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CSF Aβ42, Tau and phosphorylated Tau, APOE ε4 allele and MCI type in progressive MCI

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Abstract

Background: The patients with mild cognitive impairment (MCI) have an elevated risk for Alzheimer's disease (AD). Especially the amnestic MCI is seen as prodrome of AD. Apolipoprotein E (APOE) ε4 allele, abnormal CSF Aβ42, Tau and phosphorylated Tau (phospho-Tau) levels are associated with elevated risk for AD.
Methods: APOE genotyping was done by PCR based method and baseline CSF Aβ42, Tau and phospho-Tau were measured by ELISA from 60 controls and 79 MCI patients.
Results: Thirty-three MCI patients developed dementia during an average of 3.5 years follow-up. CSF Aβ42 was decreased and Tau and phospho-Tau were increased in the progressive MCI patients. The APOE ε4 allele was more frequent in the progressive MCI patients. The APOE ε4 allele showed a dose dependent association to the Aβ42 levels in the progressive MCI patients and to all of the markers in controls.
Conclusions: Decreased CSF Aβ42 and elevated Tau or phospho-Tau together with APOE ε4 allele are highly predictive for the dementia in MCI patients with amnestic or executive symptoms.

Keywords: Alzheimer's disease; Mild cognitive impairment; Aβ42; Tau; Phosphorylated Tau; Apolipoprotein E

1. Introduction

In the recent years the research on predementia stage of Alzheimer's disease (AD) has been focusing on the concept of MCI. The possibility of finding the patients with early AD is emphasized as the current treatments are showing faint promise of symptomatic effect in MCI patients [39]. Once new treatments that may be capable of slowing or even halting the progress of the disease become available, finding these patients becomes crucial. MCI can be defined as a state at which a patient has cognitive impairment beyond the age-adjusted norms, but not sufficient to fulfil the criteria for dementia [40]. Many studies have shown that subjects with MCI have an increased risk for dementia, but some MCI patients have a stable type of MCI and may never develop dementia [18,30,52]. Prognosis of MCI is partially dependent on the criteria used to define the state but it is obvious that MCI is a heterogeneous condition due to various causes. Previous studies suggest that the amnestic type of MCI may be a risk factor for AD whereas the executive symptoms have been seen as predictor for vascular dementia (VaD) [40].

The factors associated with increased risk for progression from MCI to dementia include CSF biomarkers, atrophy of medial temporal lobe structures, and genetic risk factors such as APOE ε4 allele [3,20,21,24,45,51]. Many studies have shown that patients with AD have lower CSF Aβ42 levels and higher Tau and phosphorylated Tau (phosho-Tau) levels than those of healthy control subjects, and these biomarkers

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are altered already in those MCI patients who will later develop dementia [3,20,21,45]. The APOE ε4 allele is the strongest genetic risk factor for AD [14]. It has also been shown to be associated with decreased levels of CSF Aβ42 [17,23,42,55].

The weakness of previous studies concerning biomarkers in MCI is rather short follow-up time. In the present study, we examined the predictive value of three CSF biomarkers, Aβ42, Tau and phospho-Tau and the most prominent genetic risk factor, APOE ε4 allele in MCI patients with different types of MCI and an extended follow-up.

2. Subjects and methods

2.1. Subjects

The study included 107 subjects examined at the Neurological Department at Kuopio University Hospital and 33 subjects from an ongoing prospective population-based study. The subjects who agreed to a lumbar puncture for the research purposes were included in the study. The patients gave written informed consent and the study was approved by the local Ethical Committee.

