

Clinical Approach to Diagnosis of Pre-Dementia Alzheimer's Disease (CAD-PAD)

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Key Words

Clinical diagnosis · Pre-dementia · Alzheimer's disease

Abstract

Objective: Our aim was to evaluate clinical and neuropsychological features to identify pre-dementia Alzheimer's disease (PAD) among mild cognitive impairment (MCI) patients. **Methods:** A longitudinal prospective study of 89 consecutive patients affected with MCI was conducted. Clinical evaluation consisted of a clinical interview protocol, neuropsychological evaluation, standard laboratory tests, and CT scan. A 6-month clinical check-up was made to determine whether patients remained in MCI, improved or progressed to AD or another dementia. **Results:** At 3-year follow-up, 47% patients developed AD dementia. Seventeen variables were significant and were evaluated by logistic regression analysis to identify the remaining optimal diagnostic criteria: age, gender, repeating comments, difficulties in understanding explanations, time of symptom evolution, history of depression, and word fluency (with animals) were identified with a sensitivity of 100% and a specificity of 93%. A computer application was developed with all these variables which we have named Clinical Approach to Diagnosis of PAD (CAD-PAD). **Conclusions:** These results suggest that CAD-PAD can help in the clinical diagnosis of PAD.

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Introduction

The publication of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria in 1984 represented a breakthrough in the diagnosis and study of Alzheimer's disease (AD) [1]. These criteria established the clinical diagnosis of AD based on dementia with certain clinical characteristics. However, according to the experience gained in recent years, the conviction has emerged that the diagnosis of AD can in many cases be established in the pre-dementia phase of AD. For a clinical approach, different criteria have been proposed to define the characteristics of these patients, who are commonly defined as amnesic mild cognitive impairment (MCI) patients, a term that is more widespread and more frequently used [2–4]. However, several studies that have monitored these patients for a prolonged period have revealed that approximately 50% of patients do not progress to dementia, so these criteria have not shown enough sensitivity and have not been specific enough to detect pre-dementia AD (PAD) [5].

So, with the aim, among others, of being more certain in the diagnosis of PAD, several reviews using the NINCDS-ADRDA criteria have been conducted [6–9]. The new criteria aim to support the diagnosis with several biological markers which have shown better sensitivity and are more specific [10, 11]. However, the role of the new criteria in daily practice remains to be defined. Cutoff points, acceptable availability and costs have not yet been established, among other issues [12].

Although the boundaries between normal cognition and MCI as well as the boundaries between nonspecific MCI and PAD are not easy to establish, we believe that the clinical history, based on a reliable informant and a neuropsychological examination (basic pillars in the evaluation of our patients), may still provide data to improve the core clinical criteria for the diagnosis of MCI due to an incipient stage of AD. Therefore, this study was designed to evaluate whether clinical and neuropsychological characteristics could be identified in patients with MCI that could substantiate the clinical diagnosis of PAD.

Methods

A longitudinal prospective observational study of MCI patients was carried out to determine the plausible existence of clinical data with a predictive value suggestive of PAD in MCI patients.

Subjects

Consecutive MCI patients attending the Behavioral Neurology and Dementia Unit of Elche University General Hospital meeting the following inclusion criteria were recruited as cases: (1) memory impairment complaint corroborated by an informant willing to report faithfully on the patient every 6 months; (2) Clinical Dementia Rating (CDR) score of 0.5; (3) Mini-Mental State Examination (MMSE) score of ≥ 24 (≥ 20 if illiterate), and (4) complete autonomy for activities of daily living (ADL) and absence of dementia. At the same time, healthy volunteers with a trustworthy informant who could confirm that they did not suffer from memory impairment were assessed at the unit, and those who had no known neurological pathology, nor depression, and showed only a minor sensory motor disorder, if at all, were recruited as controls.

Patients and controls were submitted to clinical evaluation, consisting of an interview plus the collection of clinical data and data from neuropsychological and complementary tests.

