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# Mild cognitive impairment with suspected nonamyloid pathology (SNAP)

## Prediction of progression

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### ABSTRACT

**Objectives:** The aim of this study was to investigate predictors of progressive cognitive deterioration in patients with suspected non-Alzheimer disease pathology (SNAP) and mild cognitive impairment (MCI).

**Methods:** We measured markers of amyloid pathology (CSF  $\beta$ -amyloid 42) and neurodegeneration (hippocampal volume on MRI and cortical metabolism on [ $^{18}$ F]-fluorodeoxyglucose-PET) in 201 patients with MCI clinically followed for up to 6 years to detect progressive cognitive deterioration. We categorized patients with MCI as A+/A- and N+/N- based on presence/absence of amyloid pathology and neurodegeneration. SNAPs were A-N+ cases.

**Results:** The proportion of progressors was 11% (8/41), 34% (14/41), 56% (19/34), and 71% (60/85) in A-N-, A+N-, SNAP, and A+N+, respectively; the proportion of APOE  $\epsilon$ 4 carriers was 29%, 70%, 31%, and 71%, respectively, with the SNAP group featuring a significantly different proportion than both A+N- and A+N+ groups ( $p \leq 0.005$ ). Hypometabolism in SNAP patients was comparable to A+N+ patients ( $p = 0.154$ ), while hippocampal atrophy was more severe in SNAP patients ( $p = 0.002$ ). Compared with A-N-, SNAP and A+N+ patients had significant risk of progressive cognitive deterioration (hazard ratio = 2.7 and 3.8,  $p = 0.016$  and  $p < 0.001$ ), while A+N- patients did not (hazard ratio = 1.13,  $p = 0.771$ ). In A+N- and A+N+ groups, none of the biomarkers predicted time to progression. In the SNAP group, lower time to progression was correlated with greater hypometabolism ( $r = 0.42$ ,  $p = 0.073$ ).

**Conclusions:** Our findings support the notion that patients with SNAP MCI feature a specific risk progression profile. **Neurology® 2015;84:508-515**

### GLOSSARY

**AB** =  $\beta$ -amyloid; **A $\beta$ <sub>42</sub>** =  $\beta$ -amyloid 1-42; **AD** = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **EU** = European Union; **FDG** = [ $^{18}$ F]-fluorodeoxyglucose; **FTD** = frontotemporal dementia; **KUHH** = Karolinska University Hospital Huddinge; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **MUCH** = Klinikum rechts der Isar der Technischen Universität München; **SNAP** = suspected non-Alzheimer disease pathology; **TOMC** = Translational Outpatient Memory Clinic; **VUMC** = VU University Medical Center.

The amyloid cascade hypothesis<sup>1,2</sup> has so far dominated the Alzheimer disease (AD) field. Jack et al.<sup>3,4</sup> proposed a dynamic model that relates disease stage to the best established biomarkers of AD pathology. Based on this, a National Institute on Aging-Alzheimer's Association task force developed recommendations for the diagnosis of preclinical AD based on biomarkers of amyloidosis and neuronal injury.<sup>5</sup> Soon afterward, these criteria were operationalized and a

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sizable minority of cognitively normal elders (23%) showed evidence of neuronal injury and no  $\beta$ -amyloid ( $A\beta$ ) deposition.<sup>6</sup> These subjects were collectively considered to have “suspected non-AD pathology” (SNAP).<sup>6</sup>

Patients with SNAP mild cognitive impairment (MCI) were shown to have a high 1-year rate of progression to dementia (21%–25%).<sup>7</sup> Moreover, MRI markers were found to be useful for predicting progression to dementia in amyloid-negative patients with MCI,<sup>8</sup> some of whom may be considered to have SNAP, suggesting that amyloid does not tell the whole story regarding development of dementia.

Individuals with SNAP were comparable to amyloid-positive cognitively normal individuals based on various imaging markers, clinical features, and risk factors, suggesting that the initial appearance of brain-injury biomarkers may be independent and indistinguishable from that due to amyloidosis.<sup>9</sup> Further evidence to support amyloid-independent pathology in AD has begun to accumulate.<sup>10–12</sup> Moreover, recent studies suggested that neurodegenerative pathology could emerge through a nonamyloid-related pathway even within regions usually affected by AD.<sup>13,14</sup> Given the major implications for AD research and treatment,<sup>15</sup> SNAP deserves more in-depth investigation. The aim of this study was to investigate predictors of progressive cognitive deterioration in patients with MCI-SNAP.

