

# Apathy in patients with mild cognitive impairment and the risk of developing dementia of Alzheimer's disease

## A one-year follow-up study

Philippe H. Robert<sup>a,\*</sup>, Claudine Berr<sup>d</sup>, Magali Volteau<sup>c</sup>, Christelle Bertogliati<sup>a</sup>,  
Michel Benoit<sup>a</sup>, M. Sarazin<sup>b</sup>, Sylvie Legrain<sup>e</sup>, Bruno Dubois<sup>b,c</sup>,  
members of the PréAL study

<sup>a</sup> Centre Mémoire de Ressources et de Recherche, CHU de Nice, INSERM JE 2441, France

<sup>b</sup> Centre Mémoire de Ressources et de Recherche, Hôpital de la Salpêtrière, Paris, France

<sup>c</sup> INSERM U610, France

<sup>d</sup> INSERM E 0361, France

<sup>e</sup> Hôpital Bichat, Service de Gériatrie, Paris, France

Received 20 November 2005; received in revised form 26 January 2006; accepted 19 February 2006

### Abstract

**Objective:** To evaluate the relation between apathy and development of dementia in patients with amnesic mild cognitive impairment (MCI).  
**Methods:** Two hundred and fifty-one French-speaking outpatients fulfilling the criteria of amnesic MCI were enrolled. Apathy was assessed with the Apathy Inventory (IA). Neuropsychiatric evaluation also included the Goldberg anxiety scale and the Montgomery and Asberg Depressive Rating Scale (MADRS). The main end point considered after a 1-year follow-up was the development of dementia of Alzheimer type (DAT).

**Results:** At baseline there were 86 (39.8%) subjects presenting at least one symptom of apathy among the 216 included in analysis. After a 1-year follow-up, 22 patients developed DAT. Of the patients with apathy at baseline 13 (15.1%) developed DAT in comparison with 9 (6.9%) of the non-aphathetic patients.

At the 1-year follow-up, patients developing DAT had a significantly higher frequency of apathetic symptoms (91.7%) than patients without DAT (26.9%).

**Conclusion:** Taking into account that apathy is one of the most frequently observed neuropsychiatric symptoms in MCI and in DAT the present study suggests that patients with MCI and apathy should be more closely observed.

© 2006 Elsevier B.V. All rights reserved.

**Keywords:** Mild cognitive impairment; Alzheimer's disease; Apathy; Memory; Behaviour; Diagnosis

### 1. Introduction

The concept of mild cognitive impairment (MCI) refers to the presence of cognitive change not severe enough for a diagnosis of dementia. MCI is a useful means of characterizing patients at risk of subsequently developing to dementia.

In addition to the impairment of cognitive performances, several recent studies [1] have shown that MCI patients can exhibit neuropsychiatric symptoms. Therefore it has been suggested that in some patients, these symptoms can precede the onset of dementia. Even if not specific apathy and depressive symptoms [2,3] are the most frequent neuropsychiatric symptoms in MCI and in the dementia of Alzheimer type (DAT).

MCI patients with depressive symptoms are more at risk of developing DAT than those without depression [4]. Apathy alone in patients with MCI has not been investigated.

\* Corresponding author at: Centre Mémoire de Ressources et de Recherche, Hôpital Pasteur, 30 avenue de la Voie Romaine, 06002 Nice Cedex 1, France. Tel.: +33 4 92 03 77 52; fax: +33 4 92 03 80 02.

E-mail address: philippe.robert15@wanadoo.fr (P.H. Robert).

The aim of the present study was to evaluate the relation between apathy and dementia in patients with amnesic MCI.

## 2. Methods

### 2.1. Patients

Two hundred and fifty-one French-speaking outpatients were recruited from the referral populations of the 14 centers with memory consultation facilities. Informed consent was obtained from each patient.

Inclusion criteria and cut-off scores were chosen according to the results of the PAQUID study [5,6] and are close to the criteria of amnesic MCI [7]. Patients included fulfilled the following criteria: (1) patients with memory complaints and (2) patients presenting at least one error to the mini-mental state examination (MMSE) three word recall [8], or a score lower than 29 to the Isaac-set test [9]. Patients were excluded if they had an MMSE score lower than 25, a MADRS score higher than 20 and a significant vascular pathology seen on recent (1 year or less) morphological imagery. Furthermore, all patients had to be at least 58 years old, have completed at least 4 years of education and be accompanied by an informant.

### 2.2. Neuropsychological and neuropsychiatric examination

The neuropsychological assessment battery was administered independently immediately after the clinical assessment. It included tests of episodic memory (free and cued selective reminding test, FCSR) [10], language and semantic memory (letter and category fluency; naming task, DENO 100), attention, working memory and executive functions (digit ordering [11], trail making test A & B [12]; Baddeley's dual task [13]; WAIS digit symbol substitution test; WAIS similarities [14]; Stroop word color test [15]).

