Journal of Alzheimer's Disease 101 (2024) 369–377
DOI 10.3233/JAD-240621
IOS Press



# Amyloid-Negative, Neurodegeneration-Negative Amnestic Mild Cognitive Impairment

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Accepted 24 June 2024
Pre-press 17 August 2024

**Abstract**.
**Background:** The concept of amnestic mild cognitive impairment (aMCI) was developed to identify patients at an initial stage of Alzheimer's disease (AD). However, some patients with aMCI do not present biomarkers of amyloid pathology or neuronal injury.
**Objective:** To know the natural history of amyloid-negative and neurodegeneration-negative patients with aMCI, namely to ascertain: 1) whether these patients remain cognitively stable or they present a slow decline in neuropsychological tests; 2) whether the memory complaints subside with the apparently benign clinical course of the disorder or if they persist along the time.
**Methods:** Patients who fulfilled criteria for aMCI with no biomarkers of amyloid pathology or neuronal injury were selected from a large cohort of non-demented patients with cognitive complaints, and were followed with clinical and neuropsychological assessments.
**Results:** Twenty-one amyloid-negative and neurodegeneration-negative aMCI patients were followed for $7.1 \pm 3.7$ years. At the baseline they had more pronounced deficits in verbal learning (California Verbal Learning Test) and were also impaired in Word Recall and Logical Memory. However, they did not decline in any cognitive test during follow-up. The patients maintained a high level of subjective memory complaints from baseline ($9.7 \pm 4.1$) to the follow-up visit ($9.2 \pm 4.1$, a non-significant difference), in spite of a statistically significant decrease in the depressive symptoms, with Geriatric Depression Scale (15 items) score $4.9 \pm 2.8$ at baseline and $3.2 \pm 1.8$ at the follow-up visit.
**Conclusions:** Amyloid-negative, neurodegeneration-negative aMCI is a chronic clinical condition characterized by the long-term persistence of cognitive deficits and distressing memory complaints. Adequate strategies to treat this condition are needed.

Keywords: Alzheimer's disease, amnestic mild cognitive impairment, amyloid-β, amyloid-negative, biomarkers, dementia, follow-up

## INTRODUCTION

As a consequence of population ageing, the number of people affected by neurodegenerative disorders, particularly Alzheimer disease (AD), is increasing dramatically worldwide, representing a major public health issue.[1] For many years, a transitional

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ISSN 1387-2877/$35.00 

state in AD from normal cognitive aging to a full-blown dementia stage was predicted.[2] The possibility of diagnosing consistently AD at an early phase emerged about two decades ago, with the concept of amnestic mild cognitive impairment (aMCI), characterized by subjective memory complaints, objective memory deficit, normal general cognitive performance and maintained activities of daily living.[3] Indeed, patients diagnosed with aMCI in a clinical setting have about 10% annual progression rate of conversion to dementia, usually AD.[4]

In recent years, a major breakthrough was the possibility of diagnosing AD reliably in patients that present with aMCI. Different diagnostic criteria with slight differences were advanced, namely prodromal AD[5] and MCI due to AD,[6] that rely on biomarkers reflecting pathological alterations of the AD continuum, namely the presence of amyloid in the brain,[7] detected by measuring low amyloid-β $(A\beta)_{1-42}$ concentrations in the cerebrospinal fluid (CSF),[8] and/or identifying brain deposits of Aβ with amyloid positron emission tomography (PET).[9] Interestingly, the extensive use of AD biomarkers in research and clinical settings,[10] revealed the existence of a subset of patients with aMCI who do not harbor amyloid pathology and thus do not have AD.[11–13]

Further studies revealed that amyloid-negative aMCI represents a rather heterogeneous clinical condition.[14] Some patients with amyloid negative aMCI have evidence of neurodegeneration,[15–17] and can be at an initial stage of a neurodegenerative disorder other than AD. Amyloid-negative aMCI cases that have progressed to frontotemporal dementia, progressive supranuclear palsy, primary age-related tauopathy and the Lewy body disease have been reported.[18–24] Other patients may have masked depressive symptoms or other latent psychiatric disorder that may show up later on.[14,25] The potential of non-AD MCI cases to decline and progress to dementia has been emphasized.[26] On the other hand, there is evidence that a subset of aMCI patients may remain clinically stable for long periods of time.[27] In the present study, we selected from a large cohort of non-demented patients with cognitive complaints those who fulfilled criteria for aMCI and were both amyloid-negative and neurodegeneration-negative at the baseline, and followed them up with clinical and neuropsychological assessments to select those who remain clinically stable. The purpose was to ascertain: 1) whether these patients are really cognitively stable or they present a slow decline in neuropsychological tests; 2) whether the memory complaints subside with the apparently benign clinical course of the disorder or if they persist along the time.