**METHODS Subjects.** We selected patients from 2 independent datasets: the Alzheimer’s Disease Neuroimaging Initiative (ADNI, adni.loni.usc.edu) and a European Union (EU) dataset of patients coming to observation at 4 independent European memory clinics (Brescia, Italy [Translational Outpatient Memory Clinic, TOMC]; Amsterdam, the Netherlands [VU University Medical Center, VUMC]; Stockholm, Sweden [Karolinska University Hospital Huddinge, KUHH]; and Munich, Germany [Klinikum rechts der Isar der Technischen Universität München, MUCH]). For a complete description of the 2 datasets, refer to e-Methods on the *Neurology*<sup>®</sup> Web site at Neurology.org.

At baseline, all patients enrolled in this study (89 from ADNI, 39 from TOMC, 27 from VUMC, 17 from KUHH, and 29 from MUCH) had the syndromic diagnosis of MCI as described by Petersen et al.,<sup>16</sup> and had available MRI, [<sup>18</sup>F]-fluorodeoxyglucose (FDG)-PET, and CSF sampling. Biomarker status was either not available or not considered for the baseline diagnosis. The cognitive profile was consistent with single- and multiple-domain amnesic MCI.

Clinical visual inspection of routine MRI of all patients included in the study indicated neither focal ischemic lesions nor extensive microvascular disease that could be responsible for the cognitive symptoms.

We pooled patients with MCI from ADNI and EU datasets, and then categorized them into 4 groups based on amyloid pathology and/or neurodegeneration (either hypometabolism or hippocampal atrophy) biomarker abnormality: A–N– (no amyloid pathology and no neurodegeneration), A+N– (amyloid pathology with no neurodegeneration), SNAP (A–N+ cases, no amyloid pathology with neurodegeneration), and A+N+ (amyloid pathology with neurodegeneration) (table 1).

Patients with MCI were followed up to detect progressive cognitive deterioration, defined as (1) losing more than 3 points between first and last Mini-Mental State Examination (MMSE) administration, (2) having dementia at follow-up, or (3) getting a score less than 24 at last MMSE, as described in a previously published report.<sup>17</sup>

**Standard protocol approvals, registrations, and patient consents.** Ethics/radiation committee approval of any protocol

**Table 1** Categorization of the patients with MCI included in this study based on biomarker abnormality

Pathologic event	Brain amyloidosis	Neurodegeneration	
Biomarker (unit)	CSF $A\beta_{42}$ (z scores)	FDG-PET AD score (t sum)	Hippocampal volume (w scores)
Abnormality threshold	$z < 0$ (<500 pg/mL in European dataset, <192 pg/mL in ADNI) <sup>a</sup>	$t > 13,481^b$	$w < -2.90^c$
<b>MCI groups</b>			
A–N– (no amyloid pathology, no neurodegeneration)		Normal	Both normal
A+N– (amyloid pathology, no neurodegeneration)		Abnormal	Both normal
SNAP (no amyloid pathology, neurodegeneration)		Normal	Either abnormal
A+N+ (amyloid pathology, neurodegeneration)		Abnormal	Either abnormal

Abbreviations:  $A\beta_{42}$  =  $\beta$ -amyloid 1–42; AD = Alzheimer disease; ADNI = Alzheimer’s Disease Neuroimaging Initiative; FDG = [<sup>18</sup>F]-fluorodeoxyglucose; MCI = mild cognitive impairment; SNAP = suspected non-AD pathology.

<sup>a</sup> CSF  $A\beta_{42}$  concentration was determined by commercial ELISAs in Brescia, Amsterdam, Stockholm, and Munich samples and xMAP Luminex platform with Innogenetics immunoassay kit-based reagents in ADNI samples, and was expressed in z scores, computed as deviation from the threshold in SD units. For European memory clinics, thresholds for abnormality were as follows: <500 pg/mL in Brescia, <550 pg/mL in Amsterdam, <450 pg/mL in Stockholm, and <643 pg/mL in Munich. Thresholds were rescaled to <500 pg/mL before transformation into z scores (for details see text).

<sup>b</sup> Threshold based on reference 30.

<sup>c</sup> Threshold based on reference 30.

involved in the study was obtained at each of the ADNI and EU participating centers. Written informed consent to share data for scientific research purposes was collected from each participant.

#### Biological markers of amyloidosis and neurodegeneration.

We selected CSF A $\beta$ <sub>42</sub> concentration as a biological marker of amyloidosis: lower than normal CSF A $\beta$ <sub>42</sub> was assumed to be associated with cortical fibrillar amyloid deposition. We assessed neurodegeneration using an <sup>18</sup>F-FDG-PET index of AD-related hypometabolism (the AD  $t$ -sum score)<sup>18</sup> and MRI-based automated segmentation of age-adjusted hippocampal atrophy ( $w$  scores). Information on biomarkers procedure collection and normalization is available in e-Methods.

