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Invited critical review

Evaluation of dementia by acrolein, amyloid-β and creatinine

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ABSTRACT

Plasma, urine and cerebrospinal fluid (CSF) were examined for biochemical markers of dementia. Protein-conjugated acrolein (PC-Acro) and the amyloid-β (Aβ)$_{40}$/$_{42}$ ratio in plasma can be used to detect mild cognitive impairment (MCI) and Alzheimer's disease (AD). In plasma, PC-Acro and the Aβ$_{40}$/$_{42}$ ratio in MCI and AD were significantly higher relative to non-demented subjects. Furthermore, urine acrolein metabolite, 3-hydroxypropyl mercapturic acid (3-HPMA)/creatinine (Cre) and amino acid-conjugated acrolein (AC-Acro)/Cre in AD were significantly lower than MCI. It was also shown that reduced urine 3-HPMA/Cre correlated with increased plasma Aβ$_{40}$/$_{42}$ ratio in dementia. The Aβ$_{40}$/PC-Acro ratio in CSF, together with Aβ$_{40}$ and Aβ$_{40}$/$_{42}$ ratio, was lower in AD than MCI. Increased plasma PC-Acro and Aβ$_{40}$/$_{42}$ ratio and decreased urine 3-HPMA/Cre correlated with cognitive ability (MMSE). These results indicate that the measurements of acrolein derivatives together with Aβ and Cre in biologic fluids is useful to estimate severity of dementia.

Contents

1. Introduction

Dementia and infarction are pathologies accompanied by damage of brain tissue. Although these two diseases are widespread and represent serious morbidity in the elderly, there are currently no simple useful biomarkers for these conditions. We recently reported that increased protein-conjugated acrolein (PC-Acro) and the enzymes responsible for acrolein (CH_2═CH–CHO) production, polyamine oxidases (spermine oxidase and acetylpolyamine oxidase) in plasma, were good biomarkers for brain infarction [1,2]. It was also shown that silent brain infarction, i.e., small brain infarction (SBI), could be detected with ~84% sensitivity and specificity by measuring PC-Acro with interleukin-6 and C-reactive protein in plasma [3]. Furthermore, urinary 3-hydroxypropyl mercapturic acid (3-HPMA), a metabolite of acrolein–glutathione conjugate, was reduced following stroke [4].

Cell damage is thought to be mainly caused by reactive oxygen species (ROS) [5], such as superoxide anion radical (O_2•$^-$), hydrogen peroxide (H_2O_2) and hydroxyl radical (•OH). However, when the toxicity of acrolein and ROS was compared, it was found that acrolein was more toxic than H_2O_2 [6] and slightly more toxic than •OH [7] in

Abbreviations: Aβ, amyloid-β; AC-Acro, amino acid-conjugated acrolein; AD, Alzheimer's disease; Cre, creatinine; ELISA, enzyme linked immunosorbent assay; 3-HPMA, 3-hydroxypropyl mercapturic acid; LC–MS/MS, liquid chromatography-tandem mass spectrometry; MCI, mild cognitive impairment; nd-WMH, non-demented subjects with white matter hyperintensity; PC-Acro, protein-conjugated acrolein.

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cultured cells. Furthermore, acrolein is thought to be produced by lipid peroxidation [8], but we found that it was more effectively produced from two polyamines (spermine and spermidine) [1], which are abundant and essential for cell growth in eukaryotic cells [9]. Acrolein is spontaneously formed from 3-aminopropanal [$NH_2(CH_2)_2CHO$] produced from spermine by spermine oxidase and less effectively from 3-acetamidopropanal [$CH_3CONH(CH_2)_2CHO$] produced from spermine and spermidine by spermidine/spermine N^1-acetyltransferase and acetylpolyamine oxidase [10,11]. It has been also shown that acrolein is produced from spermine and spermidine at the locus of infarction using photo-induced thrombosis model mice, and found that PC-Acro is increased together with a decrease in spermine and spermidine during infarction. The results indicate that the induction of infarction is well correlated with the increase in protein-conjugated acrolein at the locus of infarction and in plasma [12,13].