## METHODS

### *Participants*

Participants were selected from the Cognitive Complaints Cohort (CCC), established in a prospective study conducted at Faculdade de Medicina da Universidade de Lisboa, approved by the local ethics committee, conducted according to the declaration of Helsinki and requiring the participants' informed consent.[28] The CCC aimed to investigate the cognitive stability or evolution to dementia in patients with cognitive complaints, recruiting nondemented patients with cognitive complaints who underwent a comprehensive neuropsychological evaluation, as well as clinical history, neurological examination, laboratorial evaluation and brain imaging (CT or MRI). Patients with neurological, psychiatric, medical disorders or medication (namely anticholinergic drugs) that might induce cognitive deficits, history of alcohol or recurrent substance abuse, or with dementia were excluded. For the purpose of the present study, participants recruited from 2010 to 2020 were selected. The flow chart of recruitment is shown in Fig. 1.

### *Diagnostic criteria*

*Inclusion criteria*

1) Diagnosis of amnestic MCI, adapted from Petersen's criteria.[3]
    a. Memory complaints present at the clinical interview provided by the patient or informant.
    b. Abnormal memory function. Performances in at least two memory domain tests must fall 1.0 SD below norms for age and education.[29] For this purpose, in the present study the following memory tests were considered: Visual Reproduction Test, Word Recall, Logical Memory, Verbal Paired-Associate Learning, California Verbal Learning Test (see below).
    c. Normal general cognitive function, determined by the Mini-Mental State Examination (MMSE)[30] within normal values for the Portuguese population.[31]

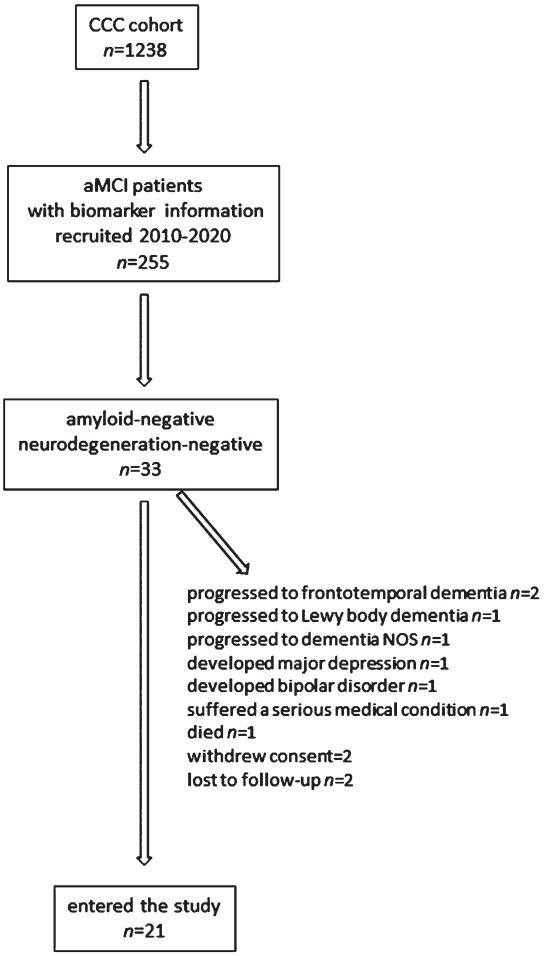


Fig. 1. Flow-chart of patient selection for the study.

