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Low Cerebrospinal Fluid $A\beta_{42}$ and $A\beta_{40}$ are Related to White Matter Lesions in Cognitively Normal Elderly

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Abstract.
Background: Low cerebrospinal fluid (CSF) levels of $A\beta_{42}$ may be the earliest manifestation of Alzheimer's disease (AD). Knowledge on how CSF Aβ interacts with different brain pathologies early in the disease process is limited. We examined how CSF Aβ markers relate to brain atrophy and white matter lesions (WMLs) in octogenarians with and without dementia to explore the earliest pathogenetic pathways of AD in the oldest old.
Objective: To study CSF amyloid biomarkers in relation to brain atrophy and WMLs in 85-year-olds with and without dementia.
Methods: 53 octogenarians took part in neuropsychiatric examinations and underwent both a lumbar puncture and a brain CT scan. CSF levels of $A\beta_{42}$ and $A\beta_{40}$ were examined in relation to cerebral atrophy and WMLs. Dementia was diagnosed.
Results: In 85-year-olds without dementia, lower levels of both CSF $A\beta_{42}$ and CSF $A\beta_{40}$ were associated with WMLs. CSF $A\beta_{42}$ also correlated with measures of central atrophy, but not with cortical atrophy. In participants with dementia, lower CSF levels of $A\beta_{42}$ were related to frontal, temporal, and parietal cortical atrophy but not to WMLs.
Conclusions: Our findings may suggest that there is an interrelationship between Aβ and subcortical WMLs in older persons without dementia. After onset of dementia, low CSF $A\beta_{42}$, probably representing amyloid deposition in plaques, is associated with cortical atrophy. WMLs may be an earlier manifestation of Aβ deposition than cortical degeneration.

Keywords: Alzheimer's disease, amyloid-β, biomarkers, cerebrospinal fluid, computerized tomography, dementia, epidemiological methods, population-based, vascular dementia, white matter lesions

INTRODUCTION

Alzheimer's disease (AD), alone or in combination with other brain disorders, is the most common cause of dementia in old age. AD is characterized by synaptic and neuronal degeneration and the presence of extensive amounts of plaques and tangles in cortical brain regions [1]. A central finding in AD is the deposition of amyloid-β (Aβ) in the brain, especially in the core of the plaques and in the microvessels [2]. According to the "amyloid cascade hypothesis", Aβ oligomerization with subsequent deposition of the peptide in plaques start a cascade of events that results in neuronal and synaptic degeneration and dementia [3–6].

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Biomarkers are valuable tools to study the temporal evolution of the central pathogenetic processes in AD [5, 7]. Low levels of cerebrospinal fluid (CSF) $A\beta_{42}$ reflect cortical Aβ deposition [8, 9], which is supported by the finding that it is related to high cortical retention of the positron-emission tomography (PET) tracer Pittsburgh Compound B (PIB) that binds fibrillar Aβ [10–12]. Low CSF $A\beta_{42}$ levels are also strongly associated with AD with dementia and incipient AD in MCI [7], as well as with future cognitive impairment in asymptomatic individuals [13–17].

Brain atrophy on magnetic resonance imaging (MRI) or computerized tomography (CT) of the brain reflects neurodegenerative processes [5, 18, 19]. The earliest changes in the evolution of Aβ deposits in AD are thought to occur in the neocortex and from there spread to allocortical regions, brainstem, and finally to the cerebellum [20].

