Injury markers predict time to dementia in subjects with MCI and amyloid pathology

Ineke A. van Rossum, MD
Stephanie J.B. Vos, MSc
Leah Burns, MPH
Dirk L. Knol, PhD
Philip Scheltens, MD, PhD
Hilkka Soininen, MD, PhD
Lars-Olof Wahlund, MD, PhD
Harald Hampel, MD, PhD
Magda Tsolaki, MD, PhD
Lennart Minthon, MD, PhD
Gilbert L'Italien, PhD
Wiesje M. van der Flier, PhD
Charlotte E. Teunissen, PhD
Kaj Blennow, MD, PhD
Frederik Barkhof, MD, PhD
Daniel Rueckert, PhD
Robin Wolz, PhD
Frans Verhey, MD, PhD
Pieter Jelle Visser, MD, PhD

Correspondence & reprint requests to Dr. van Rossum: i.vanrossum@vumc.nl

Supplemental data at www.neurology.org

Supplemental Data

ABSTRACT

Objectives: Alzheimer disease (AD) can now be diagnosed in subjects with mild cognitive impairment (MCI) using biomarkers. However, little is known about the rate of decline in those subjects. In this cohort study, we aimed to assess the conversion rate to dementia and identify prognostic markers in subjects with MCI and evidence of amyloid pathology.

Methods: We pooled subjects from the VU University Medical Center Alzheimer Center and the Development of Screening Guidelines and Criteria for Predementia Alzheimer's Disease (DESCRIPA) study. We included subjects with MCI, an abnormal level of β-amyloid$_{1-42}$ (Aβ_{1-42}) in the CSF, and at least one diagnostic follow-up visit. We assessed the effect of *APOE* genotype, CSF total tau (t-tau) and tau phosphorylated at threonine 181 (p-tau) and hippocampal volume on time to AD-type dementia using Cox proportional hazards models and on decline on the Mini-Mental State Examination (MMSE) using linear mixed models.

Results: We included 110 subjects with MCI with abnormal CSF Aβ_{1-42} and a mean MMSE score of 26.3 ± 2.8. During a mean follow-up of 2.2 ± 1.0 (range 0.4–5.0) years, 63 subjects (57%) progressed to AD-type dementia. Abnormal CSF t-tau (hazard ratio [HR] 2.3, 95% confidence interval [CI] 1.1–4.6, $p = 0.03$) and CSF p-tau (HR 3.5, 95% CI 1.3–9.2, $p = 0.01$) concentration and hippocampal atrophy (HR 2.5, 95% CI 1.1–5.6, $p = 0.02$) predicted time to dementia. For subjects with both abnormal t-tau concentration and hippocampal atrophy, HR was 7.3 (95% CI 1.0–55.9, $p = 0.06$). Furthermore, abnormal CSF t-tau and p-tau concentrations and hippocampal atrophy predicted decline in MMSE score.

Conclusions: In subjects with MCI and evidence of amyloid pathology, the injury markers CSF t-tau and p-tau and hippocampal atrophy can predict further cognitive decline. ***Neurology*® 2012; 79:1809–1816**

GLOSSARY

Aβ_{1-42} = β-amyloid$_{1-42}$; **AD** = Alzheimer disease; **CI** = confidence interval; **DESCRIPA** = Development of Screening Guidelines and Criteria for Predementia Alzheimer's Disease; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; **HR** = hazard ratio; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **p-tau** = tau phosphorylated at threonine 181; **t-tau** = total tau; **TMT** = Trail Making Test; **VUmc** = VU University Medical Center.

Recently, 2 sets of research criteria[1,2] were established, allowing a diagnosis of Alzheimer disease (AD) in subjects with mild cognitive impairment (MCI) and biomarker evidence of AD pathology. An international working group defined criteria for "prodromal AD" in 2007[2] and in 2011 the National Institute on Aging and the Alzheimer Association published criteria for "MCI due to AD."[1] However, at this moment, the prognosis of subjects fulfilling these criteria is largely unknown, which limits the use of the criteria in clinical practice. Prognostic markers

From the Departments of Neurology (I.A.v.R., P.S., W.M.v.d.F., P.J.V.), Epidemiology and Biostatistics (D.L.K., W.M.v.d.F.), and Radiology (F.B.), Alzheimer Center, VU University Medical Center, Amsterdam, the Netherlands; Department of Psychiatry and Neuropsychology (S.J.B.V., F.V., P.J.V.), School for Mental Health and Neuroscience, Alzheimer Center Limburg, Maastricht, the Netherlands; Global Health Economics and Outcomes Research (L.B., G.L.), Bristol-Myers Squibb, Wallingford, CT; Department of Neurology (H.S.), University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland; Department of NVS, Section of Clinical Geriatrics (L.-O.W.), Karolinska Institutet, Karolinska University Hospital, Huddinge, Sweden; Department of Psychiatry, Psychosomatic Medicine and Psychotherapy (H.H.), Goethe-University, Frankfurt, Germany; Aristotle University of Thessaloniki, Memory and Dementia Center, 3rd Department of Neurology (M.T.), G. Papanicolaou General Hospital, Thessaloniki, Greece; Clinical Memory Research Unit, Department of Clinical Sciences Malmö (L.M.), Lund University, Malmö, Sweden; Department of Clinical Chemistry (C.E.T.), VU University Medical Center, Amsterdam, the Netherlands; Clinical Neurochemistry Laboratory (K.B.), Göteborg University, Sahlgrenska University Hospital, Mölndal, Sweden; and Department of Computing (D.R., R.W.), Imperial College London, London, UK.