Neuropsychiatric evaluation included the Goldberg Anxiety Scale (GAS) [16] and the Montgomery and Asberg Depressive Rating Scale (MADRS) [17].

Apathy was assessed with the Apathy Inventory (IA) [18]. The three dimensions assessed in the IA were chosen according to the literature [19] and the diagnostic criteria [20] were based on the operationalization of the Marin scale [21]. These criteria were (1) lack of motivation relative to the patient's previous level of functioning or the standards of his/her age and culture; (2) presence of at least one symptom belonging to each of the following three domains: (i) diminished goal-directed behavior (lack of effort, dependency on others to structure activity); (ii) diminished goal-directed cognition (lack of interest, of concern about one's personal problems); and (iii) diminished concomitants of goal-directed behavior (unchanging affect, lack of emotional responsiveness); (3) the symptoms cause clinically significant distress or impairment in social and occupational functioning; and (4) in the

absence of a diminished level of consciousness or administration of substances such as narcotics or medications. In the IA, emotional blunting dimension refers to a lack of emotional responses. Lack of initiative refers to diminished goal-directed behavior and lack of interest to diminished goal-directed cognition.

In the present study the evaluation was carried out using a structured interview with the caregiver according to the rule of the IA caregiver version structured questionnaire. The IA caregiver version is based on responses gathered from an accompanying person familiar with the patient's behavior. The questions deal with behavioral changes that have occurred since the beginning of the illness or during a limited period of time in order to demonstrate a lack of motivation relative to the patient's previous level of functioning. Behavior traits present throughout the patient's life and unchanged since the onset of the illness are not taken into account. If the caregiver responds positively and confirms the presence of at least one dimension of the IA (emotional blunting or lack of initiative or lack of interest), the patient was recorded as presenting a symptom of apathy.

### 2.3. Statistical analysis

The main end point considered in the follow-up was the development of DAT. An independent expert group using the NINCDS-ADRDA criteria for probable dementia of Alzheimer's disease [22] made the diagnosis. The date defining onset of DAT was the date of the evaluation on which the diagnosis was done. All statistical analyses were conducted using SAS software version 8.2.

Comparisons were made between the two groups (MCI patients developing DAT versus MCI patients without DAT after 1 year of follow-up) with univariate ( $\chi^2$ ) and multivariate analysis. We performed logistic regression analysis to compare the two groups controlling for age, sex, educational level, MADRS total score and GAS.

## 3. Results

Twenty-eight patients dropped out the study and three patients developed another type of dementia. These 31 patients were excluded of the analysis. Furthermore taking into account that apathy assessment was not done for four subjects, the analysis was performed on 216 patients. The mean age of the population was  $71.9 \pm 5.4$  (range 58–81). Patients with MMSE score lower than 28 were significantly older (73.1 versus 70.6,  $p < 0.001$ ).

After a 1-year follow-up, 22 patients (10.2%) developed DAT (mean MMSE score =  $26.9 \pm 1.1$ ; mean MADRS score =  $8.2 \pm 5.9$ ) and 194 do not develop DAT (mean MMSE score =  $27.6 \pm 1.3$ ; mean MADRS score =  $6.7 \pm 4.7$ ). At baseline the factors which were significantly different between the subjects who went on to develop DAT and those who did not were age and all performances on the neuropsy-

Table 1  
Clinical and neuropsychiatric characteristics in the two MCI subgroups (non-converted vs. converted to DAT) at 1-year follow-up

	Non-converted group, <i>n</i> = 194		Converted group, <i>n</i> = 22		<i>p</i> value <sup>a</sup>
	%	Mean (S.D.)	%	Mean (S.D.)	
Sex, % of women	58.3		59.1		0.78
Age (year)		71.3 (5.4)		76.2 (3.6)	<0.001
History of psychiatric disorders	19.7		31.8		0.16
Familial cases of dementia	32.5		31.8		0.52
MMSE M0 (% <28)	47.9		81.8		0.03
Education level <sup>b</sup>	44.3		31.8		0.22
Goldberg anxiety scale M0		2.9 (2.5)		2.6 (2.5)	0.16
MADRS total score M0 (% >10)	18.6		31.8		0.26
MADRS total score M12 (% >10) <sup>c</sup>	24.3		25.0		0.99
Apathy M0	37.6		59.1		0.10
Apathy M12 <sup>c</sup>	26.9		91.7		0.002

<sup>a</sup> Logistic regression analysis controlling for age, sex, educational level, MADRS total score and GAS. M0 = baseline evaluation; M12 = 1-year evaluation; apathy, percentage (%) of patients presenting at least one dimension of apathy evaluated with the IA interview.

