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ORIGINAL ARTICLE

Cerebrospinal Fluid Biomarkers in Dementia Patients with Cerebral Amyloid Angiopathy

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Key words: cerebral amyloid angiopathy; Alzheimer's disease; cerebrospinal fluid biomarker

Objective To study the changes of biomarkers in cerebrospinal fluid (CSF) in cerebral amyloid angiopathy (CAA) dementia and Alzheimer's disease.

Methods Levels of amyloid protein β ($A\beta_{42}$, $A\beta_{40}$) and phosphorylated Tau-protein (P-tau) in CSF and ratio of $A\beta_{42}/A\beta_{40}$ were tested in 5 cases with CAA dementia and 20 cases with Alzheimer's disease collected at Peking Union Medical College Hospital from December 2001 to March 2011.

Results The levels of $A\beta_{42}$, $A\beta_{40}$, and P-tau in CSF and ratio of $A\beta_{42}/A\beta_{40}$ were (660.4 ± 265.2) ng/L, (7111.0 ± 1033.4) ng/L, (71.8 ± 51.5) ng/L, and 0.077 ± 0.033 , respectively in CAA dementia and (663.6 ± 365.6) ng/L, (5115.0 ± 2931.1) ng/L, (47.7 ± 38.8) ng/L, and 0.192 ± 0.140 , respectively in Alzheimer's disease patients. There were no statistically significant differences between CAA dementia and Alzheimer's disease in terms of these CSF biomarkers (all $P > 0.05$).

Conclusion Measurements of CSF biomarkers may not be helpful in differential diagnosis of CAA and Alzheimer's disease.

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CEREBRAL amyloid angiopathy (CAA), which is clinically characterized by ischemic attack, cerebral hemorrhage and cognitive disorder, is a common cerebrovascular disease among the older people.¹ It is pathologically identified as deposition of amyloid β -protein ($A\beta$) on the small vessel walls in cerebral cortex and cerebral dura mater. The morbidity of CAA increases along with age, which was about 4% in people

aged 50 years but over 60% in those at the age of over 90, as showed by autopsy.²⁻⁴ Because this disease may pathologically and clinically overlap with Alzheimer's disease (AD), differential diagnosis was urged to confirm the clinical diagnosis. Cerebrospinal fluid (CSF) biomarkers can help to diagnose AD, but we did not know their role in the diagnosis of CAA and differences between these two diseases. Therefore, we compared the levels of some biomarkers in the CSF in 5 cases with CAA dementia and 20 cases with AD and wished to find the biomarkers that could help distinguish the two diseases.

PATIENTS AND METHODS

Patient collection

We collected 5 cases with CAA who visited Peking Union Medical College Hospital from December 2001 to March 2011 due to chief complaints of loss of memory and social behavioral function and fulfilled the Boston criteria for Dutch-type cerebral amyloid angiopathy¹ for probable CAA (MRI findings demonstrated multiple lobar, cortical and sub-cortical hemorrhages, the patients were older than 55 years, and other causes of hemorrhage were ruled out). Dementia due to other causes such as human immunodeficiency virus infection, syphilis infection, nutrition metabolic disorder and poisoning were also excluded. All the 20 cases with AD in the same time period fulfilled the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) diagnostic criteria for AD.

Typical MRI findings (Case 1 and Case 2) were showed in Fig. 1.

Methods

Methods for determination of apolipoprotein E (APOE) genotype and the levels of CSF biomarker phosphorylated tau-protein (P-tau) and amyloid protein β ($A\beta_{42}$ and $A\beta_{40}$) are described as follows. The conventional phenol-

chloroform method was adopted to extract genome DNA from peripheral white blood cells,⁵ and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used to determine APOE. Enzyme-linked immunosorbent assay (ELISA, InnoTest, Indianapolis, IN, USA) was used to detect and measure CSF levels of Tau and $A\beta$.

