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The correlation between cerebral arterial pulsatility and cognitive dysfunction in Alzheimer's disease patients

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ABSTRACT

Background: Potential role of vascular dysfunction has been suggested in the pathogenesis of Alzheimer's disease (AD). Previous cross-sectional studies have demonstrated relations between abnormal transcranial Doppler (TCD) parameters and cognitive impairment. We aimed to investigate the associations between longitudinal changes of TCD parameters and cognitive decline in patients with AD.
Methods: We have enrolled patients with mild to moderate AD who aged 60 to 79 years. Mean flow velocity and pulsatility index (PI) of anterior (ACA), middle (MCA), and posterior (PCA) cerebral arteries were evaluated. Cognitive functions were assessed using mini-mental state examination (MMSE), clinical dementia rating sum of boxes (SOB), and Alzheimer's Disease Assessment Scale (ADAS-cog), which was further categorized as praxis, language, and memory subscores. TCD and cognitive assessments were followed up 1 year later, and the longitudinal changes (Δ) between the baseline and follow-up measurements were evaluated.
Results: A total of 51 patients completed the follow-up evaluations (baseline age 71.5 years, MMSE 21.2). In the baseline evaluations, high PI values of ACA and MCA were associated with poor MMSE score, ADAS-cog total, memory, and praxis subscores. After 1 year, the increases of ACA and MCA PI were correlated with the aggravation of ADAS language subscore, and ΔACA PI was also correlated with ΔSOB. The decrease in mean flow velocity of ACA was associated with aggravation of ADAS-cog praxis score.
Conclusions: There was significant correlation between longitudinal changes of TCD parameters and cognitive dysfunction in patients with mild to moderate AD. Serial assessment of TCD may provide useful information regarding to the disease progression.

1. Introduction

Recently, vascular contribution to the neurodegenerative dementia is an intriguing issue in dementia research. According to the large pathologic study, lacunes, multiple microinfarcts, and leukoencephalopathy was observed in 9.3%–20.1%, and vascular pathologies - atherosclerosis, arteriosclerosis, cerebral amyloid angiopathy - were in 34.6%–40.8% in patients with Alzheimer's disease (AD) [1]. Amyloid beta (Aβ) may increase vascular smooth muscle tone and decrease cerebral blood flow (CBF) [2]. Chronic cerebral hypoperfusion also down-regulates low density lipoprotein receptor-related protein 1 (LRP1), which may interfere the clearance of Aβ and overproduction of Aβ [2]. These hypotheses are regarded as possible pathophysiological explanations for the link between vascular factors and neurodegenerative dementia in many epidemiological and experimental studies [3–6].

Transcranial Doppler sonography (TCD) is a non-invasive method to measure the blood flow velocity, which may represent the cerebral perfusion status. Previous cross-sectional studies with TCD have demonstrated associations between cognitive impairment and abnormal TCD parameters [7–9]. A representative population-based study with TCD showed that those with lower flow velocity have higher risk for the development of dementia in the future [6]. Pulsatility index (PI), which is defined as the ratio between "peak systolic flow velocity - end diastolic flow velocity" and mean flow velocity, reflect the resistance of distal vasculatures. In previous studies, MCA PI was associated with poor cognitive function [7,9]. However, most of studies were cross-sectional.

Thus, we aimed to investigate the associations between the longitudinal changes of cognitive measures and TCD parameters in patients with mild to moderate AD.

2. Materials and methods

From October 2010 to November 2014, we recruited patients with mild to moderate AD dementia, who were aged from 60 to 79 years old, with mini mental state examination (MMSE) 10 to 24 points. AD

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dementia was diagnosed according to the diagnostic criteria of National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [10]. Patients who had poor temporal window to a degree that would preclude proper TCD, and those who had significant steno-occlusion over 50% in middle cerebral arteries or internal carotid arteries were excluded. We have also excluded patients whose cognitive dysfunction was due to acute cerebral infarction, transient global amnesia, metabolic encephalopathy, central nervous system infection/inflammation, and other serious underlying diseases. This study was approved by the local institutional review board, and written informed consent was obtained from all patients or their legally authorized representatives (IRB No. 06-2010-77).

