Received: 8 July 2024 | Revised: 30 August 2024 | Accepted: 9 September 2024

DOI: 10.1002/dad2.70018

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Non-Alzheimer's amnestic mild cognitive impairment with medial temporal hypometabolism

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Abstract

INTRODUCTION: The increasing use of Alzheimer's disease (AD) biomarkers has led to the recognition of a subgroup of non-AD amnestic mild cognitive impairment (aMCI) patients who have medial temporal hypometabolism on fluorodeoxyglucose-positron emission tomography (FDG-PET).

METHODS: In this academic memory-clinic-based consecutive series, 16 non-AD aMCI patients and 28 AD controls matched for sex, age, and baseline Mini-Mental State Examination (MMSE) were followed for a median duration of 4.5 years. Our primary outcome was the MMSE decline rate over the subsequent years. We also determined the final diagnosis over time.

RESULTS: FDG-PET showed more pronounced medial temporal hypometabolism in non-AD cases and more inferior parietal lobule hypometabolism in AD controls. MMSE decline was slower in non-AD ($\beta = -0.51$) than in AD ($\beta = -2.00$) patients. Five non-AD cases developed frontotemporal dementia years after symptom onset, and one developed dementia with Lewy bodies.

DISCUSSION: Non-AD aMCI patients with medial temporal hypometabolism show slower cognitive decline.

KEYWORDS

amyloid biomarkers, cognitive decline, dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), medial temporal hypometabolism, neurodegenerative diseases, neuropsychological assessment, non-AD amnestic mild cognitive impairment (non-AD aMCI)

Highlights

- Non-AD aMCI with medial temporal hypometabolism shows slower cognitive decline than AD.
- FDG-PET revealed distinct metabolic patterns between non-AD aMCI and AD patients.

- Approximately one-third of non-AD aMCI cases developed frontotemporal dementia.
- Comprehensive diagnostic biomarkers are crucial for non-AD aMCI characterization.

1 | INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia and a leading source of morbidity and mortality in aging individuals, with prevalence rising from 0.2% to 0.9% at age 60–64 years old to 10.7%–13.1% in those aged 80–84 years.[1]

A diagnosis of amnestic mild cognitive impairment (aMCI) relies on subjective memory complaints confirmed by neuropsychological assessment, with other cognitive domains and instrumental activities of daily living remaining relatively intact.[2] Individuals diagnosed with aMCI have an annual conversion rate to dementia of approximately 10% (but up to 30%).[3,4] Although difficulties with delayed recall (i.e., an amnestic deficit), are commonly associated with AD,[5] this presentation can also be caused by non-AD pathologies.

The development of biomarkers has significantly advanced AD diagnosis by enabling in vivo detection of AD pathology in patients with aMCI. Interestingly, the application of these biomarkers in clinical settings has revealed a subset of aMCI patients without amyloid pathology, indicating they do not have AD.[6] A study found that about 50% of aMCI subjects had negative amyloid-PET scans.[7] Several studies have shown that the addition of amyloid-positron emission tomography (PET) imaging often leads to a change in diagnosis in patients who were initially clinically diagnosed with AD.[8,9] This subgroup, characterized by an amnestic syndrome, suggestive of hippocampal dysfunction, as seen with AD, but with negative AD biomarkers (lumbar puncture and/or amyloid-PET[10,11]) is termed non-AD amnestic syndrome, and can only be identified through negative AD biomarker results.

Previous studies found that amyloid-negative patients with aMCI do not show a cognitive decline over a period of 3 years,[12] or even more than a decade.[6] However, a large multicentric study found that 24% of amyloid-negative aMCI cases progressed to dementia within 3 years.[13]

While a negative amyloid status, indicating the absence of AD, is generally seen as good news,[14] it does not guarantee that patients with aMCI will not deteriorate, as some may develop neuropsychiatric conditions or progress to neurodegenerative disorders with dementia.

Within this subgroup of non-AD aMCI, diagnostic imaging using fluorodeoxyglucose (FDG)-PET may reveal medial temporal hypometabolism.[15–17] The subsequent clinical trajectory and ultimate diagnosis of this subgroup remain ill-defined. These diagnostic ambiguities often leave patients and families with unresolved questions when faced with a situation where an amnestic deficit is confirmed in the absence of AD.