The monitoring period was 3 years. All patients had a follow-up visit every 6 months, where their autonomy in ADL and their neuropsychological state were re-evaluated, so that a neurologist and a neuropsychologist could reach a consensus on whether the patient remained MCI (also called MCI non-converters) or progressed to dementia (becoming a PAD patient).

All patients and controls recruited gave their informed consent. The study was developed in agreement with legal stipulations in Spain for observational epidemiologic studies and with the World Medical Association Declaration of Helsinki [13]. The study was approved by the Scientific Research Ethics Committee of Elche General University Hospital.

Clinical Interview Protocol

The following data were collected: age, gender, years and level of education, professional level, family history of dementia, sensorial/motor deficit, presence and/or history of depression [if symptoms of depression were present, the Hamilton Depression Rating Scale (HDRS) [14] was applied], presence of other diseases causing initial symptoms of cognitive decline, whether the patient came alone or was accompanied, disease course (progressive, stable, regressive, or fluctuant), time of symptom evolution, any limitation in ADL (asking about housing, shopping, cooking, finances, errands, medication, hobbies, or other usual activities), and verification of cognitive decline over the last 5 years.

Finally, questions were asked about whether the subject repeats comments or questions (spontaneously or when asked), remembers more/better remote facts than recent events (spontaneously or when asked), or shows isolated cases of (temporal and/or spatial) disorientation and difficulties in understanding explanations. In practice, the informant is asked if, in their usual contact with the patient, more detailed explanations have to be given than usual. The intention is to find out whether slight and occasional flaws exist in grasping the message of an explanation or conversation of any complexity, which could easily be compensated with a more detailed explanation and which does not interrupt the patient's ADL.

Neuropsychological Assessment

The tests performed and scales used in our patients were the CDR scale [15], the MMSE [16], several subtests of the Wechsler Memory Scale [17] revised (WMS-R) [18] and the Wechsler Adult Intelligence Scale (WAIS) [19] including the following tests: general information, orientation, mental control, logical memory, associated learning, digit span (DS) forward and reverse, digit symbol substitution, and block design. The visual memory test from 'Test de Barcelona' [20] assesses non-verbal memory: cards with geometrical figures of different sizes are shown to patients for 15 s; thereafter, they have to recognize the figures among 4 possibilities on another card without any visual cue, obtaining 1 point for each figure recognized correctly. Other tests conducted were the Trail-Making Test [21] part A, the Boston Naming Test (BNT) [22], word fluency for animals (a) and letter P [23].

Complementary Tests

Blood analysis, TSH-T4, vitamin B12, folic acid, lues (*Treponema*) serology and cranial CAT scan were performed to detect and exclude possible secondary causes of MCI.

Statistics

Descriptive statistics were applied to all variables, including measures of central tendency and of statistical variability for quantitative variables, as well as absolute and relative frequencies for qualitative variables, with 95% confidence intervals for both types of variables. The Kolmogorov-Smirnov test was applied to test for the normal assumption of vari-

ables. For those variables which did not comply with Gauss distribution, non-parametric statistics were used.

MCI non-converters were compared to PAD patients by analytical statistics. Observed differences between these two groups were analyzed by the Student t test for independent data for quantitative variables and the χ^2 test for qualitative variables. Regression analysis was performed with every variable that showed significant differences between MCI non-converters and PAD patients at baseline.

The assessments were considered statistically significant if the two-sided p value was <0.05 . The SPSS program was used for all statistical analyses.

Results

Characteristics of Cases and Controls

Eighty-nine MCI patients and 63 controls were recruited with similar baseline demographic characteristics (table 1). Significant differences were observed in their neuropsychological analysis and in other clinical variables (table 1). The MMSE score was significantly ($p \leq 0.0001$) lower in the case (25.8 ± 2.7) than in the control group (28.0 ± 2.1), and a lower percentage of cases ($p = 0.002$) reached the maximum score for the delayed memory domain.

There was a significantly higher percentage of subjects with the maximum score (better) for general information (5), orientation (5), and mental control (2–3) in the control than in the case group. Except for DS forwards, for which both groups showed similar scores, for all other Wechsler subtests, and for visual memory, BNT, and word fluency a and P, the control group showed significantly higher (better) scores. The largest difference was for the Wechsler logical memory and visual memory test, where the mean score value obtained by the cases was inferior >1 SD from the control value. For trail A, MCI patients showed a significantly higher (worse) ($p \leq 0.0001$) score than the control group.