The temporal sequence in the pathophysiological processes of AD has received increased interest recently. As suggested by Jack and co-workers [4, 5], it is supposed that the initiating event is abnormal processing of Aβ, reflected by changes in CSF Aβ [4, 21], which occurs many years before symptoms of cognitive disturbances [22]. The second event is related to tau-mediated injury and dysfunction, and the third to neurodegeneration of brain structures, i.e., cerebral atrophy ([4, 5, 23]). Cognitive symptoms are supposed to relate closely to the evolution of neuronal degeneration [5]. The hypothetical model of the pathophysiological process was intended to model pure AD [5]. However, in late-onset AD, especially in cases with very late onset, there is a high prevalence of co-existing pathological processes [4]. One important type of concomitant pathology is ischemic white matter lesions (WMLs), which are frequent both in clinical and autopsied AD cases, as well as in normal elderly [24–26]. WMLs have been shown to aggravate clinical symptoms of AD [27]. These changes are associated with lipohyalinosis causing narrowing of the lumen of the small perforating arteries and arterioles that nourish the deep white matter. The underlying cause of WMLs is not established, but the main hypothesis is that they are due to long-standing hypertension that cause lipohyalinosis and thickening of the vessel walls [28], which leads to ischemia in vulnerable areas. Animal experiments have shown that brain ischemia also may cause an acute increase in Aβ secretion through induced BACE1 protein expression, with accumulation of oligomeric Aβ in the hippocampus [29–31]. Furthermore, neuropathological studies in patients who died after acute stroke or after resuscitation from cardiac arrest have shown a marked increase in Aβ expression in hippocampus together with a marked increase in non-fibrillar Aβ plaques in cortex [32, 33]. Thus, ischemia may trigger Aβ deposition and plaque formation. In addition, a study on normal elderly individuals without dementia but with extensive AD neuropathology suggested that WMLs precede the cortical atrophy in the evolution of AD pathology [25]. WMLs have also been related to deposition of Aβ in the vessels [34], further suggesting that interactions between Aβ and WMLs may occur early in the disease process. We aimed to examine the relationship between amyloid metabolism (measured by CSF Aβ), stage of neuronal degeneration (measured as atrophy on CT), and small vessel disease (measured as WMLs on CT) in very old persons from a population-based sample of 85-year-olds with and without dementia, to provide further knowledge about the relationship between these pathogenetic markers in older persons.

STUDY POPULATION AND METHODS

Study population

A representative sample of 85-year-olds and registered for census purposes in Gothenburg, was invited to take part in a health survey. Both people living in the community and those in institutions were included. A neuropsychiatric examination was performed on a systematic sub-sample ($n = 494$, response rate 63%). The sample has been described in detail previously [35].

The first 165 individuals were invited to undergo a lumbar puncture. Sixty-nine (31 with dementia and 38 without dementia) accepted. Of these, five individuals were excluded due to technical reasons and another two due to hemorrhagic spinal taps, leaving 62 individuals (27 with dementia and 35 without, 40 women and 22 men) for the present study. AD was diagnosed in 12 individuals (four men and eight women), vascular dementia (VaD) in 13 (two men and 11 women) and other types of dementia in two individuals (one man and one woman). All had onset of dementia after age 65 years. The cohort that underwent lumbar puncture has been described in detail previously [13]. All 85-year-olds with a lumbar puncture were invited to undergo a CT scan of the head. Fifty-three accepted both examinations: 23 with

Table 1
Demographics and CSF biomarker levels in a population sample of 85-year-olds with and without dementia

Characteristic	Without Dementia ($n=30$)	With Dementia ($n=23$)	p-value[1]	Alzheimer's dementia ($n=9$)	Vascular dementia ($n=12$)	p-value[2]
No. (%)						
Women	16 (53.3)	17 (73.9)	$p=0.16$	6 (66.7)	10 (83.3)	$p=0.61$
Current/Ex-smokers	18 (60.0)	6 (33.4)	$p=0.14$	2 (28.6)	2 (22.2)	$p=1.0$
Living in care	0 (0)	16 (69.6)	$p<0.00$	6 (66.6)	9 (75.0)	$p=1.0$
Stroke	4 (13.3)	9 (39.1)	$p=0.05$	0	9 (75)	$p=0.001$
Mean (SD)						
CSF $A\beta_{42}$	632 (280)	420 (200)	$p<0.01$	381 (161)	431 (198)	$p=0.55$
CSF $A\beta_{40}$	1975 (684)	1393 (438)	$p<0.001$	1225 (408)	1530 (414)	$p=0.11$
Mean age at interview	85.4 (0.14)	85.5 (0.18)	$p<0.05$	85.1 (0.86)	85.1 (27.5)	$p=0.35$
Systolic blood pressure	163.5 (30.1)	146.1 (24.9)	$p=0.05$	145.6 (21.7)	148.2 (28.5)	$p=0.82$
MMSE	28.3 (1.5)	12.6 (8.9)	$p<0.0001$	11.7 (9.5)	13.5 (8.2)	$p=0.66$
No. (%)						
Frontal atrophy severe	12 (40.0)	15 (65.2)	$p=0.15$	6 (66.7)	7 (58.3)	$p=1.0$
Temporal atrophy	14 (60.9)	6 (20.0)	$p<0.01$	7 (77.8)	6 (50.0)	$p=0.37$
Parietal atrophy	11 (36.7)	14 (60.9)	$p=0.08$	4 (44.4)	9 (75.0)	$p=0.20$
Occipital atrophy	4 (17.4)	6 (20.0)	$p=0.92$	2 (22.2)	2 (16.7)	$p=1.0$
White matter lesions severe	3 (10)	7 (30.4)	$p<0.01$	7 (77.78)	8 (66.7)	$p=0.66$