Baseline examination of all subjects included a neurological and neuropsychological examination, imaging of the brain (mainly computed tomography), and laboratory tests for exclusion of the secondary causes of cognitive decline. The following neuropsychological tests were used for the evaluation of the different cognitive domains: *Memory:* Visual Reproduction Test (VR, immediate and delayed recall) from Wechsler Memory Scale (WMS) [48], Logical Memory Test (LM, immediate and delayed recall) from Wechsler Memory Scale-Revised (WMS-R) [57], Word List Recall (immediate and delayed recall) from the CERAD Neuropsychological Assessment Battery [36], delayed recall of the Constructional Praxis from CERAD [36]; *Language:* Abbreviated (15 items) Boston Naming Test [25], vocabulary subtest from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) [58]; *Attention and executive function:* Verbal Fluency Test [5,7], Trail Making Test [44] parts A and B; *Visuospatial skills:* Constructional Praxis from CERAD [36], block design from the WAIS-R [58]; *Global functioning:* Mini-Mental State Examination [16] (MMSE), Clock Drawing Test [36].

Subjects performing below the age-adjusted norms in at least one cognitive domain were diagnosed as having MCI if they also had a score of 0.5 on the clinical dementia rating (CDR) scale [35]. At the baseline 79 patients received MCI diagnosis. Forty-seven patients had amnestic MCI, eight had pure amnestic MCI (deficit in at least one memory test) and 39 had amnestic plus MCI (deficit in memory test and deficits in other tests), 17 patients with dysexecutive MCI (deficit in executive tests but not in memory tests with or without deficits in other tests), and 15 patients with deficits in other than memory or executive tests.

Diagnosis of dementia was based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [1] and AD was diagnosed using the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [31]. Diagnosis of dementia was done independently and blinded to the CSF biomarker data and the APOE genotype.

Control group included 42 subjects who were referred to the Neurological Department due to different symptoms, and 19 subjects from the prospective population-based study. The clinical control group included 19 subjects with depression with normal performance in the neuropsychological tests. The rest of the clinical control group suffered from headache, dizziness or other symptoms assessed not to be due to a neurological disease (except one patient had a history of epilepsy). Brain imaging was normal in all subjects. One subject with fibromyalgic pains, who entered the study as a control subject, was excluded due to the diagnosis of AD 10 years later.

2.2. Biochemical analyses

The CSF samples were collected by lumbar puncture during the baseline visit. The samples were stored in polypropylene tubes at −70 °C until analyses.

Measurement of CSF Aβ42, Tau and phosho-Tau. The measurement of CSF Aβ42, Tau and phospho-Tau were done by commercially available enzyme immunosorbent assays (Innogenetics, Ghent, Belgium) according to manufacturer's protocol. The measurements were done blinded to the diagnoses and the APOE genotype of the studied subjects.

APOE genotyping. The APOE genotyping was done by a PCR based method as described earlier [56]. The subjects were classified according to their APOE genotype: APOE ε4 negative subjects (ε2/3 and ε3/3), subjects with one APOE ε4 (ε2/4 or ε3/4) and subjects with two APOE ε4 alleles (ε4/4).

2.3. Statistical analysis

All statistical analyses were performed by SPSS software for Windows release 11.5.1. (SPSS Inc., Chicago, IL) The comparisons between the different groups of subjects were done by ANOVA with appropriate post hoc corrections. When the assumptions were not met, the non-parametric tests were used. For the categorical data the comparisons between different groups were done by Chi-square tests. The correlations between different variables were calculated by Pearson's correlation test or by Spearman's correlation test. The odds ratios for different factors that might contribute to the conversion of MCI to dementia were determined by logistic regression analysis, so that only the patients with MCI at the baseline were included. Cox regression analysis was used for survival analyses. One individual had a Tau value below the detection limit, and the detection limit given in the kit's manual was used.