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for cognitive decline in subjects with MCI due to AD[1] or prodromal AD[2] are therefore urgently needed.

Subjects can be diagnosed with MCI due to AD[1] or prodromal AD[2] when they have a clinical diagnosis of MCI and biomarker evidence of either β-amyloid pathology, AD-related neuronal injury, or both. Abnormal amyloid markers may already be present at the earliest stage of the disease and reach a plateau in a very early stage of the disease and can therefore be useful as an early diagnostic marker.[3–5] Markers of the subsequent neuronal injury, on the other hand, such as CSF tau and hippocampal atrophy on MRI, may reflect more advanced pathology and might be useful as prognostic markers.[3–5]

For the present study, we selected subjects with MCI and evidence of amyloid pathology, defined by an abnormal level of β-amyloid$_{1-42}$ (Aβ_{1-42}) in the CSF. We hypothesized that the injury markers total tau (t-tau) and tau phosphorylated at threonine 181 (p-tau)[6–8] in CSF and hippocampal atrophy on MRI[9,10] would be associated with progression to AD-type dementia and cognitive decline.

METHODS

Subjects. We selected subjects from the Development of Screening Guidelines and Criteria for Predementia Alzheimer's Disease (DESCRIPA) cohort and the memory clinic of the Alzheimer Center of the VU University Medical Center (VUmc). DESCRIPA is a European multicenter study performed in a memory clinic setting.[11] The VUmc was one of the DESCRIPA partners and contributed an additional sample of subjects that were seen outside the DESCRIPA inclusion period. Inclusion criteria were a clinical diagnosis of MCI, an abnormal level of CSF Aβ_{1-42}, based on a clinically validated cutoff (≤550 pg/mL),[12] and at least one follow-up diagnosis. Subjects with obvious causes for MCI other than AD, such as alcohol abuse or severe depression, were excluded. In 10 of the participating centers, CSF was collected. Of the subjects enrolled at these centers between 2003 and 2005, 64 subjects fulfilled the inclusion criteria. From the VUmc, 46 additional subjects were included.

Standard protocol approvals, registrations, and patient consents. The medical ethics committee at each center approved the study. All patients provided written informed consent.

Clinical assessment. Diagnosis of MCI was made according to the criteria of Petersen et al.[13] Raw scores on neuropsychological tests were corrected for age, gender, and educational level in accordance with locally collected or published normative data and are expressed as *z* scores. MCI was defined as a *z* score less than −1.5 SD on any of the following tests: the learning measure or delayed recall of a verbal memory task, Trail Making Test (TMT) part A, TMT part B, verbal fluency, or Rey Figure Copy or equivalent test, as described in more detail previously.[11,14] Follow-up assessment was performed annually up to 5 years. For subjects from the Alzheimer Center of the VUmc, follow-up was part of regular patient care. Diagnosis of AD-type dementia was made according to the *DSM-IV*[15] and National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria.[16] Time to dementia was defined as the time between the baseline visit and the date AD-type dementia was diagnosed.

CSF analyses. CSF was collected by lumbar puncture, centrifuged, and stored at −80°C in polypropylene tubes. One sample was thawed twice, but analyses without this sample revealed similar results. CSF Aβ_{1-42}, t-tau, and p-tau were measured with an InnoTest sandwich ELISA (Innogenetics, Ghent, Belgium) in Gothenburg for the DESCRIPA cohort and in Amsterdam for the VUmc cohort. We corrected for interlaboratory ELISA differences by means of 33 samples that were analyzed at both laboratories and adjusted the VUmc values to those of DESCRIPA using the equating formula: Gothenborg = (SD Gothenborg/SD VUmc) × VUmc + average Gothenborg − [(SD Gothenborg/SD VUmc) × average VUmc].[17]

MRI analyses. For the DESCRIPA cohort, subjects were scanned according to the routine MRI protocol at each site. Scanning was performed at 1.0 or 1.5 T and included a 3-dimensional T1-weighted gradient echo sequence with near-isotropic voxels and a fast fluid-attenuated inversion recovery sequence.[14,18]

Hippocampal volume was measured at the Department of Computing of Imperial College London, using LEAP, a segmentation technique based on atlas registration.[19] We tested whether the MRI field strength influenced the LEAP scores in 348 subjects with MCI from the DESCRIPA cohort. Field strength did not affect the LEAP score (difference of 0.07%, p value = 0.8 after correction for age, gender, educational level, baseline Mini-Mental State Examination [MMSE] score, and follow-up diagnosis), and, therefore, we used data from both field strengths without correction.

MRI data were available in 35 of the 64 subjects (55%) from the DESCRIPA cohort and in 30 of the 46 subjects (65%) from VUmc. Subjects with and without MRI data available did not differ with respect to age, gender, educational level, *APOE* status, CSF markers, or score on the MMSE[20] at baseline.

***APOE* genotyping.** DNA was isolated from 10 mL EDTA-blood for *APOE* genotyping, using the light cycler *APOE* mutation detection kit (Roche Diagnostics GmbH, Mannheim, Germany).

APOE genotype was determined in 99 subjects (90%). Subjects in whom no *APOE* status was determined scored higher on the MMSE at baseline (27.7 vs 26.1, p = 0.005). There were no differences with respect to age, gender, educational level, medial temporal lobe atrophy, or CSF markers between subjects with and without *APOE* data available. Subjects were classified as *APOE ε4*−positive when having 1 or 2 *APOE ε4* alleles.