Values are given as number (percent) or mean (standard deviation). CSF biomarker levels are given as pg/mL. In the statistical analyses, Fisher's exact test was used for discrete variables and Student's t-test for continuous variables. [1]Test between participants with dementia and participants without. [2]Test between participants with Vascular dementia and participants with Alzheimer's dementia. CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination.

dementia [AD was diagnosed in 9 individuals (3 men and 6 women), 12 with VaD (2 men and 10 women), and 2 with other types of dementia (one man and one woman)] and 30 without dementia. The demographic of this sample is given in Table 1. Mean age of onset of dementia in the 23 participants with dementia was 79.8 (SD 4.12) years (13 were diagnosed with dementia between 80 and 85 years, 8 between 75 and 80 years and 2 persons before age 75).

Follow-up data on this sample has been published previously [13]. During the following 3 years (age 85-88), 7 of the 35 85-year-olds without dementia developed dementia, while 28 remained dementia-free.

The study was approved by the Ethics Committee at the University of Gothenburg. All subjects (or their closest relatives) gave their informed consent to participate in the study.

General examinations

The examinations included medical history and physical examinations performed by a geriatrician, neuropsychiatric examinations and a telephone interview with a close informant performed by a psychiatrist, an electrocardiogram, a chest X-ray, a battery of blood tests, CT of the brain, and a lumbar puncture [35]. All clinical examinations were made without knowledge of the brain imaging and biochemical results and vice versa.

CSF sampling and analysis

Lumbar punctures were performed in the morning, under standardized conditions, through the L3/L4 or L4/L5 interspace. The first 12 ml of CSF was collected in polypropylene tubes and gently mixed to avoid possible gradient effects. CSF samples with more than 500 erythrocytes per μL were excluded.

CSF $A\beta_{42}$ was determined using a sandwich ELISA which is based on the 3D6 and 21F12 monoclonal antibodies, making it specific for Aβ 1-42, as previously described [36]. CSF $A\beta_{40}$ was determined using an in-house research sandwich ELISA in which an $A\beta_{40}$-specific polyclonal antibody (Quality Control Biochemicals, Hopkinton, MA, USA) was used as capturing antibody, and an N-terminal specific monoclonal antibody (3D6) was used as detecting antibody. High performance liquid chromatography purified $A\beta_{40}$ (Bachem, Bubendorf, Switzerland), was used as standard. CSF samples were analyzed in duplicates. Details of the ELISA characteristics, including intra- and inter-day variability have been presented in detail [37].

Computerized tomography evaluations

All CT scans were performed without contrast enhancement and the CT scans were examined by two experienced radiologists, who were blinded to the clinical and CSF results [26].

The occipital, parietal, frontal, and temporal lobes were categorized using a four-point scale (normal, mild, moderate and severe) according to the estimated extent of brain atrophy [18]. The rating procedure was carried out separately for the cortical and ventricular studies.

