionally, the power of study was calculated as 99.6% for AD and 94.2% for DLB by the post-hoc power calculation.

RESULTS

Of 647 patients, 13.6% had AD and 5.8% DLB. There were more females than males in all groups. Prevalence of OH1 was 43.2% in AD, 44.7% in DLB and 17.9% in non-dementia group, and OH3 was 44.3% in AD, 47.4% in DLB and 17.9% in non-dementia group. There were no significant differences between the two dementia groups in terms of comorbidities, frail people, drugs and laboratory values ($p>0.05$). Gait and balance and up & go scores, Basic and Instrumental ADLs, Nutritional evaluation were worse in the AD and DLB group than in the non-dementia group. Prevalence of frailty was higher in the patients with dementia than in the patients without dementia ($p<0.05$). It was higher in both OH1 (50%) and OH3 (49.5%) groups than in the non-OH group, too ($p=0.004$ and $p=0.006$, respectively). MMSE scores was not different between AD and DLB group ($p>0.05$). Patients' characteristics are shown in table 1.

While the prevalence OH, OH1 and OH3 was significantly higher in the AD and DLB groups than in the non-dementia group ($p <0.001$), they were similar in DLB and AD groups ($p>0.05$) (Figure 1). The percentage of asymptomatic patients with OH was 87.2% during HUT1 and 89.6% during HUT3 and this percentage was similar in three groups ($P>0.05$, for each). The significant relationship between AD and OH was maintained when adjusted for age, gender, balance and gait tests, ADLs, nutritional tests and drug usage (B:0.74 $p<0.039$ for OH1 and B:0.85 $p<0.019$ for OH3).

In addition, the prevalence of OH increases with CDR scale in AD group ($p < 0.05$), and there is no significant difference between AD and DLB groups in all three CDR stages ($p > 0.05$) (Figure 2).

DISCUSSION

In this cross-sectional study, it was demonstrated that the prevalence of OH, determined by HUT, a gold standard method for diagnosis OH, in elderly patients with AD was similar to those with DLB. It was also demonstrated that this prevalence was greater with progression of AD.

Presence of OH, a sign of autonomic dysfunction, might not only help in differential diagnosis among dementia subtypes, but it is also one of the supportive clinic criteria of DLB and crucial for the diagnosis of MSA [14,20]. On the other hand, since OH is independently associated with an increased risk of dementia and common in patients with dementia [7,21], early recognition and screening of OH are quite important to prevent for OH related complications such as, increase the risk of morbidity, institutionalization, and mortality in dementia practice [1]. As shown in our results, OH in patients with AD is similar to those with DLB (43.2%, 44.7% for OH1, and 44.3%, 47.4% for OH3, respectively) and higher than controls (17.9%). Furthermore, nearly 90% of these patients were asymptomatic during HUT. In the light of these results, it is clear that OH requires special attention in patients with AD, considering that it is a specific risk factor for falls in patients with dementia and may be a predictor of mortality in DLB patients [22]. Additionally, a recent study has demonstrated that OH is a common condition in frail older adults and it is well known that patients with dementia are more common to have frailty as shown our results [5,6].

Our results are generally consistent with the literature in contrast to several studies. The discrepancy from these studies might result from a variety of methods of OH diagnosis and small sample size. For example, a recent study reported that prevalence of OH is lower in AD than in DLB and PD Dementia and suggested that autonomic function tests, such as OH, might be useful in distinguishing DLB from AD [23], but OH was defined as a reduction in

systolic blood pressure of greater than 30 mm Hg in this study different from standard OH diagnosis [16,17,24] and our study. Moreover, those with DLB and PDD will likely be taking antiparkinsonian drugs that are well known to cause OH and there is no information about this, or antihypertensive therapy, reported in the study [23,25]. The present study was able to assess all the factors affecting OH, since comorbidities, laboratory parameters and drugs were detailed. Therefore, to the best of our knowledge, it is the first study to evaluate clearly OH in patients with AD and DLB. On the other hand, given the fact that the prevalence of coexistence of AD and DLB was reported as 9% in a study, designed for neuropathological evaluation of mixed dementia [26], it should be kept in mind that some patients may have both AD and DLB clinics, and DLB, in these patients, may also be underdiagnosed.