Table 1
The baseline demographic data and the CSF Aβ42, Tau and phospho-Tau levels of the subjects in different groups

	Controls	Stable MCI	Progressive MCI
n	60	46	33
Men/women	25/35	20/26	13/20
	41.7/58.3%	43.5/56.5%	39.4/60.6%
Age	68.28 ± 8.07	69.46 ± 8.14	71.67 ± 6.71
MMSE	26.22 ± 2.88	24.09 ± 2.49*	23.91 ± 2.69*
Follow up time (years)	3.94 ± 2.22	4.57 ± 3.09	3.52 ± 1.95
APOE ε4 +/−	21/39	15/30	26/7**
	35.0/65.0%	33.3/66.7%	78.8/21.2%
Aβ42 (pg/ml)	680 ± 242	619 ± 206	454 ± 170***
Tau (pg/ml)	323 ± 180	347 ± 176	569 ± 198***
Phospho-Tau (pg/ml)	63 ± 23	65 ± 23	89 ± 22***

The data are given as number of subjects (*n*) and percentage of all subjects in the group or as mean ± S.D.
* $p \leq 0.001$ against controls.
** χ^2 $p = 0.036$.
*** $p \leq 0.001$ against controls and stable MCI patients.

3. Results

3.1. Clinical characteristics

Table 1 presents the baseline characteristics of the subjects. Control group ($n = 60$) included 19 subjects with a clinical diagnosis of depression. They did not differ from remaining other controls ($n = 41$) in respect of baseline age or MMSE. At the baseline, 47 patients had amnestic MCI (eight patients with pure amnestic deficits and 39 patients with amnestic plus MCI), 17 patients dysexecutive MCI, and 15 patients with deficits in other than memory or executive cognitive domains. At the end of the follow-up, 46 patients (58%) had remained stable (stable MCI), 33 patients (42%) progressed to dementia (progressive MCI) of whom 27 patients received diagnosis of AD, one patient had VaD and five patients had diagnosis of mixed dementia. The follow-up times were 3.94 ± 2.22 years in the controls, 4.57 ± 3.09 years in the stable MCI patients and 3.52 ± 1.95 years in the progressive MCI patients.

There were no significant differences in gender distribution, age or MMSE scores at the baseline between progressive and stable MCI patients (Table 1). The proportion of patients progressing to dementia was significantly higher in patients with amnestic (51%) or dysexecutive (41%) MCI when compared with other MCI patients (13%) ($p = 0.036$). The mean conversion time from baseline to the diagnosis of dementia was 3.00 ± 1.41 years in the dysexecutive MCI patients, 3.50 ± 2.09 years in the amnestic MCI patients and 5.50 ± 0.71 years in the other MCI patients.

3.2. CSF markers in different groups

The baseline levels of CSF Aβ42, Tau and phospho-Tau differed significantly between the groups (Table 1).

Table 2
The effect of APOE ε4 allele on the CSF markers in different groups

APOE ε4	Controls				Stable MCI				Progressive MCI			
	n	Aβ42	Tau	Phospho-Tau	*n*	Aβ42	Tau	Phospho-Tau	*n*	Aβ42	Tau	Phospho-Tau
0	39	754 ± 254	268 ± 113	56 ± 17	30	644 ± 189	342 ± 176	64 ± 24	7	626 ± 236	541 ± 114	87 ± 19
1	17	560 ± 130	411 ± 201	74 ± 26	12	526 ± 243	345 ± 175	64 ± 24	15	437 ± 105	495 ± 118	83 ± 18
2	4	467 ± 166	484 ± 380	79 ± 42	3	722 ± 187	336 ± 231	66 ± 29	11	367 ± 117	689 ± 270	99 ± 26
p-value		0.004	0.034	0.034		0.099	0.964	0.963		0.016	0.263	0.204
−	39	754 ± 254	268 ± 113	56 ± 17	30	644 ± 189	342 ± 176	64 ± 24	7	626 ± 236	541 ± 114	87 ± 19
+	21	543 ± 138	425 ± 234	75 ± 29	15	565 ± 241	343 ± 178	65 ± 23	26	407 ± 114	577 ± 216	90 ± 23
p-value		0.001	0.011	0.010		0.194	0.791	0.933		0.012	0.983	0.983

The values are given as mean ± S.D. The significance was tested by the Kruskal–Wallis and Mann–Whitney tests. The APOE data is missing from one stable MCI patient.