TCD was applied at the baseline and follow-up evaluations. Mean flow velocity (MFV) and PI of middle cerebral artery (MCA), anterior cerebral artery (ACA), and posterior cerebral artery (PCA) were evaluated. For the analyses, MFVs and PIs of both side (right and left) were averaged.

Baseline cognitive functions were assessed using Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), frontal assessment battery (FAB), MMSE, clinical dementia rating (CDR), CDR sum of boxes (SOB), and geriatric depression scale (GDepS). ADAS-cog is useful for the evaluation of cognitive changes in patients with AD dementia, which is ranged from 0 to 70 points, and is widely used in the clinical trials [11]. ADAS-cog subscales were categorized by cognitive domains: praxis, language, and memory [12]. ADAS-cog praxis score was calculated as sum of constructional praxis and ideational praxis subscale scores. ADAS-cog language domain was consisted of word reading, speech comprehension, commands, aural comprehension, and naming. Lastly, ADAS-cog memory score was the sum of word recall, word recognition, orientation, and recall of the test instructions. FAB is sensitive tool for the evaluations of frontal function, which is ranged from 0 to 18 (the higher score is better) [13].

TCD and cognitive assessment was followed up 1 year later, and the absolute differences between the baseline and follow-up evaluations were evaluated (Δ). Main exposure variables were the absolute differences of TCD parameters of each intracranial vessel between baseline and follow-up evaluations. Main outcome was the absolute differences of ADAS-cog total scores and domain scores.

Significant differences between baseline and follow-up evaluations were tested using paired *t*-test. The associations between baseline TCD parameters and cognitive test scores were evaluated using Pearson's correlation analyses. Correlation analysis was also conducted between the changes of TCD parameters and cognitive assessment scores. All statistical analyses were performed with SPSS (version 21, IBM SPSS Inc., Chicago, IL, USA). A two-sided p value of <0.05 was considered a minimum level of statistical significance.

3. Results

3.1. Subjects characteristic

A total of 86 patients were screened, and 79 patients were finally enrolled. Twenty-eight patients were dropped out during follow-up, a total of 51 subjects have completed the follow-up evaluation (Fig. 1).

There were no significant differences in age, baseline MMSE score, ADAS-cog total score, FAB, CDR SOB, GDepS between those with or without follow-up evaluations. For those who completed follow-up, mean age was 71.5 ± 5.1 years, 32 (64.0%) subjects were male, 2 (3.9%) were illiterate (Table 1).

3.2. Baseline evaluations

Baseline neuropsychological test and TCD parameters and their correlations were presented in Tables 2 and 3. Most subjects were mild dementia, which represented with baseline MMSE score of 21.2 and CDR SOB 4.0. In the baseline evaluations, all PI values were positively associated with ADAS-cog total scores (correlation coefficients 0.44 for ACA, 0.32 for MCI, 0.32 for PCA, respectively; Table 3). ACA PI was positively correlated with ADAS-cog praxis score (correlation coefficients 0.38), while it was negatively associated with baseline MMSE score (correlation coefficients −0.31). Both ACA and MCA PI was positively associated with ADAS-cog memory score (correlation coefficients 0.42, 0.36, respectively), and CDR, a general cognitive measure (correlation coefficients 0.32, 0.34, respectively). However, TCD parameters were not significantly associated with FAB, SOB, and GDepS (Table 3).

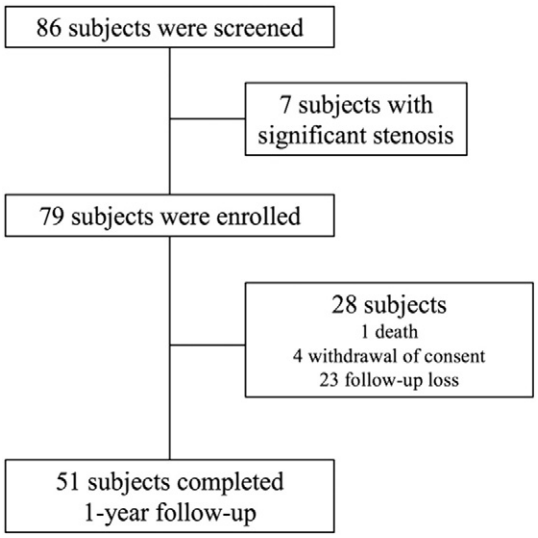

Fig. 1. Enrollment flow chart.