Statistical analyses. Analyses were performed with SPSS 18.0 for the Macintosh.

For group comparisons of subjects with and without AD-type dementia at follow-up we used χ^2 tests for categorical variables and Student's *t* tests for continuous variables. Data for the CSF markers were log-transformed to obtain an approximately normal distribution. For further analyses we used dichotomized values of the respective markers. We used clinically validated cutoff points for CSF t-tau (≥375 pg/mL) and p-tau (≥52 pg/mL).[12] For hippocampal volume, we used a summed volume of the left and right hippocampus of 5.39 cm^3 as the cutoff point.

Table 1 Baseline characteristics according to diagnosis at follow up

	All subjects	No AD-type dementia at follow-up	AD-type dementia at follow-up
No.	110	47	63
Age, y, mean ± SD	70.8 ± 7.7	70.1 ± 8.1	71.3 ± 7.4
Female, n (%)	51 (46)	20 (43)	31 (49)
Education, y, mean ± SD	10.8 ± 3.5	10.5 ± 3.5	11.1 ± 3.4
Follow-up, y, mean ± SD	2.2 ± 1.0	2.3 ± 1.1	2.0 ± 0.9
APOE ϵ4 positive, n (%)[a]	61 (62)	23 (54)	38 (68)
$A\beta_{1-42}$, pg/mL, mean ± SD	382 ± 98	369 ± 100	392 ± 97
t-tau, pg/mL, mean ± SD	564 ± 345	421 ± 252	670 ± 368[b]
t-tau, abnormal, n (%)[c]	81 (74)	28 (60)	53 (84)[b]
p-tau, pg/mL, mean ± SD	89 ± 49	71 ± 35	103 ± 54[b]
p-tau, abnormal, n (%)[c]	90 (82)	32 (68)	58 (92)[b]
Hippocampal volume, cm^3, mean ± SD[d]	5.4 ± 0.7	5.8 ± 0.8	5.2 ± 0.6[b]
Hippocampal atrophy, n (%)[e]	35 (54)	8 (31)	27 (69)[b]
MMSE score, mean ± SD	26.3 ± 2.8	26.8 ± 2.6	25.9 ± 2.8
Verbal memory, learning (*z* score), mean ± SD	−1.5 ± 1.0	−1.4 ± 1.1	−1.6 ± 0.9
Verbal memory, delayed recall (*z* score), mean ± SD	−1.6 ± 1.0	−1.3 ± 1.1	−1.9 ± 0.8[b]
Verbal fluency (*z* score), mean ± SD	−0.8 ± 1.1	−0.7 ± 1.3	−1.0 ± 0.9
TMT part A (*z* score), mean ± SD	−0.8 ± 1.8	−0.7 ± 1.6	−0.9 ± 2.0
TMT part B (*z* score), mean ± SD	−1.1 ± 1.6	−1.0 ± 1.6	−1.2 ± 1.6
Visuoconstruction (*z* score), mean ± SD	0.2 ± 1.1	0.03 ± 1.2	0.3 ± 1.0

Abbreviations: $A\beta_{1-42}$ = β-amyloid$_{1-42}$; AD = Alzheimer disease; MMSE = Mini-Mental State Examination; p-tau = tau phosphorylated at threonine 181; t-tau = total tau; TMT = Trail Making Test.
[a] *APOE* genotype was determined in 99 subjects.
[b] $p < 0.005$ compared to no dementia at follow-up.
[c] Abnormal values were defined as ≥375 pg/mL for CSF t-tau and ≥52 pg/mL for CSF p-tau.
[d] Hippocampal volume was determined in 65 subjects.
[e] Hippocampal atrophy was defined as a summed volume of left and right hippocampus of <5.39 cm^3.

This cutoff point could best differentiate between healthy control subjects and subjects with AD-type dementia in the Alzheimer's Disease Neuroimaging Initiative cohort (S.J.B. Vos, I.A. van Rossum, F. Verhey, et al., unpublished data), based on the Youden index using R.[21,22] This cutoff point was similar to the cutoff point of 5.34 cm^3 that could best predict AD-type dementia in our own dataset.[23]

We assessed the effect of *APOE* genotype, CSF levels of t-tau and p-tau, and hippocampal atrophy on time to dementia using Cox proportional hazards with correction for age, gender, education, and MMSE score at baseline. Analyses were performed for each variable alone and with all variables together using a step-forward model to select the variables that could best predict AD-type dementia.

We also assessed the association of CSF t-tau and p-tau and hippocampal volume with the decline in MMSE score. We performed mixed-model analyses with an unstructured covariance structure with correction for age, gender, educational level, and center.[24]

RESULTS

Baseline characteristics. We included 110 subjects with MCI and abnormal CSF $A\beta_{1-42}$. Subjects were 70.8 ± 7.7 years old (average ± SD), 46% were female, and 62% had at least one *APOE ϵ4* allele. Mean MMSE score was 26.3 ± 2.8. Baseline characteristics of the subjects are shown in table 1. Two subjects progressed to other types of dementia (one subject with vascular dementia and one subject with Parkinson disease dementia). They were included in the group of subjects who did not progress to AD-type dementia. Excluding those 2 subjects from the analyses did not change the results (data not shown).