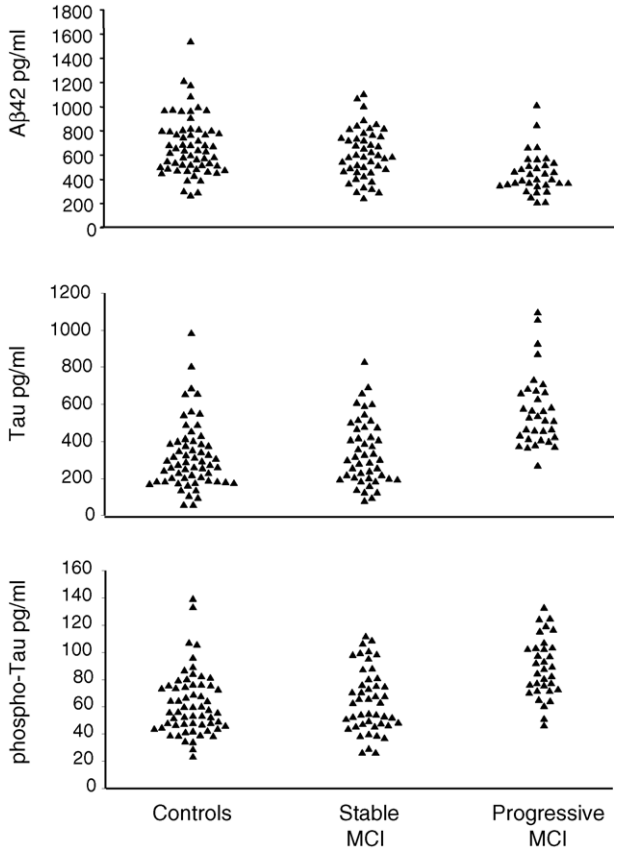

Fig. 1. CSF Aβ42, Tau and phospho-Tau values of studied subjects. Each marker represents one individual.

The controls had high levels of Aβ42, and low levels of Tau and phospho-Tau. The control subjects with depression had similar values to the other controls in all of the studied markers (data not shown). There were no significant differences in the levels of CSF markers between the controls and patients with stable MCI. In contrast, patients with progressive MCI had significantly lower CSF Aβ42, and higher Tau and phospho-Tau levels than other groups. However, there was a visible overlap between the stable MCI patients and the progressive MCI patients in all of the markers (Fig. 1).

The association of CSF markers and progression to dementia were also examined separately according to the type of MCI. Patients with amnestic and executive MCI who progressed to dementia had lower CSF Aβ42 levels than those who remained stable. The Tau and phospho-Tau levels of the progressive MCI patients were significantly higher than those of the stable MCI patients in amnestic, dysexecutive and other MCI groups.

CSF Aβ42 and phospho-Tau showed no correlation with age. However, CSF Tau had a positive correlation with age in the control group ($r = 0.290$, $p = 0.025$) but not in patients with MCI. CSF Aβ42 levels did not correlate to CSF Tau or phospho-Tau levels in any group. On the contrary, CSF Tau and phospho-Tau had very strong positive correlation in the whole population as well as within different groups ($r > 0.900$ and $p < 0.001$ in all analyses). There was no correlation between the levels of CSF markers and the length of the follow-up.

3.3. ApoE genotype, CSF markers and progression to dementia

The APOE allele distribution was significantly different between the groups (Table 1). Altogether 78.8% of the patients with progressive MCI had at least one APOE ε4 allele compared to 35.0% in the control group and 33.3% in the patients with stable MCI. The APOE ε4 was more frequent in patients with progressive amnestic MCI than in patients with stable amnestic MCI (74% versus 21%, $p = 0.0004$). There was a significant association between the age and APOE genotype in patients with progressive MCI ($p = 0.039$). The mean age at the baseline of the APOE ε4 negative progressive MCI patients was 74.43 ± 4.50 years and 73.40 ± 6.82 in patients with one APOE ε4 allele whereas the patients carrying two APOE ε4 alleles were substantially younger, 67.55 ± 6.19 years of age.