Indeed, it is not surprising that the frequency of OH in patients with AD is similar to those with DLB, due to following reasons: first, one of the most important factors for regulation of orthostatic blood pressure is hypothalamic–pituitary–adrenocortical (HPA) axis and suitable sympathetic response to postural changes. Previous studies have shown that activity of the HPA axis increases in patients with AD; thus, there are increased basal concentrations of cortisol in plasma, urine, and cerebrospinal fluid and decreased sensitivity of the HPA axis in these patients [27,28]. For example, one experimental study, by Brureau et al, demonstrated that accumulation of amyloid- β could lead to disturbance in the feedback of the HPA axis in a rodent model [28]. Also, an increased deterioration in HPA axis, basal sympathoneural activity and cardiovascular responsiveness have been repeatedly demonstrated in AD [27-29]; which can facilitate the development of OH. Second, AD reaches the insular cortex, part of autonomic function, at a “preclinical” stage according to Braak sequence and its infarction has caused both cardiac arrhythmias and cardiovascular mortality; thus, this may explain why OH and central autonomic cardio-regulatory dysfunctions can be developed in AD [30]. Third, involvement of several subcortical structures playing a role in autonomic nervous system regulation, such as the hypothalamus, locus coeruleus, cerebral neocortex, insular cortex and brainstem during the disease course were also associated with autonomic dysfunction [31,32]. The other mechanism may be the cholinergic vascular hypothesis in AD brain. In fact, loss of the cortical perivascular cholinergic nerve terminals, may contribute to the impairment of the observed reduction in cerebral blood flow in AD brain [1,30]. Additionally, there is much evidence that AD lead to functional and structural changes in large arteries, arterioles, and capillaries [33]. Therefore, those arteriolar dysfunctions can cause impairment in CBF autoregulation and develop OH. Based on these findings, it is likely

that OH and autonomic dysfunction are common in patients with AD, like DLB, and that AD may affect both cortex and subcortical structures in the brain at the beginning of the disease. For this reason, it should also be paid attention to OH and OH related consequences in the management of the patients with AD.

One strength of this study is that orthostatic blood pressure was measured by HUT, while in previous studies it was measured by the active standing test (AST) [9-12]. According to diagnosis of OH, when HUT was used as the gold standard for comparison, AST had lower sensitivity, specificity, and positive predictive value in elderly patients [34]. OH determined by HUT is likely of higher clinical significance than by AST. Another strength is that all patients were evaluated by comprehensive geriatric assessment including comorbidities, laboratory parameters and detailed drugs history. Finally, healthy controls were used. The present study has some limitations. First, the design of the study is cross-sectional. Second, the number of patients with dementia, especially DLB patients, is not enough to evaluate the comparison between different stages of dementia. Third, this study did not neuropathologically confirm the dementia diagnosis.

In conclusion, OH in patients with AD is more prevalent than in controls but has a similar prevalence to those with DLB. The prevalence of OH increases with disease progression, even if these patients are asymptomatic during test. Clinicians should be aware of OH and its related consequences in the management of the AD in older adults

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Table 1. PATIENTS CHARACTERISTICS