Predictors of progression to AD-type dementia. During a mean follow-up of 2.2 ± 1.0 years (median 2.0 years, range 0.4–5.0 years), 63 subjects (57%) progressed to AD-type dementia. These subjects had higher levels of CSF t-tau (mean ± SD, 670 ± 368 vs 421 ± 252 pg/mL, $p < 0.001$) and p-tau (103 ± 54 vs 71 ± 35 pg/mL, $p < 0.001$), a smaller hippocampal volume (5.2 ± 0.6 vs 5.8 ± 0.8 cm^3, $p = 0.002$), and a lower score on the delayed recall of a verbal memory task (*z* score −1.9 ± 0.8 vs −1.3 ± 1.1, $p = 0.004$) than subjects who did not progress to AD-type dementia (table 1).

Predictors of time to AD-type dementia. Survival analyses using Cox proportional hazards models with correction for age, gender, and education showed that time to dementia was predicted by abnormal CSF t-tau (hazard ratio [HR] 2.3, 95% confidence interval [CI] 1.1–4.6, $p = 0.03$), abnormal CSF p-tau (HR 3.5, 95% CI 1.3–9.2, $p = 0.01$), and hippocampal atrophy (HR 2.5, 95% CI 1.1–5.6, $p = 0.02$) (figure 1, table e-1 on the *Neurology*® Web site at www.neurology.org). After correction for baseline MMSE score, results remained essentially the same, with an HR of 2.0 (95% CI 1.0–4.2, $p = 0.06$) for CSF t-tau, 3.1 (95% CI 1.2–8.4, $p = 0.03$) for CSF p-tau, and 2.2 (1.0–5.0, $p = 0.06$) for hippocampal atrophy. Of the neuropsychological measures, only delayed recall predicted AD-type dementia (HR 2.1, 95% CI 1.0–4.3, $p = 0.05$) (table e-1). The *APOE ϵ4* genotype, age, gender, and education did not predict time to dementia (table e-1). Cox multivariate analyses with forward-step selection and biomarkers entered as log-transformed continuous variables selected only CSF p-tau (β 1.2, HR 3.3, 95% CI 1.4–7.5, $p = 0.005$). In the multivariate analysis, we did not find a significant interaction between CSF p-tau or t-tau with hippocampal atrophy ($p = 0.8$).

MMSE slope analyses. Subjects with abnormal CSF t-tau declined more rapidly on the MMSE, with an annual decline of −1.1, compared with −0.4 for subjects with normal CSF t-tau (table 2). At baseline there were no differences in MMSE score between

subjects with normal and abnormal CSF t-tau (26.5 and 26.3, respectively). For CSF p-tau, results were similar (table 2). Subjects with hippocampal atrophy showed a more rapid decline in MMSE score compared with subjects without hippocampal atrophy (average annual decline −1.2 vs −0.5, $p = 0.09$) (table 2). At baseline, subjects with hippocampal atrophy had lower MMSE scores than subjects without hippocampal atrophy (25.6 vs 27.0, $p = 0.02$).

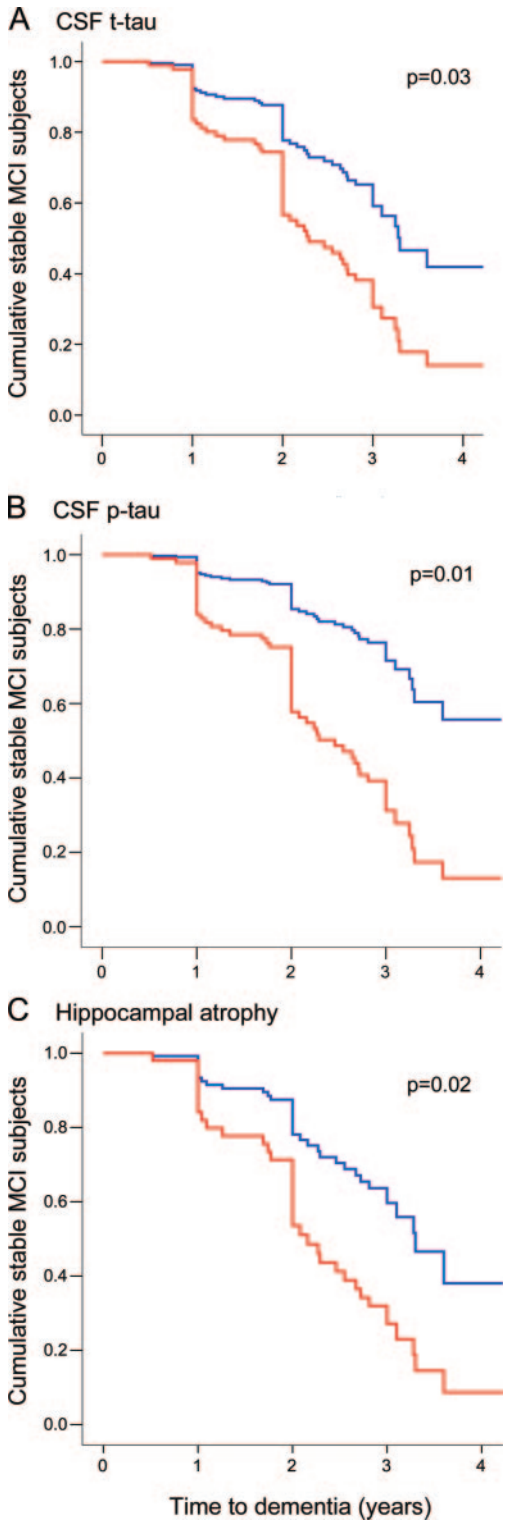
Biomarker subgroup analyses. To investigate the effect of the combination of abnormal CSF t-tau and hippocampal atrophy on progression to AD-type dementia and cognitive decline, we subdivided subjects with both CSF and MRI available (n = 65) into 3 groups, depending on their biomarker status at baseline (figure e-1): 1) normal CSF t-tau and no hippocampal atrophy (n = 9, of whom 1 progressed to AD-type dementia); 2) either abnormal CSF t-tau or hippocampal atrophy (n = 28, of whom 16 progressed to AD-type dementia); and 3) both abnormal CSF t-tau and hippocampal atrophy (n = 28, of whom 22 progressed to AD-type dementia). Compared with subjects with normal CSF t-tau and no hippocampal atrophy, subjects with either abnormal CSF t-tau or hippocampal atrophy had an HR of 5.2 (95% CI 0.7–40.3, $p = 0.1$) for progression to AD-type dementia. For subjects with both abnormal CSF t-tau and hippocampal atrophy, the HR was 7.3 (95% CI 1.0–55.9, $p = 0.06$) (table 3).