**Statistical analysis.** We assessed differences in sociodemographic and clinical features, genotype, neurodegeneration, and amyloidosis biomarkers among A–N–, A+N–, SNAP, and A+N+ patients using analysis of variance (continuous variables) or Pearson  $\chi^2$  test (dichotomous variables). We estimated cognitive deterioration as number of MMSE points lost per year (last MMSE score – baseline MMSE score/years of follow-up). We computed differences in sociodemographic factors, clinical features, and genotype between the SNAP and any other patient group, as well as between the ADNI and EU datasets, using independent Student  $t$  test (continuous variables) or Pearson  $\chi^2$  test (dichotomous variables). We assessed differences between progressor and nonprogressor SNAP patients using the nonparametric, independent 2-group Mann–Whitney  $U$  test (continuous variables) or  $\chi^2$  test (categorical variables), in order to account for the small sample size.

To assess the risk of progressive cognitive deterioration in A+N–, SNAP, and A+N+ patients, we plotted survival curves and computed hazard ratios (both crude and adjusted by age, MMSE scores, and *APOE*  $\epsilon$ 4 carrier status) with pertinent 95% confidence interval based on the A–N– reference group (6 separate models). We assessed the significance of differences in curves between SNAP and A+N+ or A+N– groups by log-rank test. We computed log-rank and Tarone tests for trend by using the *survtrend* R function (available at <https://www.ics.uci.edu/~vqnguyen/stat255/Stat255Functions.R>).

In addition, we plotted survival curves to investigate biomarker prognosis in SNAP patients. In this analysis, we divided the SNAP group into subgroups based on the biomarker abnormality thresholds reported in table 1 (FDG-PET and hippocampal atrophy but not CSF A $\beta$ <sub>42</sub>, because all patients with MCI-SNAP are negative for amyloidosis by definition), and we assessed the significance of differences in curves between normal and abnormal groups by log-rank test.

Finally, we adopted a generalized linear model for analyzing the time to progression in A+N–, SNAP, and A+N+ groups, where the time to progression was the dependent (gamma-distributed) variable and A $\beta$ <sub>42</sub>, FDG-PET, and hippocampal volume were independent continuous predictors. We investigated the linear relationship between biomarkers and time to progression by computing both Pearson and Spearman correlation coefficients.

We performed all statistical analyses using R software version 3.0.2, except for time-to-progression analysis, which was performed with SPSS version 21.0 (IBM Corp., Armonk, NY).

**RESULTS** Of the 201 patients with MCI included in the study, 41 were categorized A–N–, 41 A+N–, 34 SNAP, and 85 A+N+.

The 4 groups did not differ in age and sex. They significantly differed in follow-up duration, baseline

and follow-up MMSE, as well as in MMSE yearly change. The SNAP group showed significantly lower baseline and follow-up MMSE scores than the A–N– group ( $p = 0.007$  and  $p = 0.005$ ), and significantly higher follow-up MMSE scores than the A+N+ group ( $p = 0.020$ ), but their annual MMSE change was not significantly different from that of any other group. The 4 groups significantly differed in *APOE*  $\epsilon$ 4 proportion;  $\epsilon$ 4 proportion in the SNAP group was significantly lower than that in the A+N– and A+N+ groups ( $p = 0.002$  and  $p = 0.005$ , respectively). The proportion of progressive cognitive deterioration was significantly different among the 4 groups; progression in SNAP was significantly more frequent than in A–N– ( $p = 0.005$ ), more frequent than in A+N– ( $p = 0.098$ ), and less frequent than in A+N+ ( $p = 0.187$ ) (table 2). The proportion of progressive cognitive deterioration in the 4 groups did not significantly change when restricting to *APOE*  $\epsilon$ 4 carriers (69%, 40%, 36%, and 20% in A+N+, SNAP, A+N–, and A–N–, respectively). Of the 19 individuals with SNAP who progressed to dementia, 5 patients progressed to frontotemporal dementia (FTD), 2 patients progressed to Lewy body dementia, and the remaining 12 patients progressed to AD. Among A–N– progressors, half progressed to AD ( $n = 4$ ) and the other half to FTD ( $n = 5$ ). All amyloid-positive progressors but one A+N+ patient (who progressed to FTD) progressed to AD.

The 4 groups significantly differed in CSF A $\beta$ <sub>42</sub> concentrations, hypometabolism on FDG-PET, and hippocampal volume. Hypometabolism in SNAP was comparable to A+N+ ( $p = 0.154$ ), while hippocampal atrophy was more severe in SNAP ( $p = 0.002$ ). CSF A $\beta$ <sub>42</sub> concentrations were comparable to A–N– ( $p = 0.107$ ) (table 2). Biomarker distributions in the 4 groups, disaggregated by progression, are displayed in figure 1.