   d. No or a minimal impairment in activities of daily living, reflected in a score < 3 on the first part (items 1–8) of the Blessed Dementia Rating Scale (BDRS).[32]
   e. Minimum follow-up time of 3 years.
2) Absence of brain amyloid pathology, determined at baseline by measuring normal $A\beta_{1-42}$ concentrations in the CSF and/or the absence of brain deposits of Aβ with amyloid PET scan.[6] Whenever possible, patients had both CSF biomarkers and amyloid PET performed.
3) No evidence of neurodegeneration or neuronal injury.[7] Biomarkers considered to reflect neuronal injury were high CSF total tau or hyperphosphorylated tau, brain atrophy by volumetric measures or visual rating using CT scan or MRI, hypometabolism by FDG-PET imaging.[6]

*Exclusion criteria*

The same exclusion criteria as used in the CCC (see above), that is, patients with neurological, psychiatric, medical disorders or medication (namely anticholinergic drugs) that might induce cognitive deficits, history of alcohol or recurrent substance abuse, or with dementia according to the American Psychiatric Association criteria[33] were excluded.

*Neuropsychological assessment*

The baseline and follow-up comprehensive neuropsychological assessments were carried out by the same team of trained neuropsychologists. Patients were assisted on a clinical basis and did not undergo neuropsychological evaluations at fixed times. The neuropsychological protocol comprised the following instruments:

1) Mini-Mental State Examination (MMSE).[30] The MMSE is a brief screening instrument to assess global cognitive performance. The Portuguese version was applied, and normative data was > 27 for more than 11 years of education and > 22 for 11 or less years of education.[31]
2) Battery of Lisbon for the Assessment of Dementia (BLAD).[34,35] The BLAD is a comprehensive neuropsychological battery that includes tests from the Wechsler Memory Scale[36] and has been validated for the Portuguese population. For the present work the following cognitive domains (and tests) were considered: attention and executive functions (Cancellation Task, Digit Span Backward); initiative (Motor and Graphomotor Initiatives); non-verbal and verbal reasoning (Raven Colored Progressive Matrices and Interpretation of Proverbs); orientation (Personal, Spatial and Temporal Orientation); calculation (Basic Written Calculation); visuo-constructional abilities (Cube Copy and Clock Draw); language (Semantic Fluency); visual memory (Visual Reproduction Test); immediate memory (Digit Span Forward); learning and verbal memory (Word Recall; Logical Memory [immediate recall and delayed recall], Verbal Paired-Associate Learning).
3) California Verbal Learning Test (CVLT).[37,38] The CVLT measures verbal learning and assesses constructs such as repetition learning, serial position effects, semantic organization, intrusion, and proactive interference. The word

lists (List A and List B) are made up of 16 items from 4 different categories of "shopping list" items. The trial of interest for the present study, having better discriminating ability for different stages of cognitive decline,[39] was the total number of words from List A correctly recalled on the first 5 learning trials (CVLT 5 Trials Total Recall).

4) Trail Making Test (TMT; part A and part B).[40,41] This task measures sustained attention, visuomotor processing speed (part A), visuospatial working memory and cognitive flexibility (part B). Part A consists of 25 circles numbered 1–25 distributed over a sheet of paper and the patient should draw lines to connect the numbers in ascending order. In part B there are 25 circles as well, but the circles include both numbers (1–13) and letters (A–M) and the patient has to draw lines to connect them all in an ascending pattern with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). In the present study the measure of TMT performance was completion time in seconds.
5) Geriatric Depression Scale (GDS) – short version (15 items).[42–44] The GDS is a self-report instrument used specifically to identify depressive symptomatology in the elderly. Total scores range from 0 (absence of depressive symptoms) to 15 (maximal depressive symptoms).
6) Subjective Memory Complaints Scale (SMC).[45,46] The SMC scale comprises 10 individual questions for the assessment of subjective memory complaints, with total scores ranging from 0 (absence of complaints) to 21 (maximal complaints score). These items are considered representative of common memory complaints.[45]
7) Blessed Dementia Rating Scale (BDRS).[47,48] The BDRS is a brief behavioral scale based on the interview of a close informant. This scale is composed of 22 items that address daily life activities, habits and changes in personality. Alterations in everyday activities and habits were assessed by the first part of the scale.[32]

*Statistical analysis*

Since it was anticipated that amyloid-negative and neurodegeneration-negative aMCI would be an infrequent condition, even within a large patient cohort, the sample size was not *a priori* estimated. The neuropsychological assessments were standardized according to the age and education norms for the Portuguese population[31,34] and $z$ scores were calculated with the equation [$z = (x - \text{mean})/\text{SD}$]. Comparison of neuropsychological tests at baseline on follow-up was done, after checking for normality of the distribution and homogeneity of variances, with the paired Student's $t$ test (two-tailed). In order to keep a high sensitivity to detect temporal changes in the neuropsychological tests no correction for multiple comparisons was planned. Values of $p < 0.05$ were considered statistically significant. The Statistical Package for the Social Sciences (SPSS, version 28, SPSS Inc, Chicago, IL, USA) was used.