A significantly higher percentage of MCI patients than controls repeated comments/questions, remembered more/better remote events, showed isolated cases of place disorientation, and experienced difficulties in understanding explanations.

According to inclusion criteria, controls were only selected if they did not show depression or had not had a history of it. Among MCI patients, 16% had depression and a similar percentage had a history of it.

Characteristics of PAD and MCI Non-Converters

At the 3-year monitoring of all patients, 4 patients had dropped out (2 had a stroke, 1 lung cancer, and 1 was missing), 45 had not progressed (MCI non-converters), and 40 developed AD dementia (25% in the first, 12% in the second, and 10% in the third year), representing 47% of the MCI patients initially recruited. An analysis of clinical variables at the first visit of PAD (MCI converters) and MCI non-converter patients identified several variables for which there was a significant difference between the two groups (table 2). PAD patients included a significantly higher percentage of men ($p = 0.006$), more of them had come along with someone on their first visit ($p = 0.031$), and they were significantly older ($p = 0.002$) and had a shorter evolution time ($p = 0.016$) than non-converters. The CDR sum of box scores was calculated as a measure of disease severity, and a significantly higher percentage of PAD patients with a sum >0.5 was identified ($p = 0.01$).

Both groups had similar MMSE scores but differences in Wechsler subtests. There was a significantly lower percentage of PAD patients with the maximum score (5) for orientation ($p = 0.017$), and these patients also showed significantly worse scores for logical memory

Table 1. Demographic and clinical characteristics of MCI patients and controls

	Control (n = 63)	MCI (n = 89)	p value
Age, years	70.2 ± 6.9	72.3 ± 7.3	NS
Female gender	69.9	61.6	NS
Education, years	7.1 ± 3.5	6.51 ± 4.9	NS
Family history of dementia	33.3	30.8	NS
MMSE	28.0 ± 2.1	25.8 ± 2.7	≤0.0001
Delayed memory (2–3)	91.2	67.2	0.002
Intrusions	4.1	4.9	NS
Wechsler			
General information (5)	95.2	58.8	≤0.0001
Orientation (5)	100	78.8	0.002
Mental control (2–3)	100	91.8	0.026
Logical memory	10.6 ± 2.5	7.7 ± 3.2	≤0.0001 ^c
Associated learning	15.9 ± 3.7	12.4 ± 4.4	≤0.0001
DS forwards	4.8 ± 0.7	4.6 ± 0.8	NS
DS backwards	3.8 ± 0.8	3.3 ± 0.8	0.003
DSST	19.2 ± 7.5	15.5 ± 7.3	0.007
Block design	27.0 ± 9.5	21.8 ± 10.4	0.005
Visual memory	8.3 ± 1.2	6.9 ± 1.9	≤0.0001 ^c
BNT	49.3 ± 6.3	43.9 ± 17.1	0.001
Word fluency (a)	19.0 ± 4.6	14.4 ± 4.3	≤0.0001
Word fluency (P)	13.2 ± 4.7	10.6 ± 5.1	0.003
Trail-Making Test part A	73.6 ± 33.8	105.6 ± 51.5	≤0.0001
Repeats ^a	1.6	71.1	≤0.0001
Spontaneously	0.0	31.3	
When asked	1.6	39.8	
Remembers remote ^b	9.5	44.6	≤0.0001
Spontaneously	1.6	19.3	
When asked	7.9	25.3	
Isolated disorientation			
Place	4.8	38.6	≤0.0001
Time	1.6	6.0	NS
DIFUNEX	0.0	45.2	≤0.0001
Sensory motor defect	14.3	19.5	NS
History of depression	0.0	16.3	–
Depression	0.0	15.9	–
Another comorbidity	0.0	29.6	–

Variables are expressed as means ± SD or as percentages. DSST = Digit symbol substitution test; word fluency (a) = animal; word fluency (P) = letter P; DIFUNEX = difficulty in understanding explanations; NS = non-significant.

