Arterial Stiffness in Older People with Different Types of Dementia Compared to Older People without Cognitive Dysfunction

Ahmet Yalcin*, Volkan Atmis, Ozlem Karaarslan Cengiz, Esat Cinar, Murat Varli, Sevgi Aras and Teslime Atli

[1]Department of Geriatric Medicine, Ankara University School of Medicine İbn-I Sina Hospital, Ankara Turkey

*Corresponding author's email: ahmetemreyalcin [AT] hotmail.com

ABSTRACT---- ***Alzheimer's disease and vascular dementia are the most common causes of cognitive dysfunction among older people. Vascular damage plays a role in the etiopathogenesis of both Alzheimer's disease and vascular dementia. Arterial stiffness is a marker of vascular damage. The aim of this study was to compare arterial stiffness between Alzheimer's disease, vascular dementia and controls without memory complaints. A total of 72 older people (Alzheimer's disease=22, vascular dementia=28, controls=22) were included in the study. Demographic data were obtained and ambulatory blood pressure monitoring was applied. Arterial stiffness was evaluated with carotid to femoral pulse wave velocity measurements. Mean pulse wave velocity was 10.7±2.0 m/s, 11.3±3.1 m/s, and 10.0±3.1 m/s in Alzheimer's disease, vascular dementia and controls, respectively (p>0.05).Arterial stiffness assessed by pulse wave velocity might play a role in the development of vascular dementia and Alzheimer's disease, but further evidence is needed to confirm this relationship.***

Keywords---- Dementia, arterial Stiffness, pulse wave velocity, older people

1. INTRODUCTION

Dementia is one of the leading neurological problems in older people [1] and a decrease in cognitive function has been found to be related to increased mortality and loss of function [2-4]. This increase can be seen even in the early stages of dementia [5]. Alzheimer's disease (AD) and vascular dementia (VaD) are the most common causes of dementia [1, 6]. Parallel to the growth of the older population worldwide, the burden of health costs related to dementia is increasing. As a result, preventative strategies for preserving cognitive function and management of dementia have become more important [1, 7].

Stiffening of central arteries occurs as a result of both structural and functional changes in the aging arterial system [8-10]. Due to an increase in arterial stiffness (AS), arterial waves gain speed and reach back to the aorta during the systolic part of the cardiac cycle instead of the diastole. As a result of this, diastolic blood pressure decreases whereas systolic blood pressure and pulse pressure increase [8]. A relationship has been found between AS and vascular damage. AS was also found to be a predictor of all cause mortality and future cardiovascular events [11]. There are different methods for measuring AS. One of these methods, pulse wave velocity (PWV), measures the velocity of the pulse wave traveling between two arteries. Measurement of PWV between carotid and femoral arteries shows the stiffness of the aorta and is accepted as the best way to assess central AS [7].

Vascular factors may play role in the pathogenesis of dementia. A relationship between dementia and cardiovascular disease exists [12-14]. As a vascular factor AS may be involved in the pathogenesis of dementia. Cerebral vascular structures can be damaged by increased arterial pulse pressure [15]. Increased pulse pressure, an indicator of AS, is associated with risk of dementia [16]. The relationship between poor cognitive performance and AS has been shown in cross sectional studies and this relationship was independent of age, blood pressure and cardiovascular disease [1, 17]. Longitudinal effects of AS on cognitive function were also investigated. Poor performance on MMSE as a surrogate of cognitive function was related to AS in both community dwelling older people and nursing home residents [18, 19]. Recently, this association was confirmed by a meta-analysis [7]. However, the relationship between AS and cognitive decline or dementia could not be shown in two large studies. AS predicted decline in different domains of cognitive function, such as verbal learning, delayed recall and non-verbal memory but did not predict a decline in MMSE in the Baltimore study [20]. This result was attributed to the relatively younger cohort of the Baltimore study [7]. In the

Rotterdam study, AS predicted low scores on MMSE, stroop and word fluency tests in multiple linear regression analysis at baseline evaluation. Cognitive decline and dementia were not predicted by AS [21].