## RESULTS

Thirty-three amyloid-negative and neurodegeneration-negative aMCI patients were selected from the CCC, and 12 were excluded for various reasons shown in Fig. 1. Demographic and clinical characteristics of the 21 amyloid-negative and neurodegeneration-negative aMCI patients that entered the study are reported in Table 1. The values of CSF biomarkers ($A\beta_{1-42}$, total tau and hyperphosphorylated tau) were within the normal range as shown in Table 2. The follow-up time was $7.1 \pm 3.7$ years (Table 1). The results of the baseline and follow-up neuropsychological assessments are shown in Table 3. At the baseline patients had more pronounced deficits in verbal learning (CVLT) compared to normative values, and were also impaired in Word Recall and Logical Memory. Remarkably, the participants did not decline in any cognitive test during follow-up. Performances in all cognitive tests were stable, with the exception of an improvement Logical Memory – delayed recall (whose statistical significance would not stand correction for multiple comparisons) (Table 3). The patients had a high SMC score at baseline, $9.7 \pm 4.1$, that was not significantly different from the value at the follow-up visit, $9.2 \pm 4.1$ (two-tailed paired Student's $t$ test, $p = 0.513$). There was a decrease in the depressive symptoms, with GDS score $4.9 \pm 2.8$ at baseline and $3.2 \pm 1.8$ at the follow-up visit (two-tailed paired Student's $t$ test, $p = 0.025$).

## DISCUSSION

The present work allowed the characterization of a subset of amyloid-negative, neurodegeneration-

Table 1
Baseline demographic and clinical characteristics of amyloid-negative and neurodegeneration-negative aMCI patients

| | Amyloid-negative neurodegeneration-negative aMCI $n = 21$ |
|---|---|
| Age at first assessment, y, mean (SD) [range] | 58.1 (8.6) [45–73] |
| Formal education, y, mean (SD) [range] | 12.3 (3.7) [6–16] |
| Gender, female/male, *n* | 12/9 |
| Follow-up time, y, mean (SD) [range] | 7.1 (3.7) [3–13] |
| Time between onset of symptoms and baseline neuropsychological assessment, y, mean (SD) [range] | 2.3 (1.6) [1–5] |
| Geriatric Depression Scale, mean (SD) [range] | 4.9 (2.8) [1–13] |
| Subjective Memory Complaints Scale, mean (SD) [range] | 9.3 (4.1) [2–15] |
| Blessed Dementia Rating Scale – 1st part, daily activities, mean (SD) [range] | 0.6 (0.7) [0–2.5] |
| Mini-Mental State Examination, mean (SD) [range] | 28.5 (1.4) [25–30] |

Table 2
Baseline CSF biomarkers of amyloid-negative and neurodegeneration-negative aMCI patients

| $A\beta_{1-42}$ mean (SD) *pg/mL* | Total tau mean (SD) *pg/mL* | Hyperphosphorylated tau mean (SD) *pg/mL* |
|---|---|---|
| 967.9 (358.5) | 238.6 (85.4) | 36.9 (12.0) |

Values obtained by chemiluminescence immunoenzymatic essay (CLEIA) using Lumipulse G1200 (Fujirebio), normal values, $A\beta_{1-42}$ >620 pg/mL, total tau < 409 pg/mL, hyperphosphorylated tau < 50 pg/mL, $n = 19$ (2 patients had only PET PiB scan performed, 9 had only CSF biomarkers and 10 had both).

negative patients with aMCI who suffer from a chronic, non-progressive clinical condition, afflicting the patients virtually for decades. These patients maintain deficits in cognitive tests, mainly within the memory and learning domain, and certainly keep a high level of cognitive complaints that do not lessen in spite of the apparently benign or non-progressive clinical course of the disorder.