The APOE ε4 had a dose dependent effect on Aβ42 in the control group and in the progressive MCI group. The association between APOE genotype and the Tau and phospho-Tau was also significant in the controls. In the progressive MCI group there was a trend for higher levels of Tau and phospho-Tau in the patients with two APOE ε4 alleles, but the difference was not significant. None of the markers showed a significant relationship to the APOE ε4 allele in the stable MCI group (Table 2).

Table 3
The predictive value of baseline measures for progression of MCI

	OR	
	Each variable alone	Backward Wald method
MCI type		
Amnestic	6.783 (1.377–33.419)	10.055 (1.551–65.167)
Executive	4.550 (0.771–26.835)	11.332 (1.306–98.365)
Sex, female	1.183 (0.477–2.939)	
Age	1.042 (0.978–1.110)	
MMSE	0.973 (0.816–1.160)	
APOE ε4 presence	7.429 (2.627–21.008)	7.611 (2.141–27.056)
Aβ42	5.579 (2.045–15.221)	
Tau	9.553 (3.104–29.403)	11.217 (3.002–41.912)
Phospho-Tau	8.711 (2.840–26.718)	
Aβ42-Tau	8.712 (2.752–27.587)	
Aβ42-phospho-Tau	7.718 (2.438–24.433)	

First column shows the odds ratios (OR) of different variables for progressive MCI when each variable is entered alone without covariates. Second column shows only the significant variables from backward Wald method. The Aβ42 test is positive if the value is below 450 pg/ml, Tau is positive if the value is above 400 pg/ml and the phospho-Tau is positive if the value is above 70 pg/ml. Combinations are coded as positive if both Aβ42 and Tau or phospho-Tau are abnormal.

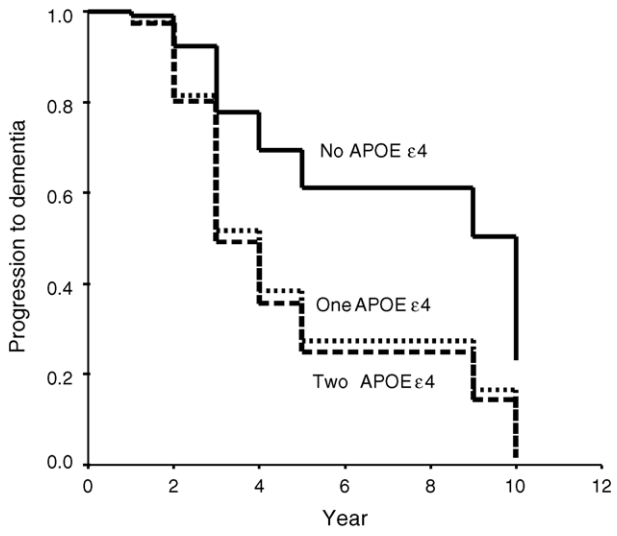

Fig. 2. Survival curves of amnestic MCI patients with different number of APOE ε4 alleles. The endpoint event was development of dementia. Covariates included APOE ε4 allele number and CSF Tau value.

3.4. Predictors of dementia

For the logistic regression analyses we coded the CSF biomarker levels as normal or abnormal using the previously published cut off values from the ROC analyses [21]. Univariate analyses showed that the presence of amnestic or dysexecutive MCI, the presence of APOE ε4, and abnormality of CSF biomarkers predicted the development of dementia (Table 3). When we performed the multivariate logistic regression analysis with backward Wald method to examine significant predictors of progression in MCI patients the significant factors were the type of cognitive dysfunction, possession of APOE ε4 allele and CSF Tau level. The results were similar when the CSF biomarkers were entered as continuous variables. When the APOE data was entered as APOE ε4 allele copy number instead of just the APOE ε4 allele absence or presence the significant factors remained the same (Fig. 2).