3.3. Follow-up evaluations

Intervals of follow-up evaluations were 378.0 ± 40.8 for TCD evaluations, and 365.5 ± 36.6 days for the neuropsychological tests. In TCD parameters, only MCA PI increased significantly, and MFVs did not show any significant alterations. For cognitive measures, ADAS-cog total score and subscores were significant aggravated, and CDR SOB was increased. However, MMSE score did not change significantly during follow-up including FAB, CDR total score, and GDepS (Table 2).

As for the correlation between change scores of TCD parameters and cognitive measures, ΔACA and ΔMCA PI increases was positively associated with ΔADAS language score increment (correlation coefficients 0.42, 0.36, respectively; Table 4). ΔACA PI was also positively associated with ΔSOB, a general cognitive measure (correlation coefficients 0.37), and ΔACA MFV was negatively associated with ΔADAS-cog praxis

Table 1
Baseline characteristics according to completion of follow-up.

	Total (n = 79)	Completion (n = 51)	Follow-up loss (n = 28)	*p*-Value
Age	71.4 ± 5.0	71.5 ± 5.1	71.4 ± 4.9	0.92
Male	46 (58.2)	32 (64.0)	14 (50.0)	0.23
Illiteracy	3 (3.8)	2 (3.9)	1 (5.0)	0.47*
Hypertension	52 (65.8)	34 (66.7)	18 (64.3)	0.83
Diabetes mellitus	21 (26.6)	11 (21.6)	10 (35.7)	0.17
Hyperlipidemia	30 (38.0)	20 (39.2)	10 (35.7)	0.76
Previous history of stroke	31 (39.2)	20 (39.2)	11 (39.3)	0.99
MMSE	21.3 ± 0.4	21.2 ± 3.3	21.5 ± 4.2	0.69
ADAS-cog	23.2 ± 8.2	23.9 ± 8.4	21.2 ± 7.3	0.22
FAB	10.2 ± 3.3	9.8 ± 3.3	11.1 ± 3.0	0.16
CDR SOB	3.8 ± 2.4	4.0 ± 2.5	3.4 ± 2.1	0.31
GDepS	17.0 ± 7.1	16.7 ± 7.5	18.0 ± 6.1	0.52

Numbers denote mean ± SD or frequency (proportion).
Abbreviations: MMSE (mini-mental state examination), ADAS-cog (Alzheimer's Disease Assessment Scale-cognitive subscale), FAB (frontal assessment battery), CDR SOB (clinical dementia rating sum of boxes), GDepS (geriatric depression scale).

Table 2
Neuropsychological parameters of baseline and follow-up evaluations.

	Baseline	Follow-up	*p*-Value
Cognitive scores			
MMSE	21.2 ± 3.3	21.7 ± 5.2	0.32
ADAS-Cog	23.9 ± 8.4	26.3 ± 8.3	<0.01
Praxis	1.8 ± 1.5	2.4 ± 1.8	0.01
Language	4.7 ± 3.3	5.5 ± 3.2	0.04
Memory	17.1 ± 4.9	18.7 ± 5.4	0.01
FAB	9.8 ± 3.3	9.9 ± 3.1	0.91
CDR	0.8 ± 0.4	0.9 ± 0.5	0.07
SOB	4.0 ± 2.5	5.0 ± 3.2	<0.01
GDepS	16.7 ± 7.4	15.0 ± 7.7	0.11
TCD parameters			
MCA MFV	52.2 ± 12.3	50.7 ± 11.8	0.18
ACA MFV	43.2 ± 8.2	43.4 ± 10.7	0.89
PCA MFV	29.4 ± 6.5	28.5 ± 5.4	0.27
MCA PI	0.89 ± 0.14	0.93 ± 0.16	<0.01
ACA PI	0.90 ± 0.15	0.93 ± 0.17	0.16
PCA PI	0.89 ± 0.15	0.90 ± 0.14	0.63