The annual decline in MMSE score was −0.1 (p value slope = 0.8) for subjects with normal CSF t-tau and no hippocampal atrophy, −0.8 ($p = 0.001$) for subjects with either abnormal CSF t-tau or hippocampal atrophy, and −1.1 ($p < 0.001$) for subjects with both abnormal CSF t-tau and hippocampal atrophy (table 3, figure 2). The slopes of decline of subjects with 1 or 2 abnormal markers differed from the slope of subjects with both markers normal, but not from each other. For subjects with only abnormal CSF t-tau (n = 21), the annual decline in MMSE score was −0.6 (−1.0 to −0.2, $p = 0.006$). For subjects with only hippocampal atrophy, no slope analyses could be performed, because of the small sample size (n = 7).

DISCUSSION In this prospective study of subjects who fulfilled the criteria for MCI due to AD[1] and prodromal AD[2] based on abnormal CSF $A\beta_{1-42}$, we found that during a mean follow-up of 2.2 years 63 subjects (57%) progressed to AD-type dementia. High CSF levels of t-tau and p-tau and hippocampal atrophy predicted progression to dementia and declines in MMSE score.

The overall annual conversion rate to dementia of approximately 20% in this study was higher than the

Figure 1 Survival curves for time to dementia in subjects with mild cognitive impairment (MCI) and abnormal CSF β-amyloid$_{1-42}$, corrected for age, gender, and education



Red lines indicate the subjects with an abnormal value of each respective marker, defined as CSF total tau (t-tau) ≥375 pg/mL (A), CSF tau phosphorylated at threonine 181 (p-tau) ≥52 pg/mL (B), and hippocampal volume <5.39 cm^3 (C). Blue lines indicate the subjects with normal values of each marker.

Table 2 Predictors for decline in MMSE score[a]

	No.	Baseline MMSE	*p* Value[b]	Slope	*p* Value[b]
CSF t-tau					
≥375 pg/mL	81	26.2 (25.1-27.4)	0.6	−1.1 (−1.4 to 0.8)	0.02
<375 pg/mL	29	26.5 (25.3-27.9)		−0.4 (−0.9 to 0.2)	
CSF p-tau					
≥52 pg/mL	90	26.2 (25.1-27.3)	0.4	−1.1 (−1.3 to 0.8)	0.005
<52 pg/mL	20	26.7 (25.3-28.2)		−0.04 (−0.7 to 0.6)	
Hippocampal volume					
<5.39 cm^3	35	25.6 (23.8-27.5)	0.02	−1.2 (−1.5 to 0.8)	0.01
≥5.39 cm^3	30	27.0 (25.2-28.8)		−0.5 (−0.9 to 0.1)	

Abbreviations: MMSE = Mini-Mental State Examination; p-tau = tau phosphorylated at threonine 181; t-tau = total tau.
[a] Baseline MMSE scores and slope values of annual change in MMSE score were estimated using mixed models with correction for age, gender, educational level, and center. Values are estimated assuming that subjects are 50% female, are 70 years of age, and have 11 years of education. Data are means (95% confidence interval).
[b] The *p* value of the difference between subjects with normal and abnormal values for each biomarker.

conversion rate typically observed in subjects with MCI unselected for biomarker status.[25] For comparison, subjects with MCI and a normal concentration of CSF $A\beta_{1-42}$ in our dataset had an annual conversion rate of less than 10% (data not shown). Still, a considerable percentage of our subjects did not develop AD-type dementia within the follow-up period. Because abnormal Aβ is suggested to be an early marker for AD,[3] higher progression rates to AD-type dementia might be expected with a longer follow-up period.

The rapid decline to dementia in subjects with high CSF levels of t-tau and p-tau and hippocampal atrophy could mean that these subjects either had a more aggressive course of the disease or were already in a more advanced stage when assessed at baseline. Slope analyses suggested that they had a more aggressive course of the disease because they showed a more rapid decline in MMSE score than subjects with normal values of these markers at baseline. This finding is in line with previous studies that showed a more rapid cognitive decline in subjects with AD-type dementia with high levels of CSF tau.[26,27] Subjects with hippocampal atrophy may have also already been in a more advanced stage of the disease at baseline because they had lower MMSE scores at baseline than subjects without hippocampal atrophy. This result is consistent with the previously suggested order of events in the amyloid cascade,[3,4] with hippocampal atrophy being a relatively late feature of AD pathology. In a previous study in subjects with MCI and biomarker evidence of Aβ pathology, hippocampal atrophy also predicted time to dementia.[28] In another study in subjects with MCI who all progressed to AD-type dementia, CSF t-tau, CSF p-tau, and hippocampal atrophy were also associated with rapid progression from MCI to AD-type dementia, whereas CSF $A\beta_{1-42}$ was not.[5] Our finding that the predictive value of the respective CSF and MRI markers for progression to AD-type dementia remained after correction for baseline MMSE score indicates that AD biomarkers can have prognostic value in addition to clinical measures alone.