<sup>b</sup> Education level expressed as the percentage of subjects with a level higher than the end of the secondary school (Bachelor).

<sup>c</sup> Comparisons were done for MADRS on 189 patients and on 183 patients for IA.

chological battery. Concerning neuropsychiatric symptoms (Table 1) there were no differences at baseline between the two groups for MADRS and GAS total score.

At baseline, there were 86 (39.8%) subjects presenting at least one symptom of apathy. The most frequently observed dimension was lack of initiative (*n* = 67; 77.9%) followed by lack of interest (*n* = 47; 54.7%) and emotional blunting (*n* = 20; 23.3%). There is no significant correlation between age or MMSE and IA score.

The proportion of conversion from MCI to DAT was significantly higher ( $\chi^2$  test, *p* = .05) for patients with apathy at baseline (*n* = 13/86) than in non-apathetic patients (*n* = 9/130). When controlling for age, sex, educational level, MADRS total score and GAS, the difference at baseline did not remain significant (*p* = 0.10).

At the 1-year follow-up, patients developing DAT had a significantly higher frequency of apathetic symptoms (91.7%) than patients without DAT (26.9%), even after adjustment (*p* = 0.002).

#### 4. Discussion

In a recent study Modrego and Ferrandez [4] demonstrated that major depression according to DSM IV criteria is an important risk factor for patients of developing DAT. Interestingly, other studies [23,24] more specifically underlined the higher predictive value of motivation-related symptoms of depression. In the present study, patients with MCI developing dementia in the first year of follow-up were not characterized by higher scores on the anxiety and depression scales but had a trend to present more frequently symptoms of apathy at baseline. In order to confirm this result and to find a statistical significance with the non-converted MCI patients we probably need to have a higher number of conversions to DAT. This will be done with the 2–3 years follow-up data.

Even if this soft behavioral symptom cannot be considered as a predictive marker for DAT it is interesting to underline the relationship with the early and specific memory disturbances [25]. Apathy can result from several different mechanisms. Stuss et al. [26] proposes to divide apathy into three subtypes: emotional, cognitive and behavioral. The cognitive subtype refers to an alteration of the cognitive processing needed to elaborate the plan of actions and goal-directed behavior. This mechanism is particularly well illustrated in MCI by the impairment in strategies to self-retrieve information from episodic memory [27]. In our Prediction for Alzheimer's disease (PréAL) cohort we already showed [28] that compared with non-apathetic subjects, MCI apathetic patients had a significantly lower performances on the free recall but not on the cued recall of the selective reminding test [10].

An important finding in our work is that 91.7% of the patients developing DAT had at least one symptom of apathy at the time of the conversion in comparison with only 26.4% in the non-converted patients. This may be related to the fact that apathy has been reported as the most frequent neuropsychiatric symptoms in mild DAT [29].

We are aware of the limitations of the study. Firstly, the fact that the patients were recruited from memory clinic, is possibly a bias selection which may explain why depressive symptoms are overrepresented. However, it must be underlined that the memory consultations involved in the study are representative of the diagnosis procedure used in France for the diagnosis of MCI. Secondly, patients developing dementia are older than patients without dementia. Thirdly, concerning the definition of apathy, on the first hand using only the presence of one symptom for defining apathy may be a shortcoming of the study. On the other hand, we reported the presence of apathy in 39.8% of the MCI subjects. This is in line with previous studies using the NPI, where apathy was reported in between 11 to 39% of subjects [30,31]. Furthermore, it does emphasize that even very mild symptoms indicating a motivational disturbance are present in MCI and

need to be searched in memory consultation services involved in the screening of dementia.

There is no specific neuropsychiatric marker for DAT. However, given their high prevalence several studies suggest that neuropsychiatric symptoms should be used as supportive symptoms for the diagnosis of prodromal Alzheimer disease. Taking into account that apathy is one of the most frequently observed neuropsychiatric symptoms in MCI and in DAT the present study suggests that patients with MCI and apathy should be more closely observed.

### Acknowledgement

The PréAL (Prediction for Alzheimer disease) study is a national multicenter study supported by grant “PHRC” from the French Ministry of Health.