	AD n=88	DLB n=38	No dementia n=521	p1	p2	p3
Female Sex (%)	60.2	60.5	71.4	0.035	0.158	0.975
Age	77.41±8.70	77.92±2.33	75.40±25.22	0.001	0.004	0.911
Recurrent falls (%)	33.0	55.3	30.4	0.822	0.007	0.019
Balance disorder (%)	39.1	60.5	49.3	0.077	0.179	0.027
COMORBIDITIES (%)						
Hypertension	62.5	60.5	68.7	0.248	0.299	0.834
Ischemic Heart Disease	10.2	21.1	20.5	0.023	0.944	0.103
Heart Failure	6.8	7.9	7.9	0.732	0.998	0.829
Peripheral Artery Disease	3.4	2.3	6.3	0.282	0.109	0.249
Cerebrovascular Events	2.3	5.3	5.8	0.175	0.897	0.380
Diabetes Mellitus	19.3	34.2	29.6	0.048	0.550	0.072
Hyperlipidemia	13.6	21.1	20.3	0.141	0.921	0.296
Depression	40.9	52.6	42.4	0.791	0.215	0.224
Frail (by FRIED criteria)	51.1	75.0	33.1	0.016	<0.001	0.052
LABORATORY VALUES						
Hemoglobin (g/dL)	12.71±1.51	12.54±1.23	12.75±1.41	0.555	0.395	0.733
TSH (mIU/L)	1.55±1.43	1.42±0.77	1.74±2.29	0.537	0.724	0.933
Vitamin B12 (pg/ml)	542.34±396.87	474.44±366.46	432.20±328.71	0.008	0.276	0.459
Vitamin D (ng/ml)	20.79±9.99	26.02±23.09	23.03±12.46	0.172	0.610	0.203
COMPREHENSIVE GERIATRIC ASSESSMENT						
MMSE	14.31±5.95	15.50±4.88	25.35±4.29	<0.001	<0.001	0.362
POMA-Balance	13.31±3.04	11.42±4.60	13.93±2.72	0.021	<0.001	0.021
POMA-Gait	10.18±1.84	8.92±3.14	10.58±2.06	0.007	<0.001	0.049
POMA-Total	23.51±4.60	20.37±7.50	24.47±4.45	0.007	<0.001	0.026
Up&Go	18.87±9.91	25.84±23.73	14.62±8.72	<0.001	<0.001	0.214
Basic ADL	81.47±17.05	75.50±17.90	91.37±10.01	<0.001	<0.001	0.061
Instrumental ADL	8.22±5.66	9.13±5.90	18.71±4.91	<0.001	<0.001	0.417
MNA-sf score	10.91±2.16	9.73±3.04	12.29±2.03	<0.001	<0.001	0.062
DRUG CLASS (%)						
ARB	26.1	18.4	37.2	0.044	0.019	0.351
ACEI	13.6	13.2	15.2	0.710	0.735	0.942
BB	25.0	21.1	30.9	0.264	0.199	0.633
CCB	28.4	26.3	25.3	0.542	0.878	0.810
Diuretics	31.8	28.9	37.8	0.312	0.292	0.749
Alfa blockers	9.1	7.9	7.9	0.697	0.998	0.827
Nitrats	4.5	7.9	3.8	0.753	0.226	0.451
Antridepressants	53.4	47.4	32.1	<0.001	0.051	0.533
Antipsychotics	13.6	15.8	3.1	<0.001	<0.001	0.751
AcHEIs	92.0	92.1				0.870

ACE: Angiotensin-Converting Enzyme Inhibitors; AcHEIs : Acetylcholinesterase Inhibitors; ADL: Activities of Daily Living; ARB: Angiotensin II Receptor Blockers; BB: Beta-Blockers; CCB: Calcium Channel Blockers; eGFR: estimated Glomerular Filtration Rate; MDRD: Modification of Diet in Renal Disease; MMSE: Mini-Mental State Examination; MNA-sf: Mini-Nutritional Assessment (short form); TSH: Thyroid Stimulating Hormone

P1: Comparisons between AD and No dementia groups; P2: Comparisons between DLB and No dementia groups; P3: Comparisons between AD and DLB groups

Figure Legends:**Figure 1: Study Design****Figure 2: Prevalence of Orthostatic Hypotension in The Study Population**

AH: Alzheimer Disease; **DLB:** Dementia of Lewy Body; **OH1:** Orthostatic Hypotension within 1st minute, **OH3:** Orthostatic Hypotension within 3rd minutes

Figure 3: Prevalence of Orthostatic Hypotension in patients with AD According to CDR

AH: Alzheimer Disease; **CDR:** Clinical Deteriorating Scale; **OH1:** Orthostatic Hypotension within 1st minute, **OH3:** Orthostatic Hypotension within 3rd minutes

HIGHLIGHTS

- OH is common in dementia with Lewy body as well as AD.
- OH is more prevalent in patients with AD than in healthy controls.
- OH should be taken into consideration in the follow-up of patients with AD as same as in DLB patients.