Conflicting results were also reported in studies evaluating the relationship between AS and dementia types (AD and VaD). Hanon et al. found the highest PWV values in individuals with VaD followed by individuals with AD and normal cognition [1]. In another study, AS assessed by brachial-ankle PWV was found to be higher in VaD compared to AD and controls [22]. Dhoat et al. reported that augmentation index and central arterial compliance were associated with VaD comparing AD and controls. In the same study, PWV was not statistically different among VaD, AD and controls but PWV was highest in the VaD group [23]. Finally, Scuteri et. al. reported AD might be more associated with AS compared to VaD [18].

The aim of this study was to investigate the relationship of AS with the most common dementia types (AD and VaD) compared to healthy controls without cognitive dysfunction.

2. MATERIALS AND METHODS

2.1

Seventy-two older patients admitted to the outpatient clinic of the geriatric medicine department of Ankara University between June 2007 and October 2007 were enrolled in this cross-sectional study. Individuals with electrolyte disorders, hypothyroidism, vitamin B_{12} deficiency, any other dementia type except VaD and AD, delirium, advanced organ failure, atrial fibrillation or any other arrhythmia affecting PWV measurement and depression or other psychiatric disorders were excluded. Individuals who were unable to cooperate with study protocols or who were unfit for magnetic resonance imaging (MRI) were also excluded. Inclusion criteria for study groups were having AD or VaD and being 65 or older. Inclusion criteria for control group were having no memory complaints, no limitation in activities of daily living and being 65 or older. Formerly diagnosed AD and VaD cases formed the dementia group. Diagnosis of AD and VaD were according to the Diagnostic and Statistical Manual of Mental Disorders IV Text Revision (DSM-IV TR) criteria for AD and the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et I'Enseignement en Neurosciences (NINDS-AIREN) criteria for VaD. Hypertension (HT) was the only comorbidity in the control group. Mini-mental state examination was applied to the candidates of control group before recruitment. Total score $\geq$27 was accepted normal. A total of 72 individuals participated. Fifty of them were in the dementia group (22 AD cases and 28 VaD cases). There were 22 individuals in the control group.

2.2

Demographic data were obtained during the evaluation of study participants. Demographic data, co-morbidities and medications were obtained by structured questionnaire. Height was measured using a tape measure. Body weight was measured using a calibrated weighing machine. Body mass index (BMI) was measured according to the following formula: Body weight (kg)/ square of height (m^2). Complete blood count, serum vitamin B_{12} levels, liver, renal and thyroid function tests were performed in order to exclude accompanying metabolic disorders. Fasting blood glucose, low density cholesterol (LDL), high density cholesterol (HDL) and triglyceride levels were also assessed. Blood samples were taken after a minimum of 12 hours of fasting and measured using standard laboratory methods.

Informed consent was obtained from study participants or from the legal proxy of participants when necessary. This study was approved by the ethical committee of the Ankara University School of Medicine.

2.3 Arterial Stiffness Assessment

AS was assessed by PWV measured between carotid and femoral arteries. All participants had a light breakfast without consuming coffee on the measurement day. PWV measurements were performed in a quiet room. Participants rested for 15 minutes before measurement. The same technician blind to clinical and laboratory data of the participants performed all PWV measurements using a *Sphygomocor® Pulse Wave System* device. The validity of this system was confirmed previously [24]. The right carotid artery and right femoral artery were the sites of measurement. Measurements were done in supine position. The arms of participants were relaxed by their sides and their head was supported. Three-lead electrocardiography was placed on the chest of the participant. After placement of electrodes, ECG signal quality was checked by the examiner. Thereafter, the distance between the right carotid artery and the right femoral artery was measured. Firstly, the distance between the suprasternal notch and the right femoral artery was measured and then the distance between the suprasternal notch and the right carotid artery was measured. Subtraction of the second measurement from the first measurement gave the pulse wave distance. Afterwards, the examiner placed the tonometer on the femoral artery and searched for a steady pulse waveform with good quality. The same process was performed on the right carotid artery. PWV was automatically calculated by the software of the device and was given in meters/seconds (m/s). An average of two measurements was taken.

2.4 Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring (ABPM) was applied to all participants. PWV measurements and ABPM were performed on different days. *Mobilograph 24h ABP-CONTROL* was used for ABPM. The device takes blood pressure readings every 30 minutes during daytime and every 60 minutes during the night. The procedure started at 09.00 am and lasted until the next day at 09.00 am. Participants were asked to keep their arms steady while measuring. Antihypertensive medications were not withheld during ABPM. The readings were transmitted to a computer and mean systolic blood pressure (MSP), mean diastolic blood pressure (MDP), and mean blood pressure (MBP) and mean pulse rate (MPR) were all calculated automatically by the software program of the device.