### References

- [1] Lopez OL, Becker JT, Sweet RA. Non-cognitive symptoms in mild cognitive impairment subjects. *Neurocase* 2005;11:65–71.
- [2] Feldman H, Scheltens P, Scarpini E, Hermann N, Mesenbrink P, Mancione L, et al. Behavioral symptoms in mild cognitive impairment. *Neurology* 2004;62:1199–201.
- [3] Gabryelewicz T, Styczynska M, Pfeffer A, Wasiak B, Barczak A, Luczywek E, et al. Prevalence of major and minor depression in elderly persons with mild cognitive impairment—MADRS factor analysis. *Int J Geriatr Psychiatry* 2004;19:1168–72.
- [4] Modrego PJ, Ferrandez J. Depression in patients with mild cognitive impairment increases the risk of developing dementia of Alzheimer type. *Arch Neurol* 2004;61:1290–3.
- [5] Dartigues JF, Commenges D, Letenneur D, Barberger-Gateau P, Gilleron V, Fabrigoule C, et al. Cognitive predictors of dementia in elderly community residents. *Neuroepidemiology* 1997;16:29–39.
- [6] Fabrigoule C. Cognitive process in preclinical phase of dementia. *Brain* 1998;0:135–41.
- [7] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;56:303–8.
- [8] Folstein MF, Folstein SE, McHugh P.R. “Mini-mental test”. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatry Res* 1975;12:189–98.
- [9] Isaacs B, Kennie AT. The Set test as an aid to the detection of dementia in old people. *Br J Psychiatry* 1973;123:467–70.
- [10] Grober E, Buschke H. Genuine memory deficits in dementia. *Neuropsychology* 1987;3:13–36.
- [11] Cooper JA, Sagar HJ, Jordan N, Harvey NS, Sullivan EV. Cognitive impairment in early, untreated parkinson’s disease and its relationship to motor disability. *Brain* 1991;2095–122.
- [12] Reitan RM, Wolfson D. The Halstead–Reitan neuropsychological test battery: theory and clinical interpretation. 0 ed. Tucson, Ariz: Neuropsychology Press; 1985.
- [13] Baddeley AD, Della Sala S. Dual-task performance in dysexecutive and nondysexecutive patients with a frontal lesion. *Neuropsychology* 1997;11(2):187–94.
- [14] Wechsler D. WAIS-R manual. 0 ed. New York: The Psychological Corporation; 1981.
- [15] Stroop J. Studies of interferences in serial verbal reactions. *J Exp Psychol* 1935:643–62.
- [16] Goldberg DP, Hillier VF. A scaled version of the General Health Questionnaire. *Psychol Med* 1979;9:139–45.
- [17] Montgomery S, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382–9.
- [18] Robert PH, Clairet S, Benoit M, Koutaich J, Bertogliati C, Tible O, et al. The Apathy Inventory: assessment of apathy and awareness in Alzheimer’s disease, Parkinson’s disease and mild cognitive impairment. *Int J Geriatr Psychiatry* 2002;17:1099–105.
- [19] Landes AM, Sperry SD, Strauss ME, Geldmacher DS. Apathy in Alzheimer’s disease. *J Am Geriatr Soc* 2001;49:1700–7.
- [20] Starkstein SE, Petracca G, Chemerinski E, Kremer J. Syndromic validity of apathy in Alzheimer’s disease. *Am J Psychiatry* 2001;158:872–7.
- [21] Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Res* 1991;38:143–62.
- [22] McKhann G, Drachman D, Folstein M, Katzman R, Pice 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;34:189–98.
- [23] Berger AK, Fratiglioni L, Forsell Y, Windblad B, Bäckman L. The occurrence of depressive symptoms in the preclinical phase of A.D. A population-base study. *Neurology* 1999;53:1998–2002.
- [24] Bartolini M, Coccia M, Luzzi S, Provinciali L, Ceravolo MG. Motivational symptoms of depression mask preclinical Alzheimer’s disease in elderly subjects. *Dement Geriatr Cogn Disord* 2005;19:31–6.
- [25] Dubois B, Albert M. Amnesic MCI or prodromal Alzheimer’s disease? *Lancet Neurol* 2004;3:246–8.
- [26] Stuss DT, Van Reekum R, Murphy KJ. Differentiation of states and causes of apathy. 0 ed. New York: Oxford university Press; 2000.
- [27] Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cerebral Cortex* 2005;1–13 [published on line October 5].
- [28] Robert P, Berr C, Volteau M, Bertogliati C, Benoit M, Mahieux F, et al. Neuropsychological performance in mild cognitive impairment with and without apathy. *Dement Geriatr Cogn Dis* 2006;21:192–7.
- [29] Benoit M, Staccini P, Brocker P, Benhamidat T, Bertogliati C, Lechowski L, et al. Symptômes comportementaux et psychologiques dans la maladie d’Alzheimer: Résultats de l’étude REAL.FR. *Revue de Médecine Interne* 2003;2003:319–24.
- [30] Geda YE, Smith GE, Knopman DS, Boeve BF, Tangalos EG, Ivnik RJ, et al. De novo genesis of neuropsychiatric symptoms in mild cognitive impairment (MCI). *Int Psychogeriatr* 2004;16:51–60.
- [31] Hwang TJ, Masterman DL, Ortiz F, Fairbanks LA, Cummings JL. Mild cognitive impairment is associated with characteristic neuropsychiatric symptoms. *Alzheimer Dis Assoc Disord* 2004;18:17–21.