^a Repeats comments/questions. ^b Remembers more/better far away events. ^c The value of the case differs from that of the control by >1 SD.

(p = 0.001), associated learning (p = 0.001), and block design (p = 0.029). However, there was a significantly higher percentage of PAD patients with the maximum score (2–3) for mental control (p = 0.003), and they also showed a significantly better score (p = 0.01) for DS backwards than non-converters.

Regarding the other cognitive tests, PAD patients had a significantly (p = 0.006) worse score for animal word fluency, and a significantly (p = 0.0001) higher percentage of them

Table 2. Demographic and clinical characteristics of PAD and MCI non-converter patients

	Non-converters (n = 45)	PAD patients (n = 40)	p value
Age, years	69.9 ± 7.6	75.1 ± 5.0	0.002
Female gender	77.8	45.0	0.002
Education, years	5.3 ± 3.2	6.6 ± 4.9	NS
Low professional level	93.4	70	0.013
Evolution time, months	31.2 ± 16.6	23.3 ± 12.3	0.016
Reason for 1st visit: memory complaint	92.5	100	NS
Initial course: insidious	95.0	97.4	NS
Evolution: progressive	80.0	89.5	NS
Comes alone	17.5	2.6	0.031
CDR sum of boxes = 0.5	90	57.5	0.01
MMSE	25.3 ± 2.7	25.8 ± 2.8	NS
Delayed memory (2–3)	75.0	68.4	NS
Intrusions	12.5	10.5	NS
Wechsler			
General information (5)	90	77.8	NS
Orientation (5)	97.5	94.5	0.017
Mental control (2–3)	90	94.5	0.003
Logical memory	8.4 ± 2.4	6.2 ± 3.4	0.001
Associated learning	13.4 ± 4.8	10.1 ± 3.1	0.001
DS forwards	4.3 ± 0.8	4.7 ± 0.8	NS
DS backwards	3.1 ± 1.0	3.3 ± 0.8	0.01
DSST	14.2 ± 8.2	14.7 ± 7.4	NS
Block design	23.1 ± 10.6	17.5 ± 8.8	0.029
Visual memory	6.6 ± 1.7	6.7 ± 1.9	NS
BNT	44.3 ± 6.3	42.5 ± 7.9	NS
Word fluency (a)	15.4 ± 3.9	12.8 ± 4.2	0.006
Word fluency (P)	10.7 ± 5.8	9.6 ± 4.1	NS
Trail-Making Test part A	119 ± 51.9	103 ± 49.9	NS
Repeats ^a	57.5	92.1	≤0.0001
Spontaneously	10.0	52.6	
When asked	47.5	39.5	
Remembers remote ^b	40.0	57.9	NS
Spontaneously	12.5	31.6	
When asked	27.5	26.3	
Isolated disorientation			
Place	40.0	34.2	NS
Time	2.5	7.9	NS
DIFUNEX	22.5	65.8	≤0.0001
Minor sensory motor defect	35.0	13.2	0.023
History of depression	55.6	2.5	0.001
Depression	17.5	13.2	NS
Another comorbidity	40.0	21.1	NS

Variables are expressed as means ± SD or as percentages. DSST = Digit symbol substitution test; word fluency (a) = animal; word fluency (P) = letter P; DIFUNEX = difficulty in understanding explanations; NS = non-significant.

^a Repeats comments/questions. ^b Remembers more/better far away events.

The screenshot shows a computer application interface for CAD-PAD. It features several input fields and dropdown menus for clinical variables: 'age', 'word fluency', 'repeat' (with options: spontaneously, asked, no repeat), 'difunex' (with options: yes, no), 'sex' (with options: woman, man), and 'Hdepre' (with options: yes, no). Below these fields is a 'time evol' field. At the bottom, there is a 'diagnosis' box containing the text 'MCI - non converter / PAD'.