4. Discussion

MCI concept was first introduced by Flicker et al. [15], and has since then undergone many modifications. The main aim has been to detect patients with AD or other progressive dementing disease as early as possible. The most recent definitions emphasize the amnestic MCI by differentiating a pure amnestic MCI, amnestic plus MCI, other single non-memory domain and multiple domain deficits to individual classes [40]. Prognosis of MCI varies in different studies partially reflecting the heterogeneity of MCI population. Possible predictors for the progressive MCI include the presence of hippocampal atrophy on brain imaging or changes in CSF biomarkers. However, in many studies the patient numbers have been limited and the follow-up time of MCI patients have been relatively short. In the present study we report a naturalistic series of memory clinic patients who were followed an extended period of time. Our results show that both amnestic and dysexecutive types of MCI, abnormal biomarker levels and the presence of APOE ε4 allele predict progression to dementia.

Some investigators have postulated that the MCI is simply a prodromal stage of AD [33] and with strict criteria the MCI patients can be clinically distinguished from the patients with mild dementia [19,40]. However, although the MCI patients do have high risk of dementia, the cognitive impairment may be stable or even reversible [18,30,52]. One possible source of these controversial results relates to the definition of MCI. An isolated non-amnestic type of cognitive deficit may precede various dementing diseases whereas amnestic type of MCI has been suggested to represent an early phase of AD [40]. However, recent studies showed that the isolated amnestic MCI is not only rare, but it also has low predictive value for the development of dementia [6,43]. Instead, deficits in other cognitive domains besides memory increased the risk of dementia [6,32,43]. In our patients, the amnestic plus MCI patients had slightly but not statistically significantly shorter conversion time (3.17 ± 1.89 years) than the pure amnestic MCI patients (4.50 ± 2.51 years). Measures of memory are among the strongest predictors of AD when the interval between the initial assessment and the development of AD is long [12,26,49]. However, the likelihood of developing dementia is much higher in patients with both amnestic and executive dysfunction when compared to the patients with isolated amnestic MCI [11], and the development of executive symptoms in patients with amnestic MCI precede conversion to dementia [46].

Dysexecutive MCI was a frequent type of cognitive decline in our study. These patients did not differ from patients with amnestic MCI in respect to the baseline age, MMSE score, APOE ε4 distribution or CSF biomarker levels. Also, progression to dementia was almost as high and slightly faster as in patients with amnestic MCI. Our results corroborate the previous study which found that the executive dysfunction may progress to dementia even faster than amnestic MCI [47]. On the other hand, one previous study showed that none of the MCI patients with isolated executive dysfunction developed dementia during an average of 3.1 years follow up [11]. The controversial results may be related to differences of patient populations in different studies. Our results indicate that in the clinical setting the dysexecutive MCI patients should not be overlooked since they have similar likelihood of developing dementia and particularly AD to the amnestic MCI patients.

Clinicopathological studies have shown that MCI patients have AD type brain pathology [4,34]. Also CSF changes characteristic for AD e.g. decreased Aβ42, and increased Tau and phospho-Tau levels can be found in those MCI patients who will later develop AD [3,20,21,45]. Our results confirm that CSF biomarkers are helpful for detection of patients with progressive disorder. Progressive MCI patients irrespectively of