The following linear distances were determined using a transparent metric ruler as described by de Leon and co-workers [18]: (a) the bifrontal span of the lateral ventricle; (b) the width of the lateral ventricles at the head of the caudate nucleus; (c) the sum of the separate widths of the left and right Sylvian fissures; (d) the minimal width of the bodies of the lateral ventricles at the waist, and (e) the width of the third ventricle. Ratios were determined by dividing the obtained values by the width of the brain at the level of the measurement, giving the following ratios: (a) bifrontal ratio, (b) bicaudate ratio, (c) Sylvian fissure ratio, (d) cella media ratio.

WMLs were defined as low-density areas in periventricular or subcortical white matter. The changes were always diffusely distributed within the white matter. Decreased density was subjectively rated as no, mild, moderate, or severe in relation to the attenuation of normal white matter [26, 38]. In cases of disagreement a consensus conference was performed.

Diagnostic methods

Dementia and its severity were diagnosed according to the DSM-III-R criteria, using information from the psychiatric examination and the close informant interview, as described previously [35]. Subjects with dementia were classified into diagnostic subgroups: AD according to the NINCDS-ADRDA criteria [39] and VaD according to the possible NINDS-AIREN criteria [40]. In the diagnostic classification, information from the psychiatric examinations, close informant interview, laboratory tests, ECG, and case records were used [35].

Statistical analyses

Fisher's exact test and independent *t*-test were used to test the hypothesis of no differences between the groups. Pitman's permutation test was used to test correlations (r) between CSF Aβ and CT variables (atrophy, WMLs), adjusted for the presence of dementia. Before stratification by dementia status, we tested if there was an interaction with dementia status, i.e., if the strength of correlations between CSF Aβ and CT measures (atrophy, WMLs) differed between 85-year-olds with and without dementia. Interactions were calculated with a permutation test as both groups were relatively small, and as the variables were not normally distributed. In cases of interactions $p < 0.20$, we stratified analyses by dementia status. Results were retested with robust regression by using STATA procedure "regress" with the parameter vce (robust). p-values<0.05 (two-sided) were regarded as statistically significant.

RESULTS

Description of the sample is presented in Table 1

Table 2 gives the correlations between CSF $A\beta_{42}$ and CT measures of brain atrophy and WMLs in the total group. Lower CSF $A\beta_{42}$ levels correlated with higher degree of temporal atrophy, bifrontal ratio, bicaudate ratio, and third ventricular width. There were interaction effects with dementia status for the associations between CSF $A\beta_{42}$ and frontal, temporal, and parietal atrophy, and WMLs. Analyses of these CT measures were therefore stratified by dementia status in further analyses. In the stratified analyses (Tables 3 and 4), lower CSF $A\beta_{42}$ was related to severity of WMLs in the group without dementia, but not in the group with dementia. In contrast, lower CSF $A\beta_{42}$ levels were related to more severe frontal and temporal lobe atrophy in the group with dementia, while no such associations were found in the group without dementia.

Table 2 also gives the correlations between CSF $A\beta_{40}$ and CT measures of brain atrophy and WMLs in the total group. Lower CSF $A\beta_{40}$ was related to higher bifrontal ratio, sella media ratio, and severity of WMLs. There were interactions with dementia status for the associations between CSF $A\beta_{40}$ and frontal atrophy and WMLs. Analyses of these CT measures were therefore stratified by dementia status in further analyses. In these analyses, lower CSF $A\beta_{40}$ was related to severity of WMLs in the group without dementia, but not in those with dementia (Table 3). The main results were unchanged using a robust regression analysis.

