ELSEVIER

Neurobiology of Aging 29 (2008) 1–11

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Conversion from cognitive health to mild cognitive impairment and Alzheimer's disease: Prediction by plasma amyloid beta 42, medial temporal lobe atrophy and homocysteine

Imrich Blasko[a], Kurt Jellinger[b], Georg Kemmler[a], Wolfgang Krampla[c,d], Susanne Jungwirth[e], Ildigo Wichart[b], Karl Heinz Tragl[d,e], Peter Fischer[e,f,*]

[a] *Department of Psychiatry, Innsbruck Medical University, Austria*
[b] *Institute of Clinical Neurobiology, Vienna, Austria*
[c] *Ludwig Boltzmann Society, L. Boltzmann Institute of Digital Radiology and Interventional Radiology, Vienna, Austria*
[d] *Danube Hospital, Vienna, Austria*
[e] *Ludwig Boltzmann Society, L. Boltzmann Institute of Aging Research, Vienna, Austria*
[f] *Department of General Psychiatry, Medical University of Vienna, Austria*

Received 18 May 2006; received in revised form 24 July 2006; accepted 6 September 2006
Available online 19 October 2006

Abstract

The changes of plasma amyloid beta (Aβ42) protein, homocysteine and medial temporal lobe atrophy (MTA) were studied by the transition from cognitive health to mild cognitive impairment (MCI) and to Alzheimer's disease (AD) in a prospective cohort of individuals aged 75 years. MTA but not plasma Aβ42 measured at baseline predicted which persons remained cognitively healthy (CH) and who developed AD 2.5 years later. The increase of plasma Aβ42 over time significantly distinguished between persons who remained CH on the one hand and MCI converters and AD converters out of cognitive health on the other (CH-to-MCI and CH-to-AD converters). Although both groups showed similar increase of Aβ42 levels, CH-to-AD converters had a higher increase of homocysteine compared to CH-to-MCI converters or to persons remaining CH. In comparison to all cognitive subgroups, the AD converters from MCI at baseline showed the smallest increase of Aβ42 levels and rather no increase of homocysteine. In logistic regression analysis, the increase of plasma Aβ42 but not change of MTA significantly predicted the conversion from CH to MCI, and changes of MTA and homocysteine but not of plasma Aβ42 predicted the conversion from CH to AD. The increase of plasma Aβ42 correctly allocated CH-to-MCI and CH-to-AD converters with low (63%) specificity (for both) and low (60%) sensitivity (54% for AD group). These results indicate that (1) plasma Aβ42 alone is not suitable as a biomarker for AD, (2) in the course of cognitive deterioration of the AD-type the increase of plasma Aβ42 seems to be an initial event, (3) similar to cerebrospinal fluid, changes of plasma Aβ42 may reflect the transition from cognitive health to AD, and (4) whether persons with MCI develop AD may depend on an accumulation of further toxic metabolites such as homocysteine.

Keywords: Plasma Aβ42; Medial temporal lobe atrophy; Alzheimer's disease; Mild cognitive impairment; Homocysteine

1. Introduction

The longitudinal changes of plasma amyloid β 42 peptide (Aβ42) might help to depict the decline from cognitive health to mild cognitive impairment (MCI) and Alzheimer's disease (AD). Aβ42 is a 42 amino acid long peptide which is deposited in the brain of AD patients. Whether the Aβ found in the plasma of AD patients originates from the brain or from peripheral tissues or from both sources is still not definitely resolved [23]. Platelets have been regarded as the primary source of circulating Aβ, although the levels of Aβ (40/42) in plasma appear not to be related to platelet activation [34]. Therefore, it seems feasible that the majority

* Corresponding author at: Department of General Psychiatry, Medical University of Vienna, AKH, Waehringer Guertel 18-20, 1090 Vienna, Austria. Tel.: +43 1 40400 3543; fax: +43 1 40400 3099.
E-mail address: Peter.Fischer@meduniwien.ac.at (P. Fischer).

0197-4580/$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.neurobiolaging.2006.09.002

of Aβ42 in plasma originates from the brain. Aβ42 is transported bidirectionally through the blood–brain-barrier (BBB) [42], and it has been suggested that a dynamic equilibrium between central and peripheral pools of Aβ may exist. Aβ42 has a short half-life of 2.5–3.0 min upon intravenous injection of the peptide in experimental animals and its intracellular catabolism in liver is responsible for its sufficient peripheral degradation [16].

