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Research report

Angiotensin converting enzyme serum activities: Relationship with Alzheimer's disease

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ABSTRACT

Objective: To determine serum activities of angiotensin-converting enzyme (ACE) as a marker in diagnosis and determine the severity of Alzheimer's disease (AD),
Methods: We measured serum ACE activities in 59 moderate-severe AD, 19 mild AD, 45 amnestic mild cognitive impairment (aMCI) and 39 controls.
Results: We found that patients in moderate-severe AD stages showed significantly higher ACE in comparison to aMCI and controls (ANOVA, LSD post hoc test: p: 0.02 and p: 0.01, respectively). Logistic regression analysis showed that if ACE activities added 200 U/L, the superiority of AD risk was 1.18 times higher than before compared with the control group (OR 1.18, 95% CI 1.01–1.74; P=0.49). By means of multivariate linear regression analysis, we found that age (β coefficient: 7.77; P: 0.01) was significantly associated with ACE activities. However, ACE activities were found to be significantly negatively associated with measures of orientation and immediate recall among the AD patients ($r<0$, $P<0.05$), whereas ACE activities were not associated with any MMSE scores among the non-AD groups ($P > 0.05$). uuuu
Conclusions: ACE serum activity that correlates with age is likely to constitute a potential risk factor for the development of AD. ACE serum activity might be a useful biomarker for disease status with increasingly high ACE from mild stage to moderate-severe stage. Moreover, patients with aMCI could take ACE inhibitor (ACEI) to decrease the incidence of AD, and patients with AD could take ACEI to retard cognitive decline in early AD.

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia (Mount and Downton, 2006), and the greatest risk factor for the development of AD is advancing age. AD is characterized by neurodegeneration and progressive cognitive dysfunction, and this has an enormous impact on the quality of life of patients and their caregivers. The pathology of AD is mainly characterized by the presence of senile plaques and neurofibrillary tangles in the medial temporal lobe structures and other cortical areas of the brain. The major constituent of the plaques is the beta amyloid peptide (Aβ) generated by enzymatic cleavage from its precursor, the amyloid precursor protein (APP). Mild cognitive impairment (MCI) is considered as a possible intermediary state, and it refers to the transition between healthy aging and very early AD (Morris et al., 2001; Petersen, 2004; Petersen et al., 2006). When episodic memory impairment is the predominant symptom, it is classified as 'amnestic MCI (aMCI)' that is considered to be prodromal AD at a higher risk of developing AD (Petersen, 2003). Shin et al. (2015) found that 63.2% old aMCI (age 65 years or older), but only 28.2% young aMCI(age below 65 years) had abnormal cerebrospinal fluid (CSF) amyloid measures consistent with AD pathology. Therefore, early identification of old aMCI may provide a unique opportunity to protect against the occurrence of overt AD, and it is crucial to develop a diagnostic tool for AD at the pre-dementia stage.

The principal effect of angiotensin converting enzyme (ACE) is the mediation of extracellular volume by producing angiotensin II (AngII), a potent vasoconstrictor, and degrading bradykinin (Andresen et al., 2006; Iadecola, 2004; Ignjacev-Lazich et al., 2005), a potent vasodilator (Rigat et al., 1990). Substantial evidence showed that angiotensin converting enzyme inhibitor (ACEI) was independently associated to the stability of cognitive function (Rozzini et al., 2006), reduced the risk of AD (Qiu et al. 2013; Yasar

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et al., 2013; Ye et al., 2015), exerted a protective function on the conversion of MCI to AD (Schneider et al., 2011), and slowed the rate of cognitive decline in AD (Hajjar et al., 2005; O'Caoimh et al., 2014; Ye et al., 2015). Nevertheless, ACE has been demonstrated to degrade Aβ, convert Aβ1−42 into the less neurotoxic Aβ1−40; retard Aβ aggregation, deposition, fibril formation; and inhibit cytotoxicity in vitro (Hu et al. 2001), mediate cleavage of Aβ ex vivo (Zou et al., 2007) and in animal models (Wang et al., 2007; Zou et al., 2007) of AD. Recently, higher CSF ACE activity was found to decrease the risk of global brain atrophy (Jochemsen et al. 2015). Moreover, ACE was found to be elevated in AD patients compared with control in the hippocampus, parahippocampus, and temporal cortex (Barnes et al., 1991; Miners et al., 2008; Savaskan et al., 2001). Miners et al. (2009) showed that ACE activity significantly increased in the frontal cortex and CSF in AD and related to the stage of disease. In peripheral, a two years follow-up study reported that plasma ACE activity was greater reduction in AD compared with controls (Vardy et al. 2009), and a cross-sectional regression analyses found that serum ACE level and activity were lower in patients with AD compared to controls (Jochemsen et al., 2014). However, Akatsu et al. (2011) and Nielsen et al. (2007) revealed no evidence of association between AD and plasma ACE activities and levels respectively.

