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Effects of medications on plasma amyloid beta (Aβ) 42: Longitudinal data from the VITA cohort

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Abstract

In the course of cognitive deterioration leading to Alzheimer's disease (AD) the increase of amyloid beta (Aβ42) in cerebrospinal fluid or plasma might be an initial event. We previously reported about the associations between concomitant medication and plasma Aβ42 levels in the non-demented population cohort of the Vienna transdanube aging study at baseline. In the present study, the longitudinal influence of insulin, gingko biloba, non-steroidal anti-inflammatory drugs (NSAIDs), oral anti-diabetics (sulfonylurea and biguanides), estrogens, fibrates, and statins on plasma Aβ42 are presented. Associated with medial temporal lobe atrophy (MTA), users of insulin showed significantly increased levels of Aβ42. Long-term users of gingko biloba, independent of their MTA, had significantly decreased plasma Aβ42 and the age-dependent increase of plasma Aβ42 was significantly smaller in long-term gingko biloba treated subjects. The use of fibrates also decreased plasma Aβ42 levels. In multiple testing considering interactions between medications, gender, APOE-ε4 presence and creatinine, insulin long-term users again showed significantly increased levels; fibrate and gingko biloba users showed a trend to rather decreased plasma Aβ42 levels compared to the non-users ($p = 0.05$–0.08). Neither statins nor NSAIDs showed a significant effect on plasma Aβ42 in this model. Measuring the effect on cognition, no single medication studied was a significant predictor of conversion to AD or mild cognitive impairment (MCI). Whether the use of gingko biloba might prevent the conversion to MCI or AD needs to be proven in prospective, clinical trials.

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

1. Introduction

A number of therapies targeting decrease of Aβ-peptides for treatment of Alzheimer's disease (AD) approach the clinical phase of studies. In these studies plasma and cerebrospinal fluid (CSF) levels of Aβ42 are considered a surrogate marker for evaluation of efficacy of anti-Aβ42 therapy. Age-dependent increase of plasma Aβ42 was described in persons remaining cognitively healthy over a period of years. Studies demonstrated that, in contrast to cross-sectional measurement, rather longitudinal measurements of Aβ42 might distinguish persons who will convert to MCI or AD (Mayeux et al., 2003; Blasko et al., 2006). The disturbed clearance of Aβ42 peptides is estimated as crucial for the development of sporadic AD. The question

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whether brain-produced Aβ42 peptides are mainly degraded in brain parenchyma or are also destined for peripheral clearance in liver or kidney is still unresolved (Ghiso et al., 2004). Transportation of newly synthesized Aβ42 peptides from the human brain to CSF undergoes very rapid clearance (Bateman et al., 2006), suggesting that the control of Aβ42 degradation undergoes strict regulation.

Recent study demonstrated that soluble low-density lipoprotein related protein-1 (sLRP) normally controls 70–90% of circulating plasma Aβ through peripheral binding. This mechanism was suggested to provide key endogenous peripheral 'sink' activity for Aβ in humans (Sagare et al., 2007). Assuming that significant amount of Aβ42 peptides is delivered throughout the blood brain barrier to plasma circulation, measurement of these changes might be of importance (Shibata et al., 2000). We hypothesize that plasma Aβ42, at least to a certain extent, mirrors the brain load of Aβ42. The peripheral Aβ42 production ascribed to platelets is in this hypothesis of lesser significance (Olsson et al., 2003).

In any model, factors influencing plasma Aβ42 content are of considerable interest. Medications taken for several internal, neurological or psychiatric disorders with high frequency in the elderly population are of particular interest in this context. In the baseline cohort of VITA-population 90% of 75-years old persons took a certain medication. Such medication, by influencing the clearance and production of Aβ42, might influence the balance between peripheral and central pools of Aβ42.

In the non-demented cohort from the Vienna transdanube aging (VITA) study at baseline users of insulin have enhanced and users of ginkgo biloba have decreased levels of Aβ42 (Blasko et al., 2005). Here we present observational data on plasma Aβ42 and its changes induced by medication expected to influence amyloid beta precursor protein (AβPP) processing and Aβ42 production. This study intended to investigate the influence of continuous medication treatment on plasma Aβ42 and cognitive changes at 2.5 years follow up. The question whether the use of concomitant medication taken up to the baseline will influence the conversion to AD at the 2.5 years follow up investigation is the topic of a subsequent study from the VITA cohort.

2. Methods

2.1. Study population

The Vienna transdanube aging study (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 (see Fischer et al., 2002; Jungwirth et al., 2004). Recruitment for baseline assessment took place between May 2000 and October 2002 and 30 months follow up measurements between November 2003 and May 2005; these procedures are described in detail elsewhere (Jungwirth et al., 2005; Grunblatt et al., 2006a,b; Fischer et al., 2007). Briefly, 606 persons underwent the complete baseline investigation, including medical and neuropsychological tests, psychiatric and neurological scales, blood tests, genetic factors, and cranial magnetic resonance imaging (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 (SD) and the mean years of education 10.4 ± 2.1 (SD). Persons (124) possessed at least one apolipoprotein E-ε4 allele (21%). At the follow up 2.5 years later, 119 patients were lost (70 persons refused to participate further, 10 could be reached only by telephone interview, 38 persons deceased and one person was excluded due to schizophrenia) and 487 probands remained in the follow up analysis. The neuropsychological testing and MRI-scans were obtained on the same day and neuropsychological test batteries and criteria were used as described previously (Fischer et al., 2002; Jungwirth et al., 2004). All procedures were performed in the same manner as at the baseline investigational time point.

2.2. Medication groups

The information on drug exposure was obtained from study participants. The participants were asked to bring

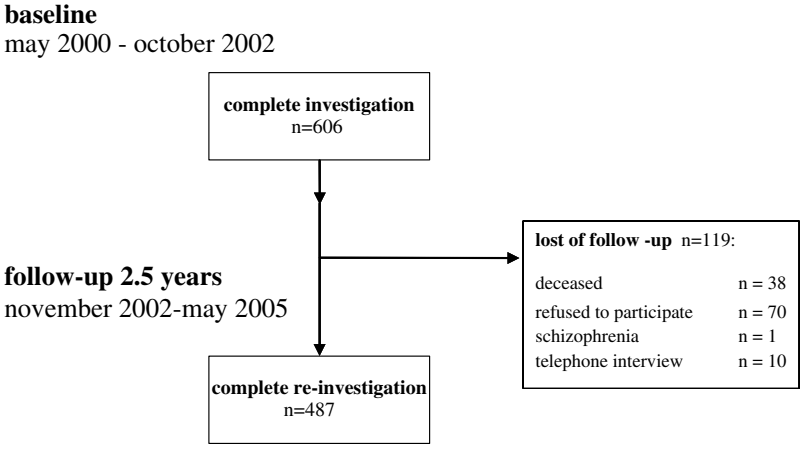

Fig. 1. Outline of the flowchart in studied subjects.