Recent experimental knowledge of the nature and regulation of Aβ transportation through the BBB support studies on the longitudinal changes of plasma Aβ42. The receptor for advanced glycosylation end products (RAGE) mediate the influx of circulating Aβ [7] and the low density lipoprotein receptor-related protein-1 (LRP) mediates efflux of brain-derived Aβ [9,42]. In experimental conditions, animal models of AD and also in AD brains, downregulation of LRP in concert with upregulation of RAGE may create an unfavorable Aβ gradient across the BBB, resulting in Aβ retention in the brain [44,53]. The capacity of these transportation systems seems to depend on age. In a transgenic mice model of Aβ-amyloidosis, LRP-mediated clearance of Aβ decreases with age [8]. The importance of transportation of Aβ at the BBB is supported by recent genetic evidence. Partial deletion of the MEOX2 gene resulted in deficient clearance of Aβ by the LRP receptor [52].

Applying these findings to clinical studies, an increase of Aβ42 plasma levels in amnestic mild cognitive impairment (aMCI) was described in female subjects [2]. The aMCI is of interest as longitudinal and pathological data indicate a 10–15% yearly conversion rate from aMCI to AD [15,17]. Another cross-sectional study showed that the plasma Aβ42 levels are significantly higher in aMCI as compared to both AD and control subjects [43].

The pivotal study by Mayeux et al. described the relation of Aβ42 and Aβ40 to age, mortality and risk for development of AD [27]. The elevation of plasma Aβ42 also in the first-degree relatives of AD patients is of interests in this context [11]. An overlap between elderly individuals developing AD and those who remained healthy was found, demonstrating that the measurement of plasma Aβ42 needs to be done before the onset of cognitive deterioration and that the differences in frequency of AD by plasma Aβ42 levels emerge only after 2–3 years of follow-up. This study suggested that rather longitudinal, not cross-sectional studies will be required to determine usefulness of Aβ42 in assessing risk for development of AD.

Because oxidative stress was frequently connected with the development of AD, we included the measurement of homocysteine in our analysis. Homocysteine is a neurotoxic amino acid, the plasma level of which may reflect the degree of oxidative stress to which an organism was exposed during the course of a disorder. Aβ42 itself is a potent inducer of oxidative stress and a positive cross-sectional association between total homocysteine and plasma Aβ levels was described [19]. Previous studies have reported an inverse association between plasma homocysteine levels and simultaneously assessed cognitive function [3,25,32,37]. A prospective study from the Framingham cohort showed an increased plasma homocysteine level as an independent risk factor for the development of dementia and AD [41]. Whether or not the increase of plasma Aβ42 precedes the increase of homocysteine has not been investigated.

We previously demonstrated that plasma Aβ42 measured cross-sectionally in a population of 75-year-old persons without dementia as defined by the clinical dementia rating (CDR = 0) significantly distinguished between persons with a normal and low degree of medial temporal lobe atrophy (MTA) [6]. By including the demented persons into calculations, a significant decrease of plasma Aβ42 in persons with moderate MTA was additionally demonstrated. This finding prompted us to conduct a longitudinal study of MTA, plasma Aβ42 and homocysteine levels, and we present here the data from Vienna Transdanube Aging (VITA) cohort as assessed at baseline and at 2.5 years follow-up. We hypothesized that similar to cerebrospinal fluid, in the course of dementia development the changes of Aβ42 will also be detectable in plasma. Thus, in the new developed MCI- or AD-cases the cerebral increase of Aβ42 might also be detectable in the peripheral compartment. Additionally, we were further interested whether the change of cognition will be reflected by the change of plasma Aβ42 and how the levels of homocysteine compare to the changes of Aβ42 over the course of time.

2. Methods

2.1. Study population

The VITA is a prospective community-based cohort-study of inhabitants aged 75 years from the 21st and 22nd districts of the city of Vienna, Austria, as described elsewhere (see [12,21]). Recruitment for baseline assessment took place between May 2000 and October 2002 and 30 months follow-up measurements between November 2003 and May 2005.

Six hundred and six persons underwent the complete baseline investigation, including medical and neuropsychological tests, psychiatric and neurological scales, blood tests, genetic factors, and cranial magnetic resonance imaging (MRI; see Fig. 1). Two hundred and forty-seven persons were male (40.6%) and 359 female (59.4%). The mean age at baseline was 75.8 ± 0.5 (S.D.) and the mean years of education 10.4 ± 2.1 (S.D.). One hundred and twenty-four persons possessed at least one apolipoprotein E-ε4 allele (21%). Because of blindness, 4 persons could not be assigned to any cognitive subgroup at baseline and 1 person was excluded for schizophrenia, 20 had possible or probable AD and 141 MCI. At the follow-up 2.5 years later, 70 persons refused to further participate, 10 could be reached