Patients with MCI from the ADNI dataset ( $n = 89$ ) did not differ from patients from the EU dataset ( $n = 112$ ) in baseline MMSE score, follow-up duration, follow-up MMSE score, MMSE yearly change, *APOE* genotype, and proportion of progressive cognitive deterioration. EU patients were significantly younger than ADNI patients, and the EU dataset had a significantly higher proportion of females. The proportion of A+N– patients in ADNI was significantly higher than in EU, while the proportion of A–N– and SNAP patients was significantly lower; the proportion of A+N+ was comparable in the 2 datasets (table e-1).

SNAP and A+N+ patients had significant risk of progressive cognitive deterioration, based on A–N– reference group, while A+N– patients did not (figure 2). The SNAP survival curve was significantly different from A+N+ but not A+N– curves

**Table 2** Descriptive features of the 201 patients with MCI included in this study

	A-N- (n = 41)	A+N- (n = 41)	SNAP (n = 34)	A+N+ (n = 85)	p
Age, y	69.3 ± 10.0	73.8 ± 8.4	70.6 ± 9.2	70.5 ± 8.5	0.117
Sex, female	19 (46)	22 (54)	11 (32)	37 (44)	0.319
Follow-up time, mo	30.2 ± 17.2	33.2 ± 11.8	26.4 ± 16.8	23.8 ± 11.9	0.003
Baseline MMSE score	27.6 ± 1.7	27.2 ± 1.8	26.6 ± 1.5 <sup>a</sup>	26.5 ± 1.7	0.004
Last follow-up MMSE score <sup>b</sup>	27.0 ± 2.9	25.7 ± 3.3	24.7 ± 3.9 <sup>a,c</sup>	22.6 ± 4.7	<0.001
MMSE yearly change <sup>b</sup>	-0.5 ± 1.9	-0.9 ± 1.6	-2.2 ± 5.6	-3.3 ± 5.1	0.002
APOE ε4 genotype carriers <sup>d</sup>	9 (29)	28 (70)	10 (31) <sup>c,e</sup>	52 (61)	<0.001
Progressors	8 (11)	14 (34)	19 (56) <sup>a</sup>	60 (71)	<0.001
CSF Aβ <sub>42</sub> z scores	1.2 ± 0.8	-0.9 ± 0.5	0.9 ± 0.7 <sup>c,e</sup>	-0.8 ± 0.5	<0.001
FDG-PET AD score, t sum	5,282 ± 2,976	6,975 ± 2,940	23,052 ± 20,019 <sup>a,e</sup>	29,150 ± 22,823	<0.001
Hippocampal volume, w scores	-0.3 ± 1.6	-0.8 ± 1.6	-4.2 ± 2.1 <sup>a,c,e</sup>	-2.8 ± 2.2	<0.001

Abbreviations: AD = Alzheimer disease; FDG = [<sup>18</sup>F]-fluorodeoxyglucose; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; SNAP = suspected non-AD pathology.

Values are mean ± SD or frequency (percentage). Progressors are defined as MCI losing more than 3 points between first and last MMSE administration, having dementia at follow-up, or getting a score <24 at last MMSE administration. The p denotes significance difference among all groups on 1-way analysis of variance (continuous variables) or χ<sup>2</sup> test (categorical variables). Significant difference of SNAP with a, c, and e on independent t test (continuous variables) or χ<sup>2</sup> test (categorical variables).

<sup>a</sup>A-N-.

<sup>b</sup>Missing data for one MCI-SNAP and 14 A+N+ patients.

<sup>c</sup>A+N+.

<sup>d</sup>Missing data for 4 A-N-, 1 A+N-, 2 SNAP, and 2 A+N+ patients.

<sup>e</sup>A+N-.

(log-rank  $p = 0.016$  and  $0.173$ , respectively). Both log-rank and Tarone tests for trend were significant ( $p < 0.001$ , both tests). Figure e-1 shows the risk of progressive cognitive deterioration in the 4 groups in APOE ε4 carriers and noncarriers, separately.

In the SNAP group, 5 of 34 subjects were FDG-positive only, 16 were hippocampus-positive only, and 13 were positive for both markers of neurodegeneration. SNAP patients with abnormal FDG-PET showed significantly higher risk of progressive cognitive deterioration than patients with normal FDG-PET, and the 2 groups showed significantly different survival distributions (log-rank  $p = 0.004$ ). In contrast, risk of progressive cognitive deterioration in SNAP patients was independent of hippocampal atrophy (figure e-2). Progressor and nonprogressor SNAP patients did not differ in age, sex, baseline MMSE score, APOE, and CSF Aβ<sub>42</sub> concentration, while they significantly differed in follow-up MMSE score and MMSE yearly change, as expected. Progressor SNAP patients had significantly lower cortical metabolism on FDG-PET and lower hippocampal volume than nonprogressor SNAP patients, although the difference was not significant (table e-2).