2.5 Statistical Analysis

The Statistical Package for Social Sciences version 11.5 (SPSS Inc; Chicago USA) program was used for statistical analysis. Continuous variables in three groups were compared using Anova and Kruskall-Wallis tests. Post hoc analysis was performed to assess which of the study groups differ from each other. Nominal and ordinal variables were compared using Chi-square test. Descriptive statistics were given as percentages and mean ± standard deviation (SD). P values less than 0.05 were accepted as statistically significant.

3. RESULTS

A total of 72 individuals participated in the study. The mean age of participants was 76.4±6.3. 40% (29) of the participants were male. None of the diabetic patients were receiving insulin.

3.1 Demographic and Medical Data of AD, VaD and Control Groups

Demographic and medical data of AD, VaD and control groups are shown in table 1. In AD and VaD groups, ASA use was significantly higher than the control group ($p<0.01$ and $p<0.01$). BMI was statistically significant higher in control group compared to AD and VaD groups ($p<0.01$ and $p=0.02$).

3.2 Laboratory Data of AD, VaD and Control Groups

Laboratory data of AD, VaD and control groups is shown in table 2. HDL values and MPR were significantly different between three groups. Serum HDL levels were significantly higher in the control group compared to VaD and AD groups ($p=0.02$ and $p=0.02$). MPR was significantly lower in the VaD and AD groups compared to the controls ($p<0.01$ and $p<0.01$). PWV was highest in the VaD group (11.3±3.1 m/s). PWV was lower in the AD group (10.7±2.0 m/s) compared to the VaD group. The control group had the lowest mean PWV value (10.0±3.1 m/s). However, there was no statistically significant difference between the three groups ($p>0.05$) (table 2).

4. DISCUSSION

We found mean PWV to be higher in the dementia cases compared to the control group. Mean PWV was highest in VaD cases, and the AD group had a higher mean PVW than the control group in our study. However these differences were not significant.

Vascular disorders like HT and atherosclerosis increase the risk of dementia, and AS is strongly linked to HT and atherosclerosis [25, 26]. Therefore, vascular damage caused by AS probably contributes to cognitive dysfunction. Stroke, white matter hyperintensities and lacunar infarctions were all found to be associated with AS [27, 28]. The count, location and size of these vascular lesions can be determinants of the path leading to dementia [1]. It is assumed that damage of unprotected small cerebral vessels against increased pulse pressure causes cognitive dysfunction [15]. Additional possible mechanisms could be endothelial dysfunction and nitric oxide deficiency [29]. AS may play a role in both the pathogenesis of VaD and AD in addition to other cardiovascular risks, genetic predisposition, environmental factors and classic AD pathology, but showing a role of AS in the etiology of vascular or non-VaD was insufficient. Although AS was accepted as a cardiovascular disease predictor, the relationship with cognitive decline was not so clear [7]. Discovering new mechanisms underlying cognitive dysfunction and dementia can lead to alternative therapeutic and diagnostic options. AS assessed by PWV would be a useful method for predicting cognitive dysfunction in the future due to the advantages of PWV measurement, such as being noninvasive and having high reproducibility. Prediction of cognitive function by measuring AS can be useful in practice only if effective treatment of AS can be achieved and if treatment results in cognitive improvement. Currently, there is insufficient evidence that cognitive function improves by treating AS [7].

Age and blood pressure was closely associated with AS. Isolated systolic hypertension and widened pulse pressure are two clinical consequences of AS. Chronic elevation of MAP can cause thickening of arterial walls especially in media [30]. In contrast to the effects of aging, intrinsic stiffness of arterial wall in hypertensive people was not different from normotensive people and arterial wall changes due to the hypertension are partly reversible after reduction of MAP [30]. There was no difference among three groups for MSP MDP and MAP which were measured using ABPM in our study. Blood pressure was well controlled and hypertension prevalence was similar in all three groups in

our study (However, number of cases was insufficient for statistical analysis). Benetos et al. showed that there were no difference between normotensive participants and participants with well controlled HT for AS progression. They used ABPM and PWV for analysis [31].