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a progressive impairment of cognitive function and behavior. AD is the most common form of dementia, particularly in the elderly [14–17]. Thus, simpler diagnostic tools, including easily accessible biomarkers for evaluation of AD, are currently being sought. Recently, the level of amyloid-β (Aβ) in plasma has been identified as a potential biomarker. However, the results concerning Aβ are contradictory. Several studies reported that plasma $Aβ_{40}$ and $Aβ_{42}$ levels were not significantly different [18–21]. Others reported that plasma $Aβ_{40}$ or the $Aβ_{42/40}$ ratio was significantly reduced in AD subjects [22–25]. In addition, an increase in PC-Acro or free acrolein in brain tissues of AD patients has been reported [26–29]. In this review, the significance of acrolein conjugates (PC-Acro, 3-HPMA and AC-Acro), Aβ and Cre in plasma, urine and CSF as biomarkers of dementia is discussed.

2. PC-Acro and $Aβ_{40/42}$ ratio in plasma as biochemical markers for MCI and AD

The MMSE (mini-mental state examination) [30] and the CDR sob (Clinical Dementia Rating Scale Sum of Boxes Scores) [31] were used for evaluation of dementia. Median values of MMSE for 33 healthy control, 68 nd-WMH (non-demented subjects with white matter hyperintensity: high risk subjects for MCI and AD), 50 MCI and 70 AD subjects were 29.5, 29.0, 23.0 and 18.0, respectively, and median values of CDR sob were 0, 0, 1.5 and 5.0, respectively. As for the biochemical markers, it was first tested whether PC-Acro in plasma represents a biochemical marker in MCI and AD patients, as it does for stroke patients [1]. As shown in Fig. 1A, the level of PC-Acro was significantly higher in MCI and AD patients than in control subjects, indicating that tissue damage is advanced in MCI and AD patients. The level of $Aβ_{40}$ and $Aβ_{42}$ was not altered significantly among control, nd-WMH, MCI and