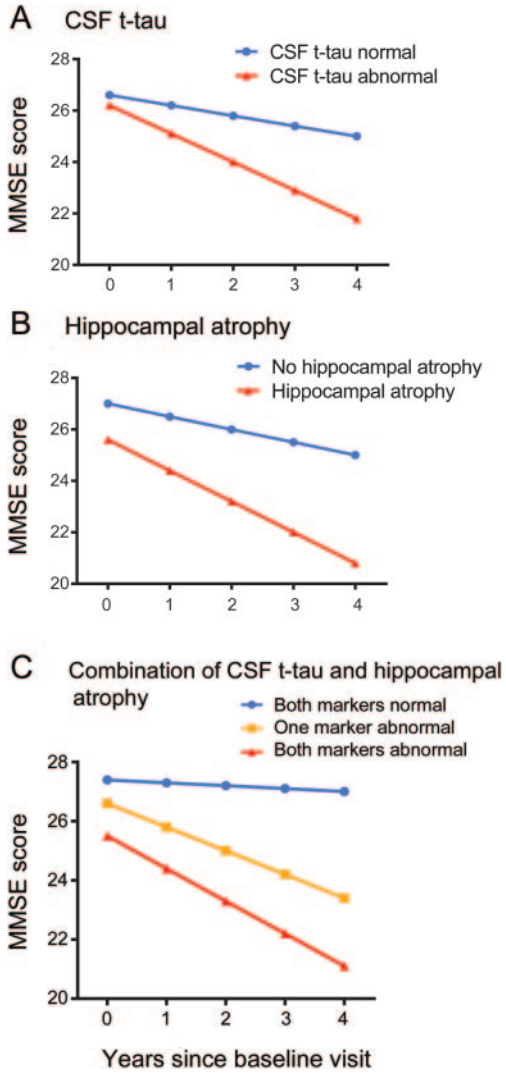
The predictive accuracy of CSF t-tau and p-tau and hippocampal atrophy we observed in our MCI subjects with abnormal CSF $A\beta_{1-42}$ was lower than that reported in studies conducted in subjects with MCI regardless of amyloid biomarker status[7–9,23] Most likely this is because in our analyses only the additional predictive effect relative to abnormal amyloid was tested, although differences could partly also be due to differences in setting and other study characteristics.

Table 3 Progression to AD-type dementia and rate of cognitive decline with respect to biomarker status at baseline[a]

CSF t-tau and hippocampal volume[b]	No.	Dementia-free survival after 4 y, mean ± SE	Dementia, HR (95% CI)	Baseline MMSE, HR (95% CI)[c]	Slope
Both normal	9	0.73 ± 0.06	Reference	27.4 (25.2-29.6)	−0.1 (−0.9 to 0.7)
One abnormal	28	0.19 ± 0.08	5.2 (0.7-40.3)	26.6 (24.7-28.5)	−0.8 (−1.2 to 0.4)[d]
Both abnormal	28	0.09 ± 0.03	7.3 (1.0-55.9)	25.5 (23.6-27.4)	−1.1 (−1.5 to 0.7)[e]

Abbreviations: AD = Alzheimer disease; CI = confidence interval; HR = hazard ratio; MMSE = Mini-Mental State Examination; p-tau = tau phosphorylated at threonine 181; t-tau = total tau.
[a] Dementia-free survival and the HR were calculated using Cox regression analyses with correction for age, gender, and educational level. Baseline MMSE scores and slope values of annual change in MMSE score were estimated using mixed models with correction for age, gender, educational level, and center. Values are estimated assuming that subjects are 50% female, are 70 years of age, and have 11 years of education.
[b] Abnormal CSF t-tau was defined as a value ≥375 pg/mL; hippocampal atrophy was defined as a volume of both left and right hippocampus of <5.39 cm^3.
[c] Differences in baseline MMSE between the groups were not statistically significant.
[d] The *p* value compared with both markers normal = 0.1.
[e] The *p* value compared with both markers normal = 0.02.

Figure 2 **Decline in Mini-Mental State Examination (MMSE) score in subjects with mild cognitive impairment (MCI) and abnormal CSF Aβ_{1-42} according to CSF total tau (t-tau) and hippocampal volume**



Slopes of decline in MMSE score in subjects with MCI and abnormal CSF β-amyloid$_{1-42}$ (Aβ_{1-42}) are shown. Subjects were classified according to their CSF t-tau levels and hippocampal volume at baseline. Abnormal values were defined as CSF tau ≥375 pg/mL and hippocampal volume <5.39 cm^3.

We found no differences in age, gender, and *APOE* status between subjects with and without dementia at follow-up, although age, gender, and *APOE* genotype are known risk factors for AD in the general population. A possible explanation for this finding is that advanced age and *APOE ε4* genotype are risk factors for development of abnormal Aβ processing but do not influence clinical progression once abnormal Aβ processing is established.