The patients recruited in the present study showed major deficits in verbal learning but many also had low performances in other memory tests compared to normative values, which represents an amnestic profile of cognitive deficits typical of patients with aMCI.[12,32,49] The diagnostic criteria for aMCI used in the present work correspond to the *comprehensive criteria* requiring that at least two performances within the memory domain fall below the established cut-off of 1 SD below the norms for age and education.[29] The comprehensive criteria represent a relatively stable diagnostic strategy, offering a good balance of sensitivity and specificity to detect impairment.[29] We could anticipate that stricter criteria for MCI, for instance requiring performances 1.5 SD below the norms, would recruit more severely affected patients carrying a higher risk of progression to AD, however, in the context of a memory clinic, the cut-off value of 1.5 SD could exclude subjects that from a clinical point of view suffer from MCI.[50]

Amyloid-negative, neurodegeneration-negative patients with aMCI showed at baseline a high level of cognitive complaints, compatible with the values of aMCI patients in previous studies.[51,52] Remarkably, they kept these high values during follow-up.

The biological basis for this subset of stable aMCI is presently not known. Certainly, the long-term clinical stability argues against the possibility that these patients might suffer from a neurodegenerative disorder. The existence of a psychiatric condition might be invoked, however patients with psychiatric disorders were excluded at the baseline, as well as one patient that developed major depression and another that had the diagnosis of bipolar disorder during the follow-up. Participants reported depressive symptoms as consistently described in clinical series of patients with aMCI, frequently conveying concerns about their cognitive symptoms and being afraid of progression to dementia.[53,54] Remarkably, patients maintained a high level of memory complaints in spite of a significant improvement in depressive symptoms. Furthermore, several patients were incidentally medicated with antidepressant drugs during the course of the disease with no apparent resolution of the cognitive complaints. A recent study found that amyloid-negative aMCI patients who convert to dementia show a brain age greater than their chronological age,[55] but it seems difficult to explain the cognitive deficits by premature ageing, particularly in subjects mostly in the late fifties and early sixties as in the present study. The diagnosis of Functional Cognitive Disorder[56] does not seem adequate either, inasmuch as the clinical symptoms and neuropsychological deficits are not internally inconsistent, or inconsistent along the follow-up. The possibility of a temporary condition attributable to circumstantial life factors is also unlikely considering the long duration of the symptoms. It should be noted that reversion from MCI to normality is more frequent in population-based studies and not as a much in clinical-based studies where patients

Table 3
Baseline and follow-up neuropsychological performances of amyloid-negative and neurodegeneration-negative aMCI patients

| Cognitive domain neuropsychological test | Baseline $n = 21$ $z$ score, mean (SD) | Follow-up $n = 21$ $z$ score, mean (SD) | Statistical significance $p^*$ |
|---|---|---|---|
| **Attention and executive functions** | | | |
| Cancellation task | –0.47 (0.9) | 0.28 (1.4) | 0.095 |
| Digit span backward | 0.28 (1.0) | 0.29 (1.4) | 0.846 |
| Trail making test A, time, s | –0.56 (1.8) | –0.86 (1.5) | 0.301 |
| Trail making test B, time, s | –0.72 (1.9) | –0.75 (1.1) | 0.098 |
| **Initiative** | | | |
| Motor initiative | –0.21 (1.6) | –0.27 (1.7) | 0.344 |
| Graphomotor initiative | 0.16 (0.76) | 0.35 (0.6) | 0.390 |
| **Reasoning** | | | |
| Raven colored progressive matrices | 0.39 (0.9) | –0.04 (1.1) | 0.085 |
| Interpretation of proverbs | 1.75 (1.6) | 1.83 (1.7) | 0.888 |
| **Orientation** | | | |
| Personal, spatial and temporal orientation | –0.72 (1.2) | –0.62 (1.9) | 0.327 |
| **Calculation** | | | |
| Basic written calculation | 1.00 (0.9) | 0.28 (0.8) | 0.764 |
| **Visuo-constructional abilities** | | | |
| Cube copy | 0.62 (1.1) | 0.83 (0.6) | 0.682 |
| Clock draw | –0.17 (1.3) | 0.17 (1.4) | 0.420 |
| **Language** | | | |
| Semantic fluency | 0.02 (1.4) | 0.35 (1.2) | 0.470 |
| **Memory and learning** | | | |
| Visual reproduction test | 0.51 (1.8) | 1.10 (1.1) | 0.308 |
| Digit span forward | 0.27 (1.1) | 0.73 (1.0) | 0.056 |
| Word recall | –0.81 (1.4) | –1.38 (1.2) | 0.152 |
| Logical memory – immediate recall | –0.99 (0.8) | –0.57 (1.1) | 0.066 |
| Logical memory – delayed recall | –0.71 (0.9) | –0.22 (1.1) | 0.012 ‡ |
| Verbal paired-associate learning | –0.34 (1.3) | –0.47 (1.4) | 0.623 |
| CVLT 5 trials total recall | –2.1 (1.2) | –1.9 (1.1) | 0.284 |