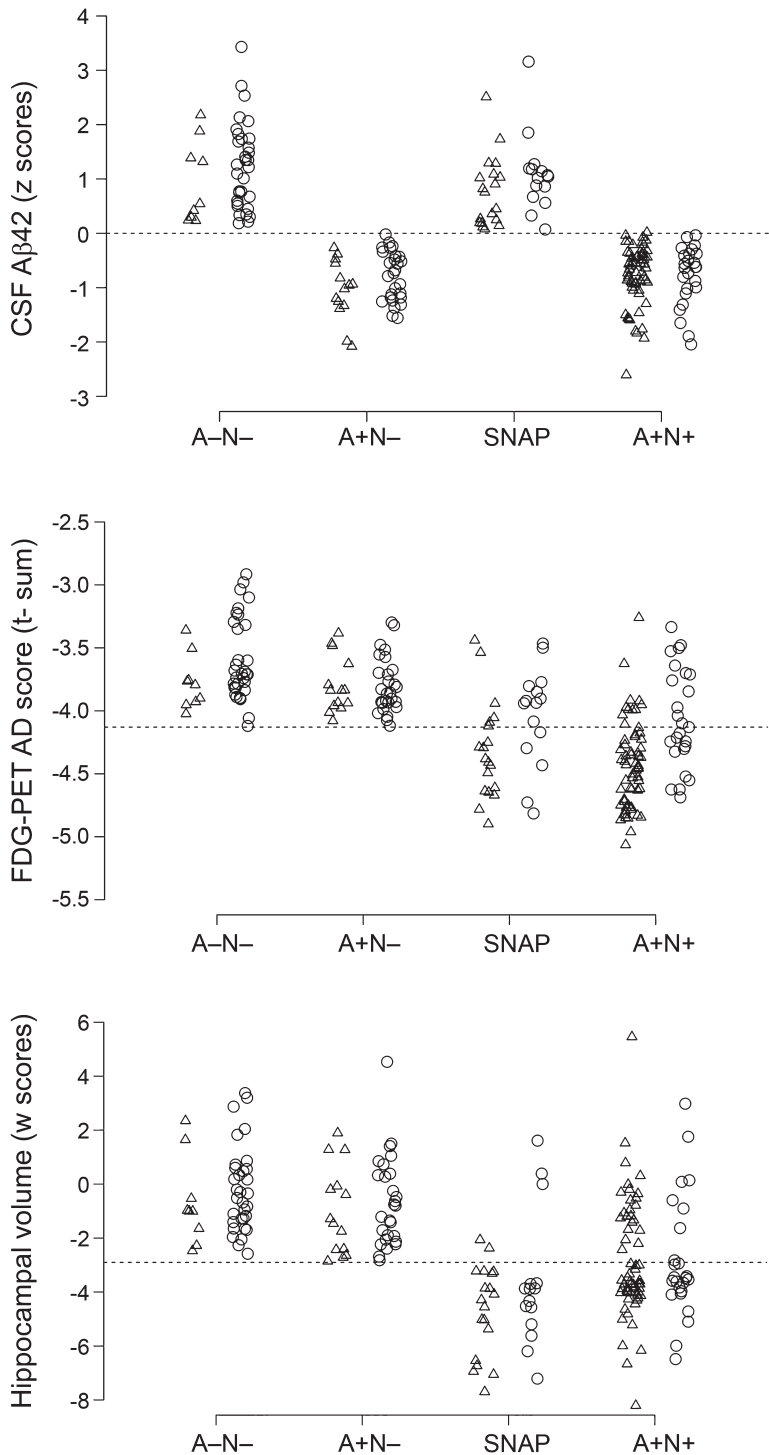
In A+N- and A+N+, none of the biomarkers predicted time to progression. In SNAP patients, lower hypometabolism predicted longer time to progression: 10,000-unit decrease in FDG-PET t sum was associated with 4-month-longer time to

progression ( $p = 0.086$ ) (table e-3). Lower time to progression was linearly correlated with greater hypometabolism (Pearson correlation coefficient  $r = 0.42$ ,  $p = 0.073$ ; Spearman correlation coefficient  $\rho = 0.42$ ,  $p = 0.076$ ) (figure 3). There was a trend toward linear correlation of lower time to progression with larger hippocampi ( $r = -0.33$ ,  $p = 0.162$ ;  $\rho = -0.36$ ,  $p = 0.134$ ), while no correlation was found between time to progression and CSF Aβ concentration ( $r = -0.12$ ,  $p = 0.637$ ;  $\rho = 0.06$ ,  $p = 0.793$ ) (figure e-3).