Diabetes is also closely associated with AS. The rate of diabetes in individuals with dementia especially in the VaD group was higher compared to the controls in our study (However, number of cases was insufficient for statistical analysis). Although FBG levels were not different among three groups, we could not say that diabetes was well controlled in the AD and VaD groups because we did not measure hemoglobin A_1C levels. In one study patients with type 2 diabetes had PWV values almost same as 15 year older people with type 2 diabetes [32]. Aortic PWV was higher in type 2 diabetic patients compared to individuals without diabetes at any level systolic blood pressure [33]. However, the independent relationship between AS and diabetes was not shown in all studies [34]. While age and blood pressure were independently associated with AS in 90% of the reported studies, diabetes was independently associated with AS only in 52% of the reported studies [35]. Diabetes was responsible for only 5% of the variation in PWV. Diabetes may not be the main determinant of AS especially in older people with hypertension because diabetes was often coexisted with hypertension [34].

In our study, HDL values were significantly lower in AD and VaD groups compared to control group. Previous studies showed that there was a relationship between AS and total cholesterol or LDL [36]. However, in a systematic review the relationship between serum lipids and AS was found only 10% of the studies [35]. Epidemiological and clinical studies evaluating the relationship between HDL and AS are rare and the results are controversial. Recently, Wang et al. also showed that HDL was inversely correlated with AS. The authors concluded that this benefit can be due to the anti-inflammatory effects of HDL [36].

Lack of a statistically significant difference between dementia cases and controls may be due to the insufficient number of cases in our study. In the geriatric population, finding older people without co-morbidities affecting AS in outpatient settings and homogeneous study groups is hard to achieve. Additionally, ASA use was significantly higher in VaD and AD groups compared to controls. Chronic subclinical inflammation was associated with impairment in elastic properties of arteries. Inflammatory markers like C-reactive protein were correlated with AS [37, 38]. Vlachopoulos et al. showed that acute systemic inflammation induced by vaccination caused an increase in AS. This effect of acute systemic inflammation disappeared after pretreatment with high dose ASA [39]. Furthermore, AS assessed by carotico-femoral PWV significantly decreased in hypertensive patients who were treated with 160 mg. ASA for two weeks [40]. ASA may decrease AS though anti-inflammatory effect and inhibition of platelet activitation. Even low dose ASA may have anti-inflammatory effect and this anti-inflammatory effect can be more obvious in individuals with cardiovascular risk factors compared to normal individuals [41, 42]. Platelet activation promote endhothelial dysfunction via release of proinflammatory molecules [43]. Since endhothelial derived nitric oxide has a significant role in arterial elasticity, platelet activation may serve as a bridge between endothelial dysfunction and AS [40].

Significantly higher BMI in controls compared to both dementia and VaD groups might contribute to AS. Obesity and BMI were related to AS in different populations from different countries [44-46]. BMI has been found to be associated with increase PWV and, hence, increase AS [47]. There was a linear relationship between AS and BMI in black and white healthy young adults [48]. [49]. Conversely, Budimir et al. found that BMI was inversely correlated with AS in both men and women. They point out that more studies were needed to confirm their findings [50]. In a recent study, Desamericq et al. found no difference between individuals with normal weight, overweight and obese individuals for AS which was assessed by carotico-femoral PWV [51]. Factors associated with obesity such as increased sympathetic activity, increased insulin and proinflammatory cytokine levels, increased lipolytic activity of visceral adipocytes and endothelial dysfunction can be the mechanisms that contributes to the development of AS [52]. Endothelial dysfunction and low grade inflammation due to obesity may contribute to AS [53].

MPR was significantly lower in the AD and VaD groups compared to the controls in our study (table 1). This can be another reason for insignificance between study groups in terms of AS. A correlation was found between AS and resting heart rate in various studies. Resting heart rate was independently associated with AS in a retrospective study from Korea [54]. Data from Multi-Ethnic Study of Atherosclerosis also showed that there was a relationship between resting heart rate and AS [55]. Albaladejo et al. investigated the relationship between 24 hour ambulatory heart rate and AS in subjects with mild to moderate untreated hypertension. 24 hour ambulatory heart rate was found as an independent factor affecting AS. This relationship was especially stronger for patients older than 65 years old [56]. Although there were insufficient number of cases for statistical evaluation between three groups, β blocker use was higher in the dementia groups than the controls (table 1). High β blocker use in dementia groups can explain the difference between the dementia subjects and the controls for MHR. Additionally, β blockers with vasodilator properties such as Nebivolol have positive effects on arterial function. Nebivolol can decrease AS through improvement of endhotelial function [57].