Fig. 1. CAD-PAD: the selected clinical variables of the LRA and its corresponding computer application. difunex = Difficulty in understanding explanations; Hdepre = history of depression; time evol = time of evolution.

repeated comments/questions and showed difficulties in understanding explanations. On the other hand, a higher percentage of non-converters had sensory motor defects ($p = 0.023$) and a history of depression ($p = 0.001$).

Regression analysis was performed with the 17 significantly different variables to select the ones that best differentiated PAD patients from non-converters. The analysis was done stepwise; thus, not only was the variable selected by the algorithm, but the order by which the variable improves the significance of the overall function was selected as well. Seven variables in the following order were selected: history of depression, difficulties in understanding explanations, word fluency (a), evolution time, gender, repetition, and age. In this type of patients, the 7 mentioned variables had an overall sensitivity of 100% and a specificity of 93.2%. A computer application was developed with all these variables to input data and obtain a score equivalent to PAD or MCI non-converter which we have named CAD-PAD (fig. 1).

Discussion

This study shows that, in MCI patients, clinical and neuropsychological features exist which allow the identification of those with PAD. In patients with PAD, 17 variables have proved to differ from those MCI who do not progress to dementia (table 2). Logistic regression analysis (LRA) of these variables selects 7 that identify patients with PAD with a sensitivity of 100% and a specificity of 93%. These variables are age, gender, repetition of comments and/or questions, difficulty in understanding explanations, evolution time, history (or not) of depression, and verbal fluency (animals). Furthermore, the LRA has been elaborated by way of a computer application for diagnostic use in medical practice which we have named CAD-PAD (fig. 1).

The inclusion criteria, using clinical and neuropsychological characteristics of patients (table 1), and the fact that 47% of patients in the AD series progressed to dementia within 3 years (which is comparable to findings of the majority of follow-up studies [5]) show, in essence, that the group studied is representative of patients with MCI included in many studies on the subject as well as of those patients we usually see in the daily clinic visits.

In this study, we have included a set of clinical variables in an attempt to collect data which, in clinical practice, help establish which features raise a suspicion of PAD. The clinical variables that showed significant differences were age, the tendency to repeat comments and/or questions, the difficulty in understanding explanations, a history of depression, gender, low professional level, time evolution of cognitive symptoms, going alone or accompanied to the visit, and the presence or absence of minor sensorial deficits and/or motor disorders. However, other clinical variables (remember more/better remote facts than recent events and isolated cases of temporal and/or spatial disorientation) that apparently may also suggest the beginning of PAD showed no statistical significance.

Age is the clinical variable that has most consistently had predictive significance in the literature on this subject, showing a clear increase in the incidence of AD with age [24, 25]. Our study also showed a predictive significance of age, and the variable is chosen in the LRA.

One of the variables that has proven to be the key element in the clinical profile of PAD has been the systematic collection of interviews is, according to the informant, the patients repeated comments and/or questions. In our study, with clear significance, cognitive impairment in patients with MCI who had this characteristic was highly likely to worsen in the following 3 years (included in the LRA). It is well known that this is a distinctive characteristic of AD, but also, based on the data provided, it seems clear that many of those with PAD may show this characteristic for some time, while their MMSE scores are still high and their daily activities do not require any kind of restriction or supervision, as they are able to perform responsible tasks without any problems, for example, caring for grandchildren, banking, and administrative matters. Another clinical variable which has shown high significance when establishing the profile of PAD has been difficulties in understanding explanations (included in the LRA). These difficulties are slight and occasional flaws in receiving the message of an explanation or conversation of any complexity that can easily be compensated with a more detailed explanation and do not significantly interfere with patients' daily activities.

In our study, although the percentage of patients with symptoms of depression in the initial assessment was similar in MCI non-converters and in the PAD group, symptoms of depression were present in the patients' previous history, and much more frequently so in the MCI non-converters ($p = 0.001$, included in the LRA). We believe that, although symptoms of depression at the beginning of MCI (especially if no prior history exists) must be considered in a special way, the presence of a history of depression, however distant and clearly overcome, may in some cases determine slight decreases in motivation and consequently in attitudes to daily activities, which in turn hinders the healthy cognitive stimulation. In any case, the influence of depression (of recent onset or distant) on cognitive impairment and its inclusion in the prognostic assessment of a patient with MCI is still controversial in the literature and, of course, in clinical practice [26–29].