**DISCUSSION** In this study, we showed that the risk of progressive cognitive deterioration in patients with MCI who had neurodegeneration but no amyloid pathology (SNAP) was higher than in patients with MCI who had no neurodegeneration and no amyloid pathology (A-N-) but comparable to patients with MCI who had both neurodegeneration and amyloid pathology (A+N+). In SNAP patients, greater hypometabolism was linearly correlated with lower time to progression. In A+N- and A+N+ patients, none of the biomarkers predicted time to progression.

Since their recent description and given potential implications, SNAP cases have generated great interest. SNAP cases have recently been described in a population of cognitively normal elderly<sup>9</sup> and were found to have lower prevalence of the APOE ε4 genotype than persons with preclinical AD, but were

**Figure 1** Biomarker abnormality in A–N–, A+N–, SNAP, and A+N+ MCI patient groups, disaggregated by progressive cognitive deterioration



Triangles denote progressors, while circles denote nonprogressors. Data were jittered to prevent overplotting. For FDG-PET AD t-sum biomarker, logarithmic scores ( $\log_{10}$ ) were polarized to improve visualization, with abnormal scores below the threshold line and toward the negative end of the distribution.  $A\beta_{42}$  =  $\beta$ -amyloid 1–42; AD = Alzheimer disease; FDG = [ $^{18}$ F]-fluorodeoxyglucose; MCI = mild cognitive impairment; SNAP = suspected non-AD pathology.

almost indistinguishable from persons with both neurodegeneration and amyloidosis on FDG-PET regional hypometabolism, MRI regional brain

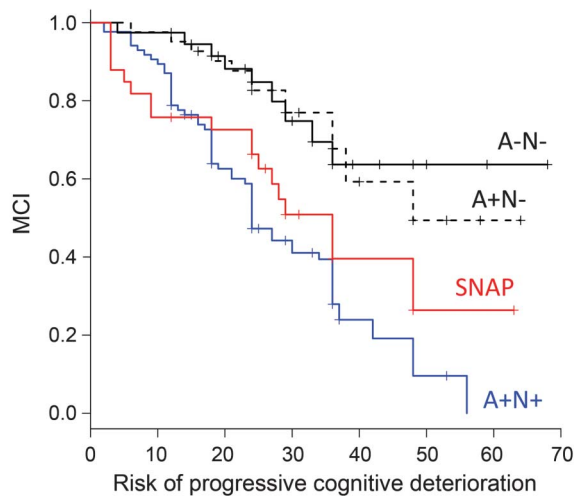
volume loss, cerebrovascular lesions on imaging, vascular risk factors, and  $\alpha$ -synucleinopathy-related features. This suggests that the initial appearance of brain-injury biomarkers in cognitively normal elderly individuals may not depend on amyloidosis.<sup>9</sup> In the current study, SNAP patients with MCI had a significantly lower proportion of *APOE*  $\epsilon 4$  genotype than both A+N+ and A+N– patients, in line with findings on cognitively healthy elders with SNAP,<sup>9</sup> but significantly more severe hippocampal atrophy than A+N+ patients.

There is only one previous study investigating progression to dementia in patients with MCI-SNAP, showing that 1-year rate of progression of SNAP was significantly higher than A–N– and A+N–, and comparable to A+N+ MCI patients.<sup>7</sup> Our findings are overall in line with these, despite differences of demographics (our patients are 6 and 11 years younger than patients from ADNI and Mayo Clinic Study of Aging included in the other study) and study design (the other study had a shorter follow-up by about a half). The 2 studies are also in agreement in the proportion of the  $\epsilon 4$  allele of *APOE* in MCI-SNAP, which was significantly lower than in amyloid-positive MCI, and comparable to biomarker-negative patients. However, our findings are in contrast to previous studies that found a relative cognitive stability of cognitively normal elders with SNAP and showed that their cognitive progression was markedly lower than in amyloid-positive persons.<sup>19,20</sup> Such discrepancy suggests that patients with MCI-SNAP may represent a different group than cognitively normal elders with SNAP.