ACCEPTED MANUSCRIPT

Registered elderly patients
n=3100

Excluded patients due to diagnosis
of other dementia subtypes and/or
contraindications for HUT

Total number of participants enrolled to this study
n=647

AD group

n=88

DLB group

n=38

No dementia
group

n=521

Figure 1

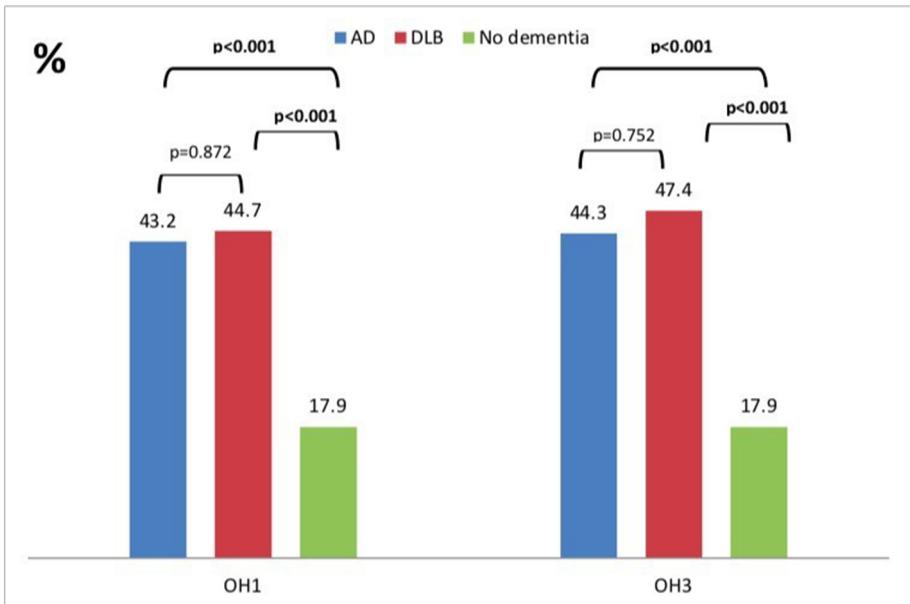


Figure 2

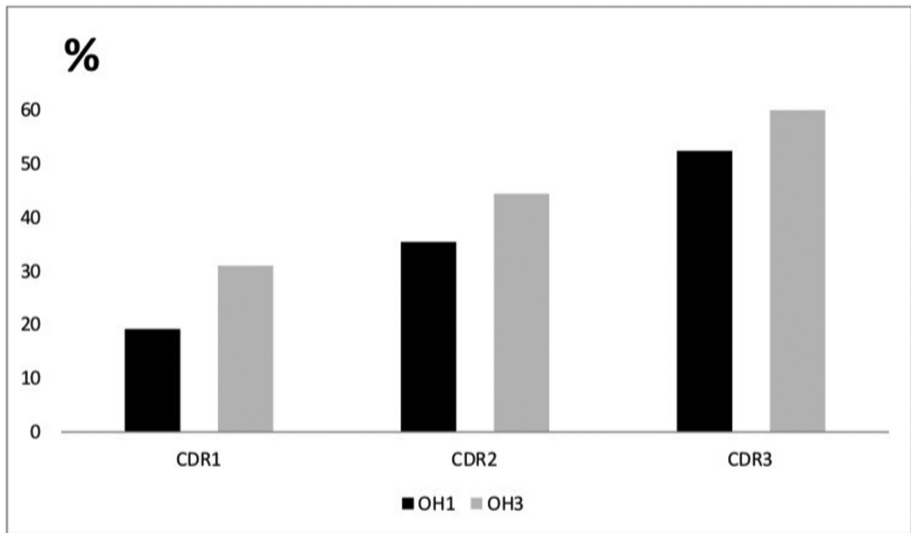


Figure 3