Numbers denote mean ± SD or frequency (proportion).
Abbreviations: MMSE (mini-mental state examination), ADAS-cog (Alzheimer's Disease Assessment Scale-cognitive subscale), FAB (frontal assessment battery), CDR (clinical dementia rating), SOB (sum of boxes), GDepS (geriatric depression scale), MCA (middle cerebral artery), MFV (mean flow velocity), ACA (anterior cerebral artery), PI (pulsatility index), PCA (posterior cerebral artery).

score (correlation coefficients −0.35). Otherwise, TCD parameters did not show any correlations with ΔADAS-cog total score nor ΔMMSE, ΔFAB, ΔSOB, and ΔGDepS.

Baseline age was not correlated with any change scores of TCD parameters and cognitive measures. The significances were retained except that between ΔMCA PI and ΔADAS language score after adjusting for baseline age (partial correlation coefficients 0.46 for ΔACA PI and ΔADAS-cog language, 0.38 for ΔACA PI and ΔSOB, and −0.39 for ΔACA MFV and ΔADAS-cog praxis score).

4. Discussion

In our study, higher PIs in the ACA and MCA were related to the lower cognitive status in mild to moderate AD. In addition, longitudinal changes of PI in the ACA and MCA were associated with cognitive decline.

Previous TCD studies regarding to the cognitive function were mostly cross-sectional [7,9]. In the Rotterdam study, a total of 1730 community-dwelling elderly aged over 55 years without dementia were followed up with MMSE for median 6.5 year [6], however, TCD has been evaluated once at the baseline. In this study, those with higher MFV were less likely to have dementia or cognitive decline, and PI was not investigated in this study. In patients with lacunar stroke, MCA PI was also associated with poor cognitive function assessed by MMSE and trail-making tests [7]. Our study broadens the understanding of the association between TCD parameters and cognitive decline to the longitudinal scope.

The exact mechanism for the associations between TCD parameters and cognitive changes remain to be investigated. The PI values of MCA territory was also significantly associated with the severity of cerebral white matter hyperintensities (WMH) in community-dwelling elderly [8]. Other studies have shown that strategically located WMH might impair cognitive functions [14,15]. Considering that increased PI reflects the microvascular resistance distal to the measurement site [16] and reduced resting-state CBF [2], chronic hypoperfusion might lead to neuronal cell death, and finally to the hippocampal atrophy, progression of WMH, cognitive decline, and dementia [5,6,17–19]. However, we could not incorporate magnetic resonance imaging in our study protocol.

PI has been also proposed to represent underlying aortic stiffness [20]. Stiff large vessels readily transmit the aortic pulsatility to the distal cerebral microvasculature. Along with impaired cerebral autoregulation, these pathological changes might cause alteration in perfusion during diastole [20]. In addition, stiffening of the arterial wall fails to buffer systolic pulsation, leads to blood-brain barrier failure and stagnation of the interstitial fluid, and eventually cause the microvascular damage, which mediate cognitive dysfunction [21]. In line with these previous pathophysiological findings, our results suggested that the longitudinal increment of PI could reflect cognitive decline mediated by the impaired cerebral autoregulation and functional hyperemia [22].

In our results, TCD parameters of ACA and MCA territories were significantly associated with cognitive measures, especially with praxis and language. In previous study, MFV of MCA territory were decreased in patients with AD, and this was interpreted as the possible link with pathologic changes of AD-signature regions including temporoparietal areas [16]. However, there were no reports about the association between ACA or MCI PI and cognitive dysfunction so far. ACA and MCA supply the frontal, parietal, and temporal areas, which mediate language and executive functions. Our subjects had mostly mild-stage dementia, and there might be still regional differences in the distribution of pathological processes in contrast with those with full-blown severe dementia.

MFV did not show any significant results in our study except the association between ΔACA MFV and ΔADAS-cog praxis score. One possibility is that the follow-up duration of 1 year might be relatively short to detect the significant changes of MFV, and the longitudinal PI changes might precede the alteration of MFV in patients with mild to moderate dementia.