DISCUSSION

We examined biomarkers for Aβ metabolism, neuronal degeneration, and WMLs in 85-year-olds

Table 2
Cerebrospinal fluid $A\beta_{40}$ and $A\beta_{42}$ in relation to measures of cerebral atrophy and white matter lesions in a population sample of 85-year-olds ($n = 53$). Pooled correlation coefficient adjusted for dementia

	$A\beta_{42}$		$A\beta_{40}$		$A\beta_{42/40}$	
	Correlation r[a]	Interaction with dementia p value	Correlation r[a]	Interaction with dementia p value	Correlation r[a]	Interaction with dementia p value
Cortical atrophy						
Frontal	–0.10	0.02	–0.05	0.11	–0.21	0.51
Temporal	–0.31[b]	0.03	–0.26	0.26	–0.26	0.27
Parietal	–0.27	0.11	–0.11	0.75	–0.37[c]	0.43
Occipital	–0.12	0.89	–0.09	0.68	–0.01	0.53
Central atrophy						
Bifrontal ratio	–0.41[c]	0.47	–0.41[c]	0.41	–0.19	0.57
Bicaudate ratio	–0.28[b]	0.97	–0.23	0.80	–0.12	0.17
Third ventricle width	–0.30[b]	0.73	–0.25	0.66	–0.18	0.40
Sylvian fissure ratio	–0.03	0.99	–0.04	0.15	–0.10	0.52
Sella media ratio	–0.25	0.44	–0.30[b]	0.49	–0.08	0.35
White Matter Lesions	–0.22	0.10	–0.31[b]	0.17	0.05	0.63

[a]Pitman's permutation test was used to test correlations (r) adjusted for dementia status, 30 participants without dementia diagnosis and 23 with a dementia diagnosis. [b]$p < 0.05$. [c]$p < 0.01$.

Table 3
Stratified analyses in those correlations between brain atrophy/white matter lesions and CSF Aβ where interaction effect by dementia status had a p-value of < 0.20 and the correlation was significantly not equal in any subgroup

	CSF $A\beta_{42}$			CSF $A\beta_{40}$			CSF $A\beta_{42}/A\beta_{40}$		
	Without Dementia ($n = 29$)	With Dementia ($n = 22$)	Test of Interaction*	Without Dementia ($n = 29$)	With Dementia ($n = 22$)	Test of Interaction*	Without Dementia ($n = 29$)	With Dementia ($n = 22$)	Test of Interaction*
Cortical atrophy									
Frontal	0.12	–0.52[b]	$p = 0.02$	0.11	–0.37	$p = 0.11$			
Temporal	–0.15	–0.70[d]	$p = 0.03$			$p = 0.26$			
Parietal	–0.13	–0.59[c]	$p = 0.11$			$p = 0.75$			
Central atrophy									
Bicaudate ratio							0.10	–0.25	$p = 0.234$
White Matter Lesions	**–0.39**[b]	0.03	$p = 0.10$	–0.46[b]	–0.08	$p = 0.17$			

*Significance of interaction evaluated by a permutation test. [b]$p < 0.05$. [c]$p < 0.01$. [d]$p < 0.001$.

Table 4
Stratified analyses between brain atrophy/white matter lesions and CSF Aβ according to Alzheimer's dementia and vascular dementia status

	CSF $A\beta_{42}$			CSF $A\beta_{40}$			CSF $A\beta_{42}/A\beta_{40}$		
	Alzheimer's Dementia ($n = 9$)	Vascular Dementia ($n = 12$)	Test of Interaction*	Alzheimer's Dementia ($n = 9$)	Vascular Dementia ($n = 12$)	Test of Interaction*	Alzheimer's Dementia ($n = 9$)	Vascular Dementia ($n = 12$)	Test of Interaction*
Cortical atrophy									
Frontal	–0.61	–0.67[b]	$p = 0.84$	–0.74[b]	–0.15	$p = 0.14$	–0.11	–0.47	$p = 0.44$
Temporal	–0.61	–0.67[b]	$p = 0.83$	–0.54	–0.23	$p = 0.49$	–0.35	–0.51	$p = 0.71$
Parietal	–0.48	–0.70[b]	$p = 0.49$	–0.35	–0.13	$p = 0.65$	–0.29	–0.64[b]	$p = 0.37$
White Matter Lesions	–0.016	0.13	$p = 0.82$	0.23	–0.18	$p = 0.43$	–0.22	0.27	$p = 0.39$

*Significance of interaction evaluated by a permutation test. [b]$p < 0.05$. [c]$p < 0.01$. [d]$p < 0.001$.