The pathophysiology of cognitive impairment in MCI-SNAP is still a matter of debate. It can be hypothesized that the category represents a mixed bag of several different types of amyloid-unrelated pathologies that may resemble AD clinically, such as hippocampal sclerosis, argyrophilic grain disease, tangle-only dementia, frontotemporal degeneration, or Lewy body disease, in line with the fact that a nonnegligible minority of patients diagnosed with clinically probable AD do not meet neuropathologic criteria for AD at histopathology.<sup>21</sup> The poor stability of current assays for CSF  $A\beta_{42}$  and the uncertainty of abnormality thresholds<sup>22</sup> suggest that a proportion of MCI-SNAP diagnoses could be false-negative and these patients could actually have underlying amyloid pathology.

We showed that in MCI-SNAP progressors, FDG-PET almost significantly predicted time to progression; CSF  $A\beta_{42}$  was not predictive of progressive cognitive deterioration, in line with previous findings in amyloid-negative patients with MCI<sup>8</sup> and the notion that brain amyloidosis is not related to cognitive symptoms.<sup>23</sup> Despite that these findings from a

**Figure 2** Risk of progressive cognitive deterioration in 34 SNAP, 41 A+N-, and 85 A+N+ patients with MCI, compared with 41 A-N- patients with MCI as the reference



	Crude		Adjusted	
	HR (95% CI)	p	HR (95% CI)	p
MCI A+N-	1.13 (0.49 – 2.62)	0.771	0.83 (0.34 – 2.09)	0.689
MCI SNAP	2.66 (1.20 – 5.93)	0.016	2.38 (1.00 – 5.62)	0.049
MCI A+N+	3.85 (1.91 – 7.78)	<0.001	3.36 (1.55 – 7.27)	0.002

The + denotes censored cases. Adjusted by age, baseline Mini-Mental State Examination score, and APOE ε4 carrier status. Crude and adjusted HRs were computed in 6 separate Cox regression models. SNAP and A+N+ patients had significant risk of progressive cognitive deterioration, while A+N- patients did not. CI = confidence interval; HR = hazard ratio; MCI = mild cognitive impairment; SNAP = suspected non-Alzheimer disease pathology.

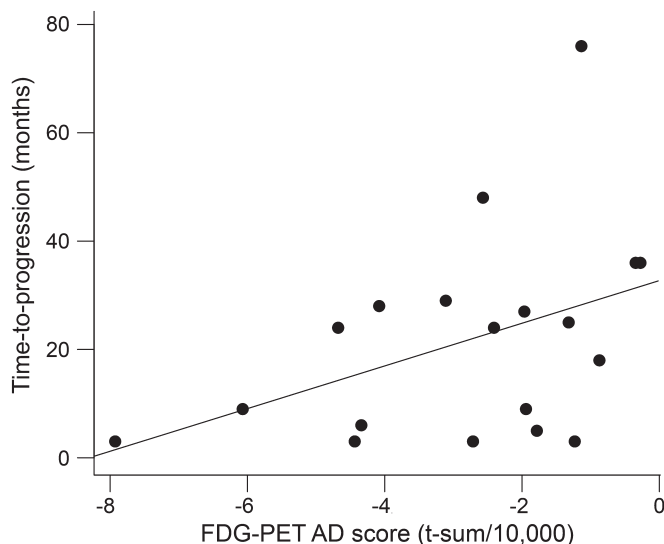
small sample of MCI-SNAP progressors should be considered preliminary, they could represent relevant information toward understanding underlying SNAP pathology. We propose that the SNAP group could include 2 different subgroups: (1) patients with severe cortical damage and no hippocampal atrophy, who might have underlying frontotemporal degeneration or tangle-only dementia, and rapidly progress to dementia; and (2) patients with hippocampal atrophy but relatively preserved cortical metabolism, who might have either hippocampal sclerosis or argyrophilic grain disease. This hypothesis is in line with the observation that medial temporal lobe atrophy is related to primary degenerative hippocampal pathology in pathologically confirmed very old patients<sup>24</sup> who progress to dementia remarkably slowly.

Current findings could have been influenced by the choice of biomarkers. CSF Aβ<sub>42</sub> protein concentration was included as an established marker of amyloid deposition.<sup>25</sup> Although we did not measure cortical amyloidosis (because of the paucity of amyloid imaging data available), previous studies demonstrated good concordance between CSF Aβ<sub>42</sub> and cortical amyloid, assessed by [<sup>11</sup>C]-Pittsburgh

compound B-PET.<sup>26,27</sup> Both hippocampal atrophy on MRI and *t* sum on FDG-PET are relatively specific topographic markers of AD neurodegeneration, and are by definition not specific to SNAP. However, defining SNAP patients with non-SNAP-specific topographic measures will only lead to selecting those SNAP patients with the most severe degrees of neurodegeneration, i.e., will lead to select a SNAP group including relatively few false-positives. This might have caused us to miss SNAP patients with milder degrees of neurodegeneration, but assures that those SNAP patients that we selected did indeed have neurodegeneration.