Therefore, there is no accordant conclusion of the effect of plasma ACE on AD. ACE activity produces AngII, and forasmuch, it is arguably more biologically meaningful than ACE level. No study has concerned about the association of serum ACE activity and the severity of the development of AD, thus, the purpose of this study was to explore the association of serum ACE activity and severity of AD, and to determine whether there is association between serum ACE activity and cognitive function. Moreover, we intend to investigate the role of serum ACE activity in the diagnosis of AD and provide theoretical basis for clinical intervention of early prevention and subsequent progression of AD.

2. Results

2.1. Clinical and demographic characteristics

Demographic and clinical profiles of the four groups of individuals included in this study are summarized in Table 1. The AD patients were statistically significantly older than the non-AD subjects. The prevalence of male gender was lower in controls and mild AD compared with moderate-severe AD. The years of education in moderate-severe AD group were fewer compared with mild AD and non-AD groups. A lower MMSE score was observed in AD compared with non-AD individuals. The prevalence of hypertension was higher in mild AD group compared with moderate-severe AD and control groups.

2.2. ACE serum activities in AD, aMCI and controls

As shown in Fig. 1, the mean activity of ACE was progressively lower from moderate-severe AD (425.09 ± 223.39), to mild AD (383.29 ± 304.40), to aMCI (313.02 ± 290.52), to controls (282.77 ± 194.48). We found that ACE serum activities of the AD group were higher than that of aMCI and controls, when considering different stages of AD altogether (ANOVA, LSD post hoc test: P:0.03 and P:0.01, respectively). Moreover, moderate-severe AD showed significantly higher ACE compared with aMCI and controls (ANOVA, LSD post hoc test: P:0.02 and P:0.01, respectively).

2.3. Multivariate logistic regression analysis

The ACE activity was divided into seven groups from 0 U/L upward in increments of 200 U/L and transformed into an ordered categorical variable. The age, sex, years of education and ACE activity were included in the multivariate logistic regression analysis. Logistic regression analysis showed that age was a risk factor for AD compared with the control group [odds ratio (odds ratio, OR) 1.13, 95% CI (confidence interval, CI) 1.04–1.21; $P < 0.01$] and aMCI group (OR 1.10, 95% CI 1.03–1.18; $P < 0.01$). And low levels of education was a risk factor for AD (OR 0.80, 95% CI 0.71–0.89; $P < 0.01$) and aMCI (OR 0.84, 95% CI 0.76–0.94; $P < 0.01$) compared with the control group. If ACE activities added 200 U/L, the superiority of AD risk was 1.18 times higher than before compared with the control group (OR 1.18, 95% CI 1.01–1.74; P=0.49). And the superiority of AD risk was 18% higher than before, when ACE activities added 200 U/L. And ACE measures were not influenced by age, sex, and years of education (Table 2).

Table 1
Principal characteristics of elderly patients with controls, aMCI, mild AD, and moderate-severe AD (means ± standard deviation or median–interquartile range).

	AD (n = 78)		No AD (n = 84)		P
	Moderate-severe AD (n=59)	Mild AD (n=19)	aMCI (n=45)	Controls (n=39)	
Age (y)	83 ± 7	82 ± 7	76 ± 7[*,§]	75 ± 6[*,§]	< 0.01[a]
Male gender (n, %)	18, 21.4	11, 47.8[*]	19, 26.8	23, 41.8[*]	0.02[c]
MMSE score (/30)	12(8–15)	20 (19–22)[*]	27(25–28)[*,§]	29(29–30)[*,§,#]	< 0.01[b]
Years of education	3(0–5)	8.5(2.25–15.25)[*]	8(5–11)[*]	12(9–15)[*,#]	< 0.01[b]
Glucose (mmol/L)	5.01(4.59–6.44)	4.86(4.45–5.39)	4.84(4.57–5.60)	4.94(4.32–5.91)	0.58[b]
Triglycerides (mmol/L)	1.30(1.01–1.89)	1.29(0.89–2.10)	1.25(0.94–1.79)	1.15(0.91–1.78)	0.73[b]
Total cholesterol (mmol/L)	5.06 ± 1.03	5.01 ± 0.97	4.88 ± 1.26	4.97 ± 1.19	0.90[a]
LDL cholesterol (mmol/L)	2.79 ± 0.71	2.75 ± 0.76	2.82 ± 0.98	2.88 ± 0.83	0.94[a]
ACE activities (U/L)	425.09 ± 223.39	383.29 ± 304.40	313.02 ± 290.52[*]	282.77 ± 194.48[*]	0.03[a]
Hypertension (n/%)	22, 44.0	15, 78.9[*]	25, 55.6	18, 46.2[§]	0.03[c]
Hyperlipoidemia (n/%)	13, 30.2	7, 38.9	19, 45.2	19, 48.7	0.18[c]
Smoking (n/%)	9, 18.8	6, 31.6	13, 28.9	9, 23.1	0.39[c]
CHD (n/%)	19, 38.8	7, 36.8	21, 60.0	17, 43.6	0.75[c]

Notes: MMSE, Mini Mental State Examination; LDL, Low Density Lipoprotein; CHD, Coronary Heart Disease.

[a] ANOVA.
[b] Kruskal–Wallis Test.
[c] Chi-squared test.
[*] vs Moderate-severe AD $P < 0.05$.
[§] vs Mild AD $P < 0.05$.
[#] vs aMCI $P < 0.05$.