Statistical analysis

SPSS 12.0 software package was used for statistical analysis. *T* test was used for the comparison of CSF biomarkers between CAA dementia and AD. $P < 0.05$ was considered statistically significant.

RESULTS

The clinical information of the 5 CAA dementia patients was shown in Table 1, the levels of P-tau, $A\beta_{42}$, $A\beta_{40}$ in the CSF and the ratio of $A\beta_{42}/A\beta_{40}$ in each CAA dementia case were listed in Table 2. The 5 cases of CAA dementia were all male with the mean age of 74.4 ± 4.82 years old, while the mean age of the AD patients was 67.3 ± 7.79 years, smaller than that of the CAA dementia patients, although with no statistical significance (Table 3). The comparison between CAA dementia and AD patients in terms of levels of P-tau, $A\beta_{42}$, $A\beta_{40}$ in the CSF and the ratio of $A\beta_{42}/A\beta_{40}$ all showed no significant differences (all $P > 0.05$, Table 3).

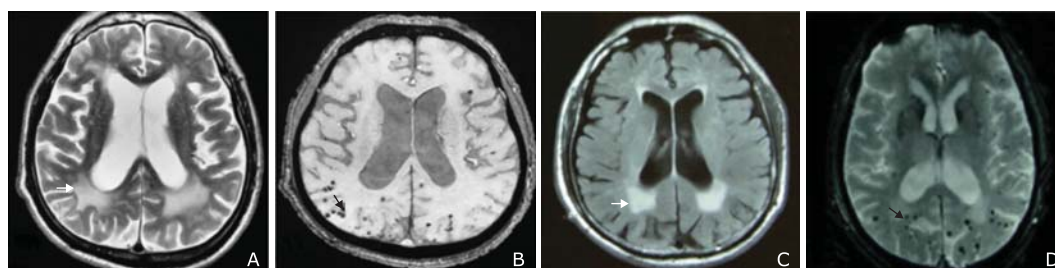


Figure 1. T2-weighted imaging (T2WI) (A) and susceptibility weighted imaging (SWI) (B) of Case 1 of cerebral amyloid angiopathy (CAA) dementia. Fluid-attenuated inversion recovery (FLAIR) (C) and gradient echo image (D) of Case 2 of CAA dementia. White arrows in T2WI and FLAIR indicate prefrontal multiple white matter demyelination, and black arrows in SWI and gradient echo image show small hemorrhage.

Table 1. Clinical data of the 5 selected CAA dementia cases

Case no.	Age (yrs)	Gender	Onset time	Cognitive test results			APOE genotype	Head MRI lesions		
				MMSE	MoCA	FOM		Periventricular multiple white matter demyelination	Small hemorrhagic focus by gradient echo	Hippocampal atrophy
1	74	Male	1/2 year	6	7	7	$\epsilon 2, 4$	Yes	Yes	No
2	72	Male	2 years	16	16	5	$\epsilon 3, 4$	Yes	Yes	Suspected
3	69	Male	2 years	19	12	11	$\epsilon 3, 3$	Yes	Yes	No
4	75	Male	2 months	20	16	8	$\epsilon 3, 3$	Yes	Yes	Suspected
5	82	Male	4 years	17	22	14	$\epsilon 3, 4$	Yes	Yes	No

MMSE: mini-mental state examination; MoCA: Montreal cognitive assessment; FOM: Fuld object memory evaluation; APOE: apolipoprotein E; MRI: magnetic resonance imaging.

Table 2. The results of CSF biomarkers in CAA dementia

Case no.	P-tau* (ng/L)	A β ₄₂ (ng/L)	A β ₄₀ (ng/L)	A β ₄₂ /A β ₄₀ [#]
1	47	456	6783	0.067
2	34	311	5528	0.056
3	170	933	7894	0.118
4	55	843	8127	0.104
5	53	759	7223	0.041

*Normal < 62 ng/L; [#]normal > 0.149; CSF: cerebrospinal fluid; P-tau: phosphorylated Tau-protein; A β : amyloid protein β .