We included subjects with MCI and abnormal amyloid. According to the criteria of the National Institute on Aging and the Alzheimer Association,[1] these subjects would meet the criteria for "MCI due to AD—intermediate likelihood." Of the 65 subjects with both CSF and MRI data available, 9 subjects (14%) had both normal CSF t-tau and normal hippocampal volume and met the criteria for "MCI, biomarker evidence uninformative." The course of the disease in these subjects was relatively benign with a 27% conversion rate to AD-type dementia after 4 years, although the interpretation is limited by the small sample size. Twenty-eight subjects (43%) had both abnormal CSF t-tau and hippocampal atrophy and fulfilled the criteria for "MCI due to AD—high likelihood."[1] Their prognosis was poor, with 91% progressing to AD-type dementia after 4 years. In 28 subjects (43%), the injury markers were conflicting, with either CSF t-tau abnormal or hippocampal volume abnormal. According to the National Institute on Aging and the Alzheimer Association criteria, it is not clear whether these subjects should be diagnosed as "MCI, biomarker evidence uninformative" or "MCI due to AD—high likelihood."[1] Our data suggest that these subjects should be considered as "MCI due to AD—high likelihood" because the decline in MMSE score and progression rate to AD-type dementia (81%) was similar to that of subjects with both markers abnormal, whereas the rate of decline on the MMSE was worse than that of subjects with both markers normal, although group comparisons are hampered by the small sample size.

Two subjects included in the study progressed to other types of dementia, despite abnormal CSF Aβ_{1-42} levels at baseline. One subject, aged 75 years, had extrapyramidal signs at baseline and was later diagnosed with Parkinson disease dementia. CSF Aβ_{1-42} was 326 pg/mL, CSF t-tau and CSF p-tau were normal, and hippocampal volume was not available. Decreased CSF Aβ_{1-42} has been described before in subjects with alpha-synucleinopathies.[29] This finding highlights the importance of ruling out causes for the cognitive symptoms other than AD before the criteria for MCI due to AD can be applied.[1] The other subject, aged 61 years, was diagnosed with vascular dementia at follow-up. She had a CSF Aβ_{1-42} concentration of 357 pg/mL and abnormal CSF t-tau and p-tau concentrations. On the MRI scan she had multiple vascular white matter lesions and parietal atrophy, in the absence of hippocampal atrophy. In retrospect, this subject may have had mixed dementia with both vascular and AD pathology.

A major limitation of our study is that we did not have MRI data available for all subjects, which limited the possibilities for multivariate analyses. Another limitation is the limited follow-up. Studies

with longer clinical follow-up are needed to assess whether all subjects with MCI due to AD will indeed develop dementia eventually.

Our results indicate that markers of AD-related neuronal injury, such as CSF levels of t-tau and p-tau and hippocampal atrophy, could help to identify those subjects with MCI due to AD who will more rapidly progress to dementia. Subjects with both abnormal CSF $A\beta_{1-42}$ and abnormal injury markers, thereby fulfilling the criteria for "MCI due to AD−high likelihood," showed the most rapid cognitive decline and a high progression rate to AD-type dementia, even within our limited follow-up period.

AUTHOR CONTRIBUTIONS

L. Burns, G. L'Italien, and P.J. Visser designed the study. I.A. van Rossum analyzed the data and wrote the manuscript with assistance from P.J. Visser. S.J.B. Vos, P. Scheltens, H. Soininen, L.-O. Wahlund, H. Hampel, M. Tsolaki, L. Minthon, W.M. van der Flier, K. Blennow, F. Barkhof, and F. Verhey were involved in data collection. C.E. Teunissen, K. Blennow, D. Rueckert, and R. Wolz performed biomarker analyses. D.L. Knol helped with statistical methods. All authors reviewed the manuscript and approved the final draft.

DISCLOSURE

I.A. van Rossum received research support via Lipididiet from European Community's Seventh Framework Programme (FP7/2007–2013), grant agreement no 211696. S.J.B. Vos receives research support from the Center for Translational Molecular Medicine, project LeARN (grant 02N-01). L. Burns is an employee of Bristol-Myers Squibb. D.L. Knol reports no disclosures. P. Scheltens serves/has served on the advisory boards of Genentech, Novartis, Roche, Danone, Nutricia, Baxter, and Lundbeck. He has been a speaker at symposia organized by Lundbeck, Merz, Danone, Novartis, Roche, and Genentech. For all his activities he receives no personal compensation. He is a member of the scientific advisory board of the EU Joint Programming Initiative and the French National Plan Alzheimer. The Alzheimer Center receives unrestricted funding from various sources through the VUMC Fonds. H. Soininen is supported by University of Eastern Finland for UEFBRAIN. L.-O. Wahlund and H. Hampel report no disclosures. M. Tsolaki serves on scientific advisory boards for Novartis, Pfizer, and Iasis and receives research support from EU (DESCRIPA, ICTUS, Addneuromed, EDAR, and ENIR) projects. L. Minthon serves on advisory boards for Pfizer, Sweden. G. L'Italien is an employee of Bristol-Myers Squibb. W.M. van der Flier reports no disclosures. C.E. Teunissen serves as a member of the scientific advisory board of Innogenetics SA and received grants from the European Commission. K. Blennow has served on advisory boards for Innogenetics, Ghent, Belgium. F. Barkhof has received the following funding: consulting fees or honoraria from UCB, Bayer Schering, sanofi-aventis, Novartis, Roche, Merck-Serono, Synthon BV, Janssen Research, Lundbeck, and Biogen-Idec. He declared also to be a member of UCB, Bayer Schering, sanofi-aventis, Novartis, and Roche advisory boards. D. Rueckert is founder and consultant for IXICO. He received research support via the PredictAD project funded by the 7th Framework Programme by the European Commission. R. Wolz is consultant for IXICO and received research support via the PredictAD project funded by the 7th Framework Programme by the European Commission. F. Verhey receives research support from the Center for Translational Molecular Medicine, project LeARN (grant 02N-01). P.J. Visser has served as an advisory board member for Myriad, Guidage study Ipsen, and Bristol-Myers Squibb. He receives/received research grants from Bristol-Myers Squibb, European Commission 6th and 7th Framework programme, Life Sciences, Genomics and Biotechnology for Health, Diagenic, Norway, and Innogenetics, Belgium. **Go to Neurology.org for full disclosures.**