the type of cognitive deficit had significantly lower Aβ42 levels and higher Tau and phospho-Tau levels in CSF than controls, including depressive subgroup, or patients with stable MCI. The follow-up time in our study was longer than in previous studies. However, even longer follow-up time would be advantageous. A good example of the importance of the follow-up is our patient who was examined when suffering from fibromyalgic pains but developed AD 10 years after the collection of CSF. She had two APOE ε4 alleles and the biomarker values were abnormal already 10 years before any cognitive disorder. This patient and previous findings showing that even asymptomatic subjects who develop dementia after 3 years follow up have decreased CSF Aβ42 [51] illustrate the complexity of studying the clinical based population. The development of AD pathology is suggested to begin even two decades before the development of cognitive symptoms [33,50] and many studies have shown the presence of AD pathology in asymptomatic patients [10,37]. Recent studies have shown that CSF biomarker levels are associated with the brain AD pathology [8,54], and may detect patients who will develop symptoms after an extended period of time.

The APOE ε4 allele is a known risk factor for AD [14,53]. Some studies have also shown that APOE ε4 increases the risk of development of AD in MCI patients [22,41]. However, the latter association was not confirmed in other studies [2,11,27,29,30]. Our stable MCI patients had similar prevalence of the APOE ε4 allele that has previously been found in the young, cognitively healthy Finnish population [28] as opposed to the progressive MCI patients who had significantly elevated APOE ε4 allele prevalence. Currently the examination of APOE genotype is not recommended in routine clinical practise. However, recent large MCI trial showed that APOE ε4 carriers with MCI responded to treatment with donepezil whereas other patients did not [39]. Thus it is becoming extremely important to be able to diagnose early AD reliably. In the present study, the progressive MCI patients with two APOE ε4 alleles were younger at the baseline than the patients with one APOE ε4 allele or the APOE ε4 negative patients. This finding is consistent with previous studies showing that in the APOE ε4 positive AD patients the age of onset of dementia is lower than in the APOE ε4 negative AD patients [9,13].

Many previous studies have demonstrated an association between the APOE ε4 allele and decreased levels of Aβ42 in the patients with AD [17,23,42,55]. The association between APOE ε4 and Aβ42 was also found in a recent study that examined cognitively healthy subjects, many of them at high risk for dementia due to a family history of AD [55]. In our study population we found a negative correlation between the APOE ε4 allele number and the Aβ42 levels in patients with progressive MCI whereas there was no correlation between the APOE ε4 and Tau or phospho-Tau levels in these patients. Also the control subjects had a significant dose dependent negative association between the APOE ε4 allele and the CSF Aβ42 levels, and unlike in the previous studies, positive association with the Tau and phospho-Tau values as well. These findings further indicate that some control subjects may have an underlying AD type pathology that is reflected as changes in CSF biomarker levels [8].

One limitation of our study is the lack of MR imaging and the assessment of atrophy of medial temporal lobe structures. Therefore we couldn't compare the added value of these tests in this population. The MRI measurement of medial temporal lobe structures have shown that similar but less prominent atrophy occurs in MCI as in AD. The volume of hippocampus and entorhinal cortex can separate the MCI patients from control subjects and AD patients with relatively high accuracy [27,38] and the low hippocampal volume is also associated with elevated risk for dementia in the MCI patients [2,24].

The follow up period was extended to several years, but even longer follow up period may be required. On the other hand, the reliable prediction of the progression of MCI to dementia even in few years span would be of great value for both clinicians and clinical dementia prevention studies. The number of the patients in our study is relatively high when compared to other similar studies, but nonetheless, these results should be validated in a larger study.

Our patients represent well the average patients in the memory clinic. The results showed that the dysexecutive syndrome is relatively common and these patients frequently develop AD. Therefore clinicians should not concentrate only on memory problems when trying to identify the patients with developing dementia. CSF biomarker changes predicted the development of dementia. Importantly, the levels were normal in patients with depression, condition that may otherwise be difficult to differentiate from mild dementia in the elderly. Therefore we conclude, that decreased CSF Aβ42 and elevated Tau or phospho-Tau particularly with APOE ε4 allele are highly predictive for the dementia in MCI patients with amnestic or executive symptoms.

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