*two-tailed paired Student's $t$ test; ‡$p$ values < 0.05 were considered statistically significant, no correction for multiple comparisons was done; CVLT, California Verbal Learning Test.

undergo a detailed and comprehensive clinical evaluation.[57]

Amnestic MCI in the absence of biomarkers of amyloid pathology and biomarkers of neuronal lesion thus appears a chronic non-progressive condition, associated with a high level of cognitive complaints and deficits in cognition, mainly within the memory and learning domain. The patients should thus be clinically followed, and there is the need to find treatments to ameliorate them. In the context of memory clinics, and in the absence of known pharmacological therapies, a program of cognitive training, cognitive stimulation or cognitive rehabilitation is commonly proposed. However, we must realize that the principles and techniques behind these exercises were developed to help people with initial forms of AD or other dementing disorders[58] and might not be appropriate to the essentially stable aMCI patients. We advance that multicomponent sessions, namely composed of cognitive training, cognitive rehabilitation, psychoeducation and lifestyle intervention, as proposed in patients with subjective cognitive decline, that is, patients with cognitive complaints but no objective deficits,[59] as well as in older adults without cognitive impairment,[60] might be particularly suitable. The enhancement of coping strategies to deal with memory problems in daily life[61] seems realistic in such a long lasting clinical condition. Clinical

studies comparing the efficacy of distinct cognitive intervention approaches are certainly needed.

A word of caution is worthwhile. It was previously reported that amyloid negative aMCI patients may later manifest psychiatric conditions, or evolve to neurodegenerative disorders.[14,62] In the present study some patients were excluded for different disorders that usually became manifest within two to three years after the diagnosis. Thus, the absence of biomarkers of amyloid pathology and biomarkers of neuronal lesion does not guarantee a benign evolution in patients with aMCI. Even though no evidence for a neurological or psychiatric condition is apparent at the initial evaluation, patients with aMCI should be surveyed.

The present study has limitations regarding the small number of participants, and replication of the present findings in future studies is needed. We must acknowledge that the biological basis for aMCI not due to neurodegenerative or psychiatric conditions remains obscure. In any case, the recognition and characterization of a subgroup of amyloid-negative, neurodegeneration-negative patients with stable aMCI should be the first step to foster further clinical studies in this poorly understood condition. The major strengths of the present study are the long follow-up time, and the small number of patients lost to follow-up.

In conclusion, amyloid-negative, neurodegeneration-negative aMCI represents a chronic condition characterized by the long-term persistence of cognitive deficits and distressing memory complaints. Adequate strategies to treat this condition are needed.

## AUTHOR CONTRIBUTIONS

Alexandre de Mendonça (Conceptualization; Methodology; Supervision; Writing – original draft; Writing – review & editing); Sandra Cardoso (Data curation; Formal analysis); Manuela Guerreiro (Conceptualization; Investigation); Alexandre Montalvo (Writing – review & editing); Dina Silva (Writing – review & editing); Luísa Alves (Writing – review & editing).

## ACKNOWLEDGMENTS

The authors thank Memoclínica for the facilities provided.

## FUNDING

The authors have no funding to report.

## CONFLICT OF INTEREST

The authors have no conflict of interest to report.

## DATA AVAILABILITY

The data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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