Table 3. Comparison of CSF biomarkers between CAA dementia and Alzheimer's disease (AD) patients

Groups	<i>n</i>	Gender (M/F)	Age (yrs) [§]	P-tau (ng/L) [§]	A β ₄₂ (ng/L) [§]	A β ₄₀ (ng/L) [§]	A β ₄₂ / A β ₄₀
CAA	5	5/0	74.4±4.8	71.8±51.5	660.4±265.2	7111.0±1033.4	0.077±0.033
AD	20	12/8	67.3±7.8	47.7±38.8	663.6±365.6	5115.0±2931.1	0.192±0.140
<i>t</i>			1.929	1.167	0.018	1.492	1.797
<i>P</i>			0.066	0.250	0.986	0.153	0.086

§: Plus-minus values are means±SD.

DISCUSSION

The incidence of CAA is strongly age-dependent and presents with female predominance;⁶ however, all the 5 cases of CAA dementia reported in the present study were male, which may be due to the small sample size with CSF specimens.

All the cases showed an insidious disease progression that was either fast or slow. Case 1 developed into a severe condition within one year after onset of CAA; while Case 2 and 3 had a longer course of disease progression. Among the cognitive function test results of all the cases, MMSE, MoCA and FOM scores declined, fulfilling the diagnosis of dementia. Because obvious vascular lesions were found in all the cases, susceptibility weighted imaging (SWI) or gradient echo imaging was further performed to demonstrate multiple small hemorrhagic focuses that distributed widely in multiple lobes, including the cerebral hemisphere cortex and sub-cortex, brain stem, and the cerebellar hemispheres. These focuses could not be discovered by the conventional T1/T2 scanning. Such findings in imaging were consistent with those previously reported and could help to confirm CAA.⁷

APOE ϵ 2 allele may play a role in the severity and clinical course of CAA lobar intracranial hemorrhage.⁸ APOE ϵ 4 allele may be a risk factor in the development of CAA dementia.⁹ However, there were no consistent reports on the relationship between APOE genotype and CAA.¹⁰

Therefore, we did not analyze APOE genotype as a marker for the differential diagnosis of CAA and AD. The relationship between APOE genotype and CAA complicated by dementia still needs to be identified through further research.

Neuro-pathological studies suggest that vascular and parenchymal A β deposits can either occur relatively independently or overlap.¹¹ A β not only accumulates in the brain parenchyma as senile plaques in AD, but also in brain vessels in CAA.¹² CAA dementia is associated with both vascular mechanism and A β deposition.¹⁻³ The proportion of CAA complicated by dementia was over 40%, while that of AD complicated by CAA was greater than 80%. Because CAA may pathologically and clinically overlap with AD, it is important to differentiate in diagnosis.

In contrast to the parenchymal depositions with A β ₄₂ in AD, CAA contains both A β ₄₀ and A β ₄₂ but primarily A β ₄₀. Some findings of previous studies confirm that the decreased CSF A β ₄₀ concentrations in CAA were not significantly lower than that in controls, but significantly lower than that in AD.^{12, 13}

In this study, CSF biomarker measurement was performed for all the 5 CAA cases, showing that all the cases had an increased level of A β ₄₀ in the CSF and decreased A β ₄₂/A β ₄₀ ratio, but changes in their Tau protein were not characteristic. CSF biomarkers were not significantly different between AD and CAA dementia, indicating that CAA dementia may have the same pathological basis as AD. Therefore, amyloid substances that deposit in the

blood vessels may be from the same sources as those deposit in the brain parenchyma and thus cause intelligence-related demyelination. The finding of this study was not consistent with previous reports which showed that the A β ₄₀ concentration in CSF was decreased in CAA dementia compared with AD. It may be due to this small sample size of CAA dementia in this study. Further study is need to confirm whether CSF biomarkers could help distinguish CAA dementia from AD.

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