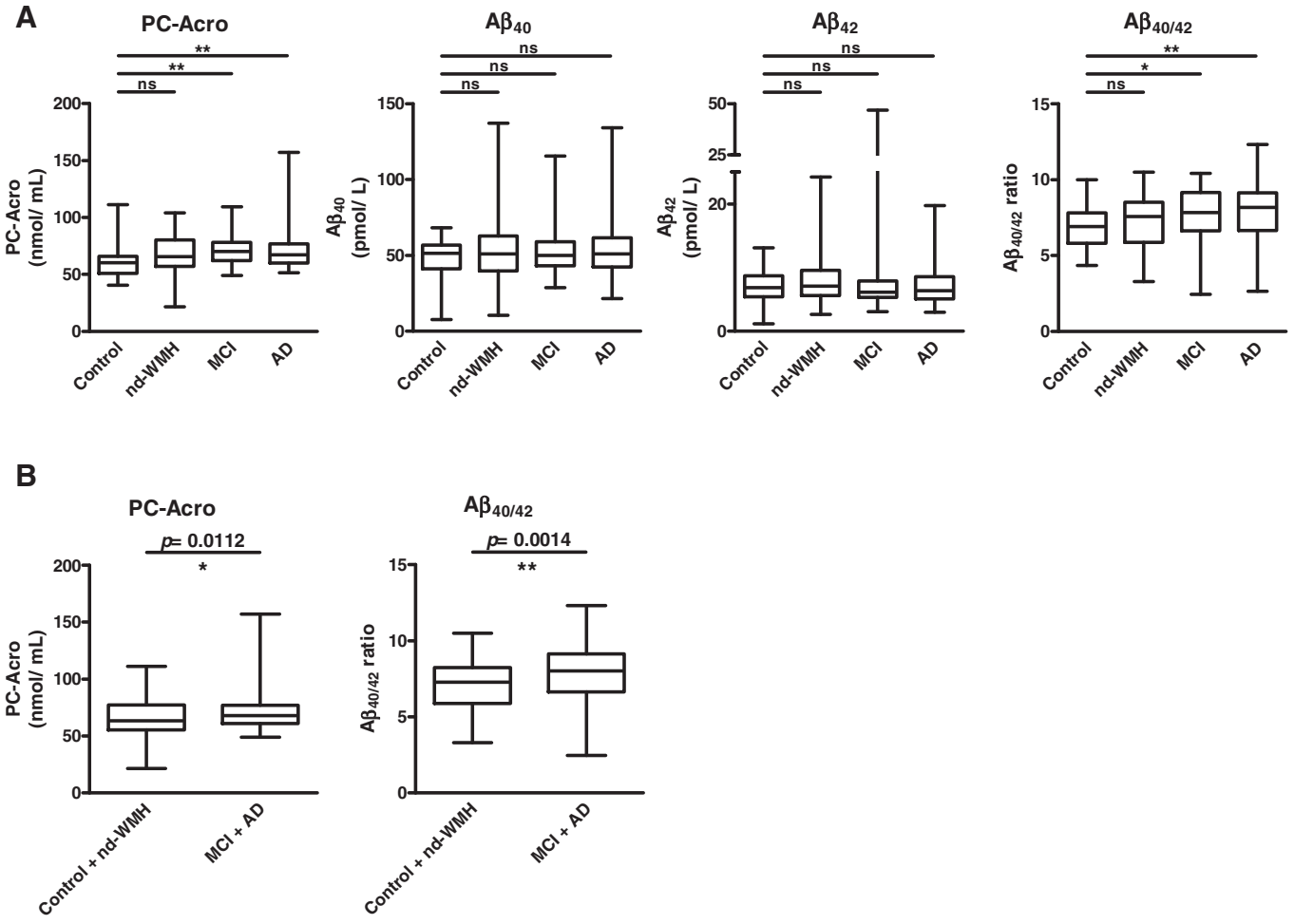

Fig. 1. Levels of PC-Acro and Aβ in plasma of control, nd-WMH, MCI and AD subjects. A. PC-Acro, $Aβ_{40}$, $Aβ_{42}$ and $Aβ_{40/42}$ ratio were measured. The number and age (in parenthesis) of control, nd-WMH, MCI and AD subjects were 33 (64.0 ± 10.3 years old), 68 (75.5 ± 6.3 years old), 50 (79.5 ± 5.8 years old) and 70 (81.0 ± 4.5 years old), respectively. PC-Acro, $Aβ_{40}$ and $Aβ_{42}$ were measured by ELISA. Horizontal line within a box indicates median, the bottom and the top of boxes indicate the 25th and 75th percentiles, and whiskers (vertical lines) indicate the minimum and maximum values. Median values of PC-Acro, $Aβ_{40}$, $Aβ_{42}$ and $Aβ_{40/42}$ ratio for control, nd-WMH, MCI and AD subjects were 60.2, 65.7, 70.3 and 67.3 nmol/ml, 51.4, 51.1, 50.0 and 51.0 pmol/l, 6.9, 7.1, 6.2 and 6.4 pmol/l, and 6.9, 7.6, 7.8 and 8.2, respectively. B. Comparison of the levels of PC-Acro and $Aβ_{40/42}$ ratio between control plus nd-WMH subjects, and MCI plus AD patients. Median values of PC-Acro and $Aβ_{40/42}$ for control plus nd-WMH subjects, and MCI plus AD patients were 63.4 and 67.9 nmol/ml, and 7.3 and 8.0, respectively. ns, $p \geq 0.05$; $^*p < 0.05$; $^{**}p < 0.01$.