with and without dementia to learn more about the early pathogenetic processes in very late-life sporadic dementia. Lower CSF levels of $A\beta_{42}$ are supposed to be the earliest event in the evolution of AD, occurring approximately 15–20 years before brain atrophy and clinical symptoms [5]. We found that lower CSF levels of $A\beta_{42}$ and $A\beta_{40}$ were related to WMLs in 85-year-olds without dementia, and $A\beta_{42}$ to degree of frontal, parietal, and temporal cortical brain atrophy in those with dementia. This may indicate that disturbed metabolism of Aβ is related to cerebrovascular disease, such as WMLs, in the very early phases of the disease, and to the stage of neuronal degeneration, as measured by brain atrophy on CT, only in

the later disease stages with manifest dementia. The latter is in line with the hypothesis of Jack et al. [5], that symptoms of dementia do not occur until the start of neurodegeneration.

Lower CSF levels of both $A\beta_{42}$ and $A\beta_{40}$ correlated with severity of WMLs in individuals without dementia, but not in those with dementia. Amyloid PET studies show a correlation between cortical amyloid load and CSF $A\beta_{42}$, but no relation with CSF $A\beta_{40}$ [14, 41, 42]. Thus, the correlation between low CSF levels of both $A\beta_{40}$ and $A\beta_{42}$ and WMLs suggest that our finding might reflect a disturbance in Aβ metabolism or clearance rather than amyloid deposition in plaques. Indeed, neuropathological studies have reported that the periventricular white-matter in individuals without dementia and with WMLs contain deposits of Aβ, while the white matter in those without WMLs does not [43]. Other studies also report increased quantities of parenchymal Aβ in AD white matter [44, 45], strengthening the hypothesis that WMLs may be connected to the amyloidogenic process early in AD. There are also data supporting a relation between Aβ and WMLs in preclinical AD. One neuropathology study on individuals without dementia but with extensive neurofibrillary tangles and plaques in the cerebral cortex suggested that WMLs precede the cortical atrophy in AD [25]. Further support for our findings comes from a recent clinical study reporting that white matter hyperintensities on MRI were related to lower CSF levels of $A\beta_{42}$ in controls and in individuals with VAD, but not in individuals with manifest AD dementia [46]. Also other studies suggest that WMLs may cause or precede brain atrophy [47]. WMLs have previously been related to AD in both clinical and autopsy studies [24–26]. These data, together with our findings that CSF measures of Aβ neuropathology are associated with WMLs in 85-year-olds without dementia and with cortical atrophy among individuals with dementia, suggest that there is an interrelationship between Aβ and WMLs in those without dementia. The timing of the event is uncertain, but WMLs may be an even earlier manifestation than cortical neurodegeneration. However, this finding needs to be further elucidated using the more sensitive MRI technique in a larger sample. It must be emphasized that in octogenarians it may be hard to disentangle age-related pathology, preclinical dementia pathology and co-morbidities.

In line with our study, van Westen et al. [48] reported that lower $A\beta_{40}$ was related to WMLs in non-demented persons. However, in contrast to our findings, they found that WMLs were only associated with lower CSF $A\beta_{42}$ in AD dementia, and not in the cognitively healthy. One reason for the latter may be that study participants in that study were younger.