Table 3
Correlations among baseline scores of cognitive measures and transcranial Doppler parameters.

	ACA MFV	MCA MFV	PCA MFV	ACA PI	MCA PI	PCA PI
ADAS-cog total score	0.21 (0.19)	0.04 (0.78)	−0.11 (0.48)	0.44 (<0.01)*	0.32 (0.03)*	0.32 (0.04)
ADAS-cog Praxis	0.10 (0.51)	0.05 (0.74)	−0.13 (0.42)	0.38 (0.01)*	0.20 (0.19)	0.26 (0.09)
ADAS-cog language	0.04 (0.78)	0.10 (0.52)	0.01 (0.98)	0.21 (0.17)	0.13 (0.19)	0.13 (0.40)
ADAS-cog memory	0.26 (0.10)	−0.02 (0.88)	−0.19 (0.24)	0.42 (0.01)*	0.36 (0.02)*	0.27 (0.08)
MMSE	−0.05 (0.74)	−0.05 (0.75)	−0.05 (0.75)	−0.31 (0.045)*	−0.19 (0.21)	−0.29 (0.053)
FAB	−0.12 (0.45)	−0.04 (0.81)	0.01 (0.94)	−0.23 (0.14)	−0.10 (0.50)	−0.17 (0.28)
CDR	0.28 (0.07)	0.04 (0.79)	−0.06 (0.72)	0.32 (0.04)*	0.34 (0.02)*	0.26 (0.09)
SOB	0.22 (0.15)	0.02 (0.90)	−0.15 (0.34)	0.29 (0.06)	0.25 (0.09)	0.20 (0.19)
GDepS	−0.08 (0.64)	0.002 (0.99)	−0.05 (0.78)	−0.04 (0.80)	−0.07 (0.64)	0.01 (0.96)

Numbers denote correlation coefficients (*p*-values).
Abbreviations: ADAS-cog (Alzheimer's Disease Assessment Scale-cognitive subscale), MMSE (mini-mental state examination), FAB (frontal assessment battery), CDR SOB (clinical dementia rating sum of boxes), GDepS (geriatric depression scale), MCA (middle cerebral artery), MFV (mean flow velocity), ACA (anterior cerebral artery), PCA (posterior cerebral artery), PI (pulsatility index).
* Correlation is significant at 0.05 level (2-tailed).

Table 4
Correlations among change scores of cognitive measures and transcranial Doppler parameters.

	ΔACA MFV	ΔMCA MFV	ΔPCA MFV	ΔACA PI	ΔMCA PI	ΔPCA PI
ΔADAS-cog total score	−0.06 (0.73)	−0.04 (0.82)	−0.16 (0.34)	0.28 (0.09)	0.14 (0.40)	0.04 (0.81)
ΔADAS-cog praxis	−0.35 (0.04)*	−0.003 (0.98)	−0.13 (0.45)	0.19 (0.25)	0.10 (0.53)	0.22 (0.19)
ΔADAS-cog language	−0.12 (0.50)	0.02 (0.92)	−0.21 (0.20)	0.42 (0.01)*	0.36 (0.02)*	0.21 (0.19)
ΔADAS-cog memory	0.14 (0.42)	−0.09 (0.56)	−0.14 (0.41)	0.09 (0.60)	−0.09 (0.56)	−0.12 (0.49)
ΔMMSE	−0.21 (0.21)	0.15 (0.35)	−0.01 (0.97)	−0.06 (0.70)	−0.15 (0.35)	−0.18 (0.27)
ΔFAB	−0.16 (0.35)	0.08 (0.61)	−0.08 (0.62)	−0.04 (0.80)	0.02 (0.89)	0.14 (0.40)
ΔSOB	−0.10 (0.58)	−0.04 (0.79)	−0.03 (0.88)	0.37 (0.02)*	0.23 (0.14)	0.19 (0.24)
ΔGDepS	0.001 (0.99)	−0.04 (0.83)	0.15 (0.39)	−0.03 (0.87)	0.14 (0.41)	0.16 (0.35)

Numbers denote correlation coefficients (*p*-values).
Abbreviations: ADAS-cog (Alzheimer's Disease Assessment Scale-cognitive subscale), MMSE (mini-mental state examination), FAB (frontal assessment battery), SOB (sum of boxes), GDepS (geriatric depression scale), MCA (middle cerebral artery), MFV (mean flow velocity), ACA (anterior cerebral artery), PCA (posterior cerebral artery), PI (pulsatility index).
* Correlation is significant at the 0.05 level (2-tailed).