Our study has several limitations. Cross-sectional design of our study prevents assessing causality. Also smaller sample of our study might underestimate the relationship between dementia and AS.

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Table 1. Demographic, clinical and laboratory data of AH, VaD and control groups

Variables	AH[1] (n=22)	VaD[2] (n=28)	Controls (n=22)	P value
	n/(%)-mean±SD	n/(%)-mean±SD	n/(%)-mean±SD	
Age (years)	78.9±7.3	76.5±6.8	73.9±6.0	NS[17]
Male/Female (n(%))	10(46%)/12(54%)	9(32%)/19(68%)	10(46%)/12(54%)	NS
Hypertension (n(%))	18(82%)	21(75%)	18(82%)	-
AHD[3] (n(%))	4(18%)	4(14%)	0(0%)	-
Diabetes (n(%))	4(18%)	12(43%)	0(0%)	-
ACEI[4] (n(%))	6(27%)	11(39%)	3(14%)	NS
ARB[5] (n(%))	1(4%)	2(7%)	3(14%)	-
ASA[6] (n(%))	13(59%)[a]	19(68%)[b]	4(18%)[a,b]	<0.01
Ca channel blocker (n(%))	7(32%)	9(32%)	5(23%)	-
β-blocker[7] (n(%))	3(23%)	7(25%)	1(5%)	-
Statins (n(%))	5(23%)	3(11%)	0(0%)	-
Diuretics (n(%))	2(9%)	1(4%)	2(9%)	-
ACEI+diuretics (n(%))	0(0%)	2(7%)	6(27%)	-
ARB+diuretics (n(%))	2(9%)	4(14%)	0(0%)	-
BMI[8] (kg/m^2)	27.1±5.8[f]	27.7±5.4[g]	30.1±4.7[f,g]	0.03

a,b,c,d,e,f: p<0.01, g: p=0.02,
-: Statistical analysis was not applied to variables with insufficient number of cases
[1]Alzheimer's disease, [2]vascular dementia, [3]atherosclerotic heart disease, [4]angiotensin converting enzyme inhibitor, [5]angiotensin receptor blocker, [6]acetyl salicylic acid, [7]β-blocker, [8]body mass index

Table 2. Laboratory data of AD, VaD and control groups

Laboratory Parameters	**AH[1] (n=22)**	**VaD[2] (n=28)**	**Controls (n=22)**	**P value**
	mean±SD	**mean±SD**	**mean±SD**	
FPG[3] (mg/dl)	95.0±36.3	105.0±33.1	83.4±8.4	NS[11]
LDL[4] (mg/dl)	107.9±26.9	111.3±21.7	123.4±39.3	NS
HDL[5] (mg/dl)	49.5±11.7[a]	47.0±13.1[b]	56.8±15.6[a,b]	0.04
Triglycerides (mg/dl)	130.4±56.3	134.5±46.7	136.2±59.7	NS
MSP[6] (mmHg)	116.2±11.6	120.9±15.4	113.3±13.3	NS
MDP[7] (mmHg)	68.7±9.3	68.7±9.5	68.1±7.0	NS
MAP[8] (mmHg)	86.7±12.1	87.5±9.9	83.6±7.9	NS
MPR[9] (n/min)	71.7±10.3[c]	70.9±12.5[d]	77.5±7.9[c,d]	0.02
PWV[10] (m/s)	10.7±2.0	11.3±3.1	10.0±3.1	NS

a,b: p=0.02, c,d: p<0.01
[1]Alzheimer's disease, [2]vascular dementia, [3]fasting plasma glucose, [4]low density lipoprotein, [5]high density lipoprotein, [6]mean systolic pressure, [7]mean diastolic pressure, [8]mean arterial pressure, [9]mean pulse rate, [10]pulse wave velocity, [11]not significant