Received March 31, 2012. Accepted in final form June 18, 2012.

REFERENCES

1. Albert MS, Dekosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270–279.
2. Dubois B, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 2007;6:734–746.
3. Jack CR Jr, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9:119–128.
4. Jack CR Jr, Vemuri P, Wiste HJ, et al. Evidence for ordering of Alzheimer disease biomarkers. Arch Neurol 2011;68:1526–1535.
5. van Rossum IA, Visser PJ, Knol DL, et al. Injury markers but not amyloid markers are associated with rapid progression from mild cognitive impairment to dementia in Alzheimer's disease. J Alzheimers Dis 2012;29:319−327.
6. Hampel H, Teipel SJ, Fuchsberger T, et al. Value of CSF β-amyloid$_{1-42}$ and tau as predictors of Alzheimer's disease in patients with mild cognitive impairment. Mol Psychiatry 2004;9:705–710.
7. Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Minthon L. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. Lancet Neurol 2006;5:228–234.
8. Herukka SK, Hallikainen M, Soininen H, Pirttila T. CSF Aβ42 and tau or phosphorylated tau and prediction of progressive mild cognitive impairment. Neurology 2005;64:1294–1297.
9. Korf ES, Wahlund LO, Visser PJ, Scheltens P. Medial temporal lobe atrophy on MRI predicts dementia in patients with mild cognitive impairment. Neurology 2004;63:94–100.
10. Jack CR Jr, Petersen RC, Xu YC, et al. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. Neurology 1999;52:1397–1403.
11. Visser PJ, Verhey FR, Boada M, et al. Development of screening guidelines and clinical criteria for predementia Alzheimer's disease: the DESCRIPA Study. Neuroepidemiology 2008;30:254–265.
12. Mulder C, Verwey NA, van der Flier WM, et al. Amyloid-β(1−42), total tau, and phosphorylated tau as cerebrospinal fluid biomarkers for the diagnosis of Alzheimer disease. Clin Chem 2010;56:248–253.
13. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–308.
14. Bouwman FH, Schoonenboom SN, van der Flier WM, et al. CSF biomarkers and medial temporal lobe atrophy predict dementia in mild cognitive impairment. Neurobiol Aging 2007;28:1070–1074.
15. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Association; 1994.
16. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services

Task Force on Alzheimer's Disease. Neurology 1984;34:939–944.
17. Kolen M, Brannan RL. Test Equating: Methods and Practices. New York: Springer-Verlag; 1995.
18. van de Pol LA, Verhey F, Frisoni GB, et al. White matter hyperintensities and medial temporal lobe atrophy in clinical subtypes of mild cognitive impairment: the DESCRIPA study. J Neurol Neurosurg Psychiatry 2009;80:1069–1074.
19. Wolz R, Aljabar P, Hajnal JV, Hammers A, Rueckert D. LEAP: learning embeddings for atlas propagation. Neuroimage 2010;49:1316–1325.
20. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician J Psychiatr Res 1975;12:189–198.
21. Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. Biometrics 2000;56:337–344.
22. R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2010.
23. Vos S, van Rossum I, Burns L, et al. Test sequence of CSF and MRI biomarkers for prediction of AD in subjects with MCI. Neurobiol Aging 2012;33:2272−2281.
24. Visser PJ, Verhey F, Knol DL, et al. Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective cohort study. Lancet Neurol 2009;8:619–627.
25. Visser PJ, Kester A, Jolles J, Verhey F. Ten-year risk of dementia in subjects with mild cognitive impairment. Neurology 2006;67:1201–1207.
26. Kester MI, van der Vlies AE, Blankenstein MA, et al. CSF biomarkers predict rate of cognitive decline in Alzheimer disease. Neurology 2009;73:1353–1358.
27. Samgard K, Zetterberg H, Blennow K, Hansson O, Minthon L, Londos E. Cerebrospinal fluid total tau as a marker of Alzheimer's disease intensity. Int J Geriatr Psychiatry 2010;25:403–410.
28. Jack CR Jr, Wiste HJ, Vemuri P, et al. Brain β-amyloid measures and magnetic resonance imaging atrophy both predict time-to-progression from mild cognitive impairment to Alzheimer's disease. Brain 2010;133:3336–3348.
29. Schoonenboom NS, Reesink FE, Verwey NA, et al. Cerebrospinal fluid markers for differential dementia diagnosis in a large memory clinic cohort. Neurology 2012;78:47–54.