This study has some strengths and limitations. First, the group of 201 patients with MCI under study is the largest available with all 3 core biomarkers available at baseline (CSF Aβ<sub>42</sub>, MRI, and FDG-PET), paired with information on progressive cognitive deterioration on a reasonably long follow-up (30 months on average). Despite the large size of the overall MCI group, the relatively low proportion of SNAP patients results in a relatively small sample size, requiring caution in the interpretation of the results. However, to our knowledge, there is only one previous study<sup>7</sup> reporting a similar case series (n = 36 SNAP with MCI from Mayo Clinic Study of Aging and n = 10 SNAP with MCI from ADNI), followed for shorter follow-up (15 and 12 months on average in Mayo Clinic Study of Aging and ADNI cohorts, respectively). Second, CSF total tau protein concentration, despite being an established marker of neurodegeneration, was not included in the study because of the paucity of available data (CSF tau was missing for 58 patients with MCI from the EU dataset). Although no measure of cerebrovascular disease (either risk factor or MRI measure) was included because of lack of consistent data across centers, clinical visual inspection of routine MRI of all patients included in the study indicated neither focal ischemic lesions nor extensive microvascular disease that could be responsible for the cognitive symptoms. It would have been valuable to assess differences in memory features in the SNAP group compared with the other groups. Unfortunately, this was not possible because of the multicenter nature of the study: heterogeneous neuropsychological tests with heterogeneous norms were administered in different centers, and pooling and standardizing neuropsychological data, albeit possible, was beyond the scope of this study. Finally, ADNI patients were significantly older than EU patients and had a lower proportion of SNAP, probably reflecting the different recruitment strategies of ADNI and dementia research centers in the United States and Europe and the interlaboratory variability in methods and protocols used to assess CSF Aβ<sub>42</sub> concentration. However, standard operating

**Figure 3** Linear correlation between time to progression and FDG-PET in the 19 SNAP progressors



FDG-PET t-sum scores were polarized for more negative values to denote greater abnormality. Lower time to progression was linearly correlated with greater hypometabolism. AD = Alzheimer disease; FDG = [<sup>18</sup>F]-fluorodeoxyglucose; MCI = mild cognitive impairment; SNAP = suspected non-AD pathology.

preanalytical procedures for CSF biomarkers are just now being developed<sup>28,29</sup> and cannot be applied to historical cohorts.

We provided further evidence that neurodegenerative dementia pathology can emerge and develop through nonamyloid pathways. We showed that MCI patients with SNAP are similar to A+MCI patients in terms of risk of progressive cognitive deterioration, suggesting that SNAP prognosis can be challenging. However, patients with SNAP featured a specific risk progression profile, confirming a specific underlying pathology other than AD. The identification of SNAP patients is of particular interest to clinical trialists. Recent clinical trials with anti-amyloid drugs (bapineuzumab and solanezumab) have recruited up to 30% amyloid-negative patients, which might have diluted their therapeutic effect. Future studies, larger samples, and pathologic confirmation are needed to verify or falsify the hypothesis that the MCI-SNAP group does indeed comprise 2 distinct subgroups, denoted by different cortical damage/hippocampal atrophy and different time to progression, and ultimately different neuropathology.

#### AUTHOR CONTRIBUTIONS

Dr. A. Caroli contributed to study design, led manuscript preparation and discussion of the results. Dr. A. Prestia performed data analysis, helped in manuscript preparation. Dr. S. Galluzzi contributed to discussion of the results and manuscript revision. Dr. C. Ferrari significantly helped in the statistical analysis. Drs. W. van der Flier and R. Ossenkoppele provided MRI data for VUMC patients, were involved in the discussion of the results, contributed to the manuscript revision. Drs. B. Van Berckel, F. Barkhof, and C. Teunissen were involved in imaging and

CSF data collection, in the discussion of the results, contributed to the manuscript revision. Drs. A. Wall, S. Carter, M. Schöll, A. Nordberg, A. Drzezga, and P. Scheltens were involved in the writing of the manuscript, in the discussion of the results, contributed to the manuscript revision. Dr. I.H. Choo computed AD  $t$  sum for KUH patients, provided KUH MRI data, was involved in the discussion of the results, and contributed to the manuscript revision. Dr. T. Grimmer computed AD  $t$  sum for MUCH patients, provided MUCH MRI data, was involved in the discussion of the results, and contributed to the manuscript revision. Dr. A. Redolfi computed hippocampal volumes on MRI data, contributed to the manuscript revision. Dr. G.B. Frisoni led study conception and design, coled discussion of the results, contributed to manuscript revisions.

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#### DISCLOSURE

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