The association between CSF $A\beta_{42}$ and $A\beta_{40}$, and WMLs in individuals without dementia should also be seen in light of the hypothesis that vascular factors may be involved in the pathogenesis of AD [49]. The metabolism of AβPP and generation of Aβ may be affected by intracerebral small-vessel arteriolosclerosis [50], which may cause hypoperfusion and ischemia [51] that may further exacerbate Aβ oligomerization and deposition [52]. This hypothesis is supported by both experimental animal studies and human post-mortem studies suggesting that ischemia may cause an upregulation of Aβ production with subsequent accumulation and oligomerization of Aβ and formation of non-fibrillar plaques [29, 30, 33]. The vessel changes related to WMLs may also lead to disturbance in clearance of Aβ from the brain, leading to lower levels of CSF Aβ. High blood pressure has been reported to precede AD onset by 10–15 years [53]. Hypertension is also a risk factor for WMLs [54]. Furthermore, middle-aged hypertensive individuals without dementia have an increased amount of senile plaques in their brains [55], which should translate into lower CSF $A\beta_{42}$ values [8, 9]. Recently, a PET study in individuals free from dementia and aged 83 years and above reported that arterial stiffness was associated with progressive deposition of Aβ in the brain [56]. The direction of the association is not clear. These findings, as well as those in the present study, may either reflect that similar mechanisms may be involved in the pathogenesis of both disorders or that vascular diseases may exacerbate the AD process, by for instance inducing blood-brain barrier dysfunction, oxidative stress and ischemia [51, 52, 57]. Finally, recent studies suggest that WMLs may influence the expression and/or processing of AβPP, which may cause a downstream reduction in the levels of $A\beta_{42}$ and $A\beta_{40}$, not related to deposition of the peptides in the brain parenchyma [58, 59]. Whether this change contributes to neurodegeneration is unclear.

The cortical atrophy in AD is due to neuronal and synaptic degeneration and loss. In the present study, the strongest correlation between atrophy and lower CSF $A\beta_{42}$ was found for the temporal lobe, which is in line with studies reporting a relation between CSF $A\beta_{42}$ and temporal lobe atrophy visualized on MRI [60–62]. We could not find any correlation between CSF $A\beta_{42}$ and cortical atrophy in

85-year-olds without dementia, despite that CSF $A\beta_{42}$ levels were lower in cognitively healthy individuals who later developed dementia in this sample [13, 15] and in women who developed cognitive impairment in another of our population samples [15]. These findings support the hypothesis that a disturbance in brain Aβ metabolism occurs before cortical neuronal degeneration in AD [4, 6]. Furthermore, a PET study found that Aβ burden was not associated with brain atrophy measured over 10 years in elderly individuals without dementia, indicating that Aβ load has not yet affected brain volume in individuals without dementia [63, 64], and that clinical symptoms of dementia start to occur when Aβ gives rise to brain atrophy and neurodegeneration. In contrast, another PET study reported that lower levels of CSF $A\beta_{42}$ at baseline were related to brain volume reductions during 1 year of follow-up in cognitively healthy elderly controls [65].

Some limitations of the study have to be considered. First, the number of individuals in some of the groups was relatively small. However, the findings were in the expected direction, even when the sample was divided into several subgroups, and may be considered biologically plausible. Second, although the sample is drawn from the general population, only 30% consented to a lumbar puncture. However, it seems unlikely that this should have affected the associations between CSF levels of Aβ and brain atrophy. Third, linear measurements and visual ratings of cortical atrophy and WMLs on CT is a rather crude method. However, if anything, this should decrease the possibility of finding differences between the groups. In addition, we have previously shown a high interrater reliability in the CT measures [66]. Furthermore, CT is less sensitive than MRI in detecting WMLs and is more severely affected by bone hardening artifacts, which is particularly severe in the region of the medial temporal lobe [67]. However, CT is better in delineating clinically relevant WMLs [68] and comparable to MRI in detecting brain atrophy [67]. On the other hand, if very mild changes are not detected, it may have influenced the results. Also, CT may be more suitable than MRI for the elderly, as it is less sensitive to motion artefacts. CT is also the most used brain imaging tool world-wide. Fourth, all scans were rated by a single person which may increase the risk for systematic error. Fifth, we cannot exclude the possibility that some cases of AD in this very old population might have mixed dementia. Finally, the cross-sectional design limits conclusions regarding cause-effect relations.

In summary, we found that low levels of CSF $A\beta_{42}$ and $A\beta_{40}$ correlated with WMLs in individuals without dementia, suggesting that this might be an early event in the dementia process, maybe related to deficient clearance of amyloid or ischemia. In contrast, CSF $A\beta_{42}$ correlated with cerebral cortical atrophy only in individuals with dementia. These findings suggest that Aβ deposition manifests itself earlier in subcortical white matter compared with cortical brain regions and that subcortical arteriolosclerosis may play a role in the pathogenetic process of AD.

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