In our study, it was found that a low-ranking job is more frequent in those with MCI who did not develop dementia, which can be explained by these patients' lower capability and/or ease in performing the neuropsychological tests leading to a misinterpretation of the test results, which indicate greater cognitive impairment and distort the overall assessment of these patients. On the contrary, and unlikely according to population-based studies, the level of education was not significantly different in MCI patients whose cognitive impairment progressed and in those where it did not. The design of the study, the origin of our patients from a memory clinic, fewer case studies compared to population studies, as well as the small in-

fluence of this aspect on the evolution of an established MCI are facts which do not allow us to evaluate this observation.

On the other hand, the gender of the patients showed significant differences (included in the LRA). Although in the initial global MCI group the proportion of women was higher (61.6%), 3-year monitoring showed a greater number of women (77.8%) in the MCI non-converter group and only 45% in the PAD group. That is to say, there is a higher predisposition in males for MCI due to PAD. The lower predisposition for PAD among women in our study required additional analyses (data not shown) which revealed that the women's group presented statistically significant differences at the first assessment compared to the male group: lower professional level, more frequent history of depression, and lower scores on the MMSE and DS reverse. The presence of these variables in the women's group (possibly influenced by socio-cultural aspects) can influence the development of a non-specific MCI which moves away from the clinical profile of PAD. In the literature, although some studies suggest a higher prevalence of MCI in men [30, 31], this is a detail which is not confirmed [32].

Another clinical variable which was statistically significantly more frequent in MCI non-converters than in PAD patients was an increased presence of small sensory deficits (auditory or visual) or motor deficits (mobility defects due to osteoarthritis or other reasons), an aspect that may contribute to a decrease in daily activities with a consequent loss of cognitive stimulation and difficulties in carrying out the tests during clinical assessment. On the other hand, it was found that a greater proportion of patients who were MCI non-converters came alone to the clinic compared to PAD patients (17.5 and 2.5%, respectively), which offers additional proof of the benignancy of the cognitive impairment of MCI non-converters compared to PAD patients.

The evolution time of symptoms at the time of the first assessment (variable included in the LRA) was shorter in patients with PAD, which has been shown to a greater or lesser degree in other studies [25]. We believe that longer periods of evolution in an MCI patient, although they may be due to a slow onset of AD, must make us doubt that a true PAD can be related to other non-specific factors, such as those mentioned above.

In relation to the CDR scale and the neuropsychological tests performed, the results are similar to those described in the literature [33–35]. Compared to MCI non-converters, PAD patients, at the initial evaluation (table 2), showed a higher score on the CDR sum of box areas, worse results on memory tests (logical memory and associated learning) and also on block design and orientation. On the contrary, they showed better results in mental control and DS reverse, suggesting that the MCI non-converters could have slight defects in attention compared to patients suffering from PAD. Finally, word fluency (animals) was significantly lower in those with PAD, the only neuropsychological variable which the LRA selected in its predictive analysis. We believe that the results of the memory tests, although showing clearly significant differences, were not selected in the LRA because the memory defects of patients with PAD will probably be identified by the clinical variable 'repetition of comments/questions'.

In this CAD-PAD, no doubt, the presence of a reliable informant is essential to be able to obtain this information, as well as a clinic with time and sufficient expertise to assess the reliability of said information. These requirements, although elementary, can be a major limitation if they cannot be adequately met, so we believe that these results should be corroborated by additional studies. On the other hand, the availability of the computer application will facilitate the use of CAD-PAD in clinical practice. So, based on the data of the 7 selected variables of every patient, the computer application predicts the patient's final diagnosis. It is therefore neither an invasive nor expensive tool and easy to apply in clinical practice.

To sum up, this study shows that PAD can be identified by way of a CAD. We believe that the CAD-PAD can help in the clinical diagnosis of PAD and in subsequent decisions taken in daily clinical practice and in the selection of patients for clinical trials or other research on PAD.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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