There are some limitations in our study. High dropout rates might compromise the statistical power to detect the meaningful associations. We have not conducted the neuroimaging evaluations including magnetic resonance imaging or computed tomography, thus we have no information about the baseline WMH or their longitudinal changes. In addition, there might be a residual confounding effect of age and various vascular risk factors, though baseline age was not correlated with any change scores of TCD parameters and cognitive measures in our results. Though our study subjects showed much greater changes of PI values over a year (0.04 for MCA PI, 0.03 for ACA PI) compared to that of previous report (0.01) [23], further study with age-, sex-, education-matched control is needed. In addition, long-term follow-up over several years might show more detailed trajectories of cognitive function and vascular changes.

These data have clinical implications for future research, especially for the design of clinical trials of exploring the potential role of vascular dysfunction in AD. The PI might be a good surrogate marker of vascular dysfunction in AD, and has the advantages of low cost and easy application compared to magnetic resonance imaging biomarkers.

In conclusion, longitudinal changes of PI and MFV were associated with cognitive decline in patients with mild to moderate AD. These findings shed light on the pathophysiological link between vascular pathology and neurodegenerative dementia. Longitudinal assessment of TCD parameters might be reasonable surrogate markers for cognitive decline.

Disclosure

None.

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References

[1] J.B. Toledo, S.E. Arnold, K. Raible, J. Brettschneider, S.X. Xie, M. Grossman, S.E. Monsell, W.A. Kukull, J.Q. Trojanowski, Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre, Brain 136 (Pt 9) (2013) 2697–2706.
[2] C. Iadecola, The overlap between neurodegenerative and vascular factors in the pathogenesis of dementia, Acta Neuropathol. 120 (3) (2010) 287–296.
[3] K.A. Johnson, M.S. Albert, Perfusion abnormalities in prodromal AD, Neurobiol. Aging 21 (2) (2000) 289–292.
[4] D. Kogure, H. Matsuda, T. Ohnishi, T. Asada, M. Uno, T. Kunihiro, S. Nakano, M. Takasaki, Longitudinal evaluation of early Alzheimer's disease using brain perfusion SPECT, J. Nucl. Med. 41 (7) (2000) 1155–1162.
[5] G. Rodriguez, P. Vitali, P. Calvini, C. Bordoni, N. Girtler, G. Taddei, G. Mariani, F. Nobili, Hippocampal perfusion in mild Alzheimer's disease, Psychiatry Res. 100 (2) (2000) 65–74.
[6] A. Ruitenberg, T. den Heijer, S.L.M. Bakker, J.C. van Swieten, P.J. Koudstaal, A. Hofman, M.M.B. Breteler, Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam study, Ann. Neurol. 57 (6) (2005) 789–794.
[7] M. Altmann, B. Thommessen, O.M. Ronning, J.S. Benth, A.S. Reichenbach, B. Fure, Middle cerebral artery pulsatility index is associated with cognitive impairment in lacunar stroke, J. Neuroimaging 26 (4) (2016) 431–435.
[8] V. Mok, D. Ding, J. Fu, Y. Xiong, W.W.C. Chu, D. Wang, J.M. Abrigo, J. Yang, A. Wong, Q. Zhao, Q. Guo, Z. Hong, K.S. Wong, Transcranial Doppler ultrasound for screening cerebral small vessel disease: a community study, Stroke 43 (10) (2012) 2791–2793.
[9] B. Sabayan, S. Jansen, A.M. Oleksik, M.J.P. van Osch, M.A. van Buchem, P. van Vliet, A.J.M. de Craen, R.G.J. Westendorp, Cerebrovascular hemodynamics in Alzheimer's disease and vascular dementia: a meta-analysis of transcranial Doppler studies, Ageing Res. Rev. 11 (2) (2012) 271–277.
[10] B. Dubois, H.H. Feldman, C. Jacova, S.T. Dekosky, P. Barberger-Gateau, J. Cummings, A. Delacourte, D. Galasko, S. Gauthier, G. Jicha, K. Meguro, J. O'Brien, F. Pasquier, P. Robert, M. Rossor, S. Salloway, Y. Stern, P.J. Visser, P. Scheltens, Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria, Lancet Neurol. 6 (8) (2007) 734–746.
[11] W.G. Rosen, R.C. Mohs, K.L. Davis, A new rating scale for Alzheimer's disease, Am. J. Psychiatry 141 (11) (1984) 1356–1364.
[12] J.F. Benge, S. Balsis, L. Geraci, P.J. Massman, R.S. Doody, How well do the ADAS-cog and its subscales measure cognitive dysfunction in Alzheimer's disease? Dement. Geriatr. Cogn. Disord. 28 (1) (2009) 63–69.
[13] B. Dubois, A. Slachevsky, I. Litvan, B. Pillon, The FAB: a frontal assessment battery at bedside, Neurology 55 (11) (2000) 1621–1626.
[14] L. Shi, D. Wang, W.C. Chu, S. Liu, Y. Xiong, Y. Wang, Y. Wang, L.K. Wong, V.C. Mok, Abnormal organization of white matter network in patients with no dementia after ischemic stroke, PLoS One 8 (12) (2013), e81388. .
[15] C. Bocti, R.H. Swartz, F.Q. Gao, D.J. Sahlas, P. Behl, S.E. Black, A new visual rating scale to assess strategic white matter hyperintensities within cholinergic pathways in dementia, Stroke 36 (10) (2005) 2126–2131.
[16] A. Tomek, B. Urbanová, J. Hort, Utility of transcranial ultrasound in predicting Alzheimer's disease risk, J. Alzheimers Dis. 42 (Suppl. 4) (2014) S365–S374.
[17] J.C. de la Torre, Is Alzheimer's disease preceded by neurodegeneration or cerebral hypoperfusion? Ann. Neurol. 57 (6) (2005) 783–784.
[18] J.R. Marstrand, E. Garde, E. Rostrup, P. Ring, S. Rosenbaum, E.L. Mortensen, H.B. Larsson, Cerebral perfusion and cerebrovascular reactivity are reduced in white matter hyperintensities, Stroke 33 (4) (2002) 972–976.
[19] J. Hatazawa, E. Shimosegawa, T. Satoh, H. Toyoshima, T. Okudera, Subcortical hypoperfusion associated with asymptomatic white matter lesions on magnetic resonance imaging, Stroke 28 (10) (1997) 1944–1947.
[20] A.J. Webb, M. Simoni, S. Mazzucco, W. Kuker, U. Schulz, P.M. Rothwell, Increased cerebral arterial pulsatility in patients with leukoaraiosis: arterial stiffness enhances transmission of aortic pulsatility, Stroke 43 (10) (2012) 2631–2636.
[21] A.E. Roher, S.L. Tyas, C.L. Maarouf, I.D. Daugs, T.A. Kokjohn, M.R. Emmerling, Z. Garami, M. Belohlavek, M.N. Sabbagh, L.I. Sue, T.G. Beach, Intracranial atherosclerosis as a contributing factor to Alzheimer's disease dementia, Alzheimers Dement. 7 (4) (2011) 436–444.
[22] V. Novak, I. Hajjar, The relationship between blood pressure and cognitive function, Nat. Rev. Cardiol. 7 (12) (2010) 686–698.
[23] S.L. Bakker, F.E. de Leeuw, T. den Heijer, P.J. Koudstaal, A. Hofman, M.M. Breteler, Cerebral haemodynamics in the elderly: the Rotterdam study, Neuroepidemiology 23 (4) (2004) 178–184.