In this study, we look at the non-AD (amyloid-negative) aMCI group (cases) with isolated medial temporal hypometabolism on FDG-PET and compare them to a control cohort with biomarker-proven AD in a prodromal or mild dementia stage (controls), matched for sex, age, and baseline Mini-Mental State Examination (MMSE).

The primary research questions are: Are there any between-group differences in the rate of cognitive decline, and secondly, what are the eventual diagnostic outcomes of the non-AD aMCI group? We also evaluated between-group differences in baseline cognitive profile and between-group differences in FDG-PET.

Overall, this investigation aims to enhance our understanding of non-AD, that is, amyloid-negative, aMCI by exploring its clinical evolution and providing a comparison with amyloid-positive/AD aMCI.

2 | METHODS

2.1 | Study design, data collection, and patient cohort

This retrospective study utilized electronic clinical records from UZ Leuven, Belgium, covering patients seen at the academic neurology memory clinic between February 2007 and May 2022.

The study included a consecutive series of non-AD aMCI cases, defined as patients with pure aMCI, confirmed by neuropsychological assessment and clinically compatible with prodromal AD, but with negative AD biomarkers (cerebrospinal fluid or amyloid-PET). Additional inclusion criteria were medial temporal hypometabolism on FDG-PET, follow-up of at least 6 months and at least three MMSE evaluations. None of the 16 non-AD aMCI cases had a history of epilepsy or were on antiepileptic drugs.

A database search identified 16 eligible patients. Their negative amyloid status was confirmed through normal cerebrospinal fluid (CSF) biomarkers (10 cases), normal brain amyloid PET scan (4 cases) or both (2 cases). The clinical-diagnostic procedure for determining biomarker negativity is detailed in the supplementary data, along with a table with the CSF biomarker concentrations for each case (Table S1). Data were extracted from outpatient visit reports, including age, sex, MMSE scores at baseline, and neuropsychological assessments. The follow-up period had a median duration of 4.5 years, ranging from 0.5 to 11 years.

Controls with amyloid biomarker-proven AD in a prodromal or mild dementia stage were selected from a prospective cohort study. From this cohort of 190 patients, 28 AD controls were matched for sex, baseline age and MMSE-scores with the non-AD aMCI cases. Amyloid-status was determined through CSF (19 cases), PET (7 cases), or both (2 cases). Of the 28 controls, 20 received an FDG-PET scan, with one excluded due to incomplete brain coverage. The follow-up period for controls had a median of 4.5 years, ranging from 2 to 14 years.

2.2 | Data acquisition

2.2.1 | Neuropsychological evaluation

Neuropsychological tests included Rey Auditory Verbal Learning Test (AVLT) total learning (TL) and free delayed recall (DR), Trail Making Test Ratio B/A (TMT B/A), Letter Verbal Fluency (LVF), Animal Verbal Fluency (AVF), and Boston Naming Test (BNT).

2.2.2 | FDG-PET

For detailed FDG-PET acquisition procedures, we refer to the Supplementary Appendix.

2.2.3 | Rate of cognitive decline

To evaluate the rate of cognitive decline, the longitudinal trajectories of MMSE scores, obtained on occasion of the clinical baseline and follow-up visits, were compared between the two groups, with median follow-up times of 4.5 years (see the statistical data analysis section).

2.2.4 | Eventual diagnostic outcome

We reviewed the final diagnostic outcomes, and – where available – *post mortem* data. We were particularly interested in which and how many cases received a diagnosis of a non-AD neurodegenerative disorder during follow-up. This was based on the diagnosis mentioned in the report of the last available outpatient visit at the memory clinic.

2.3 | Statistical data analysis

2.3.1 | Neuropsychological evaluation

Statistical analysis was performed using R (version 4.2.2). The statistical analysis process involved a systematic exploration to discern differences and associations between the cohort of 16 non-AD aMCI cases and the control group comprising 28 AD individuals for the first analysis. Shapiro–Wilk tests were used to examine the normality of continuous data. Continuous variables were compared using Welch's *t*-tests, if normally distributed, and using a non-parametric Mann–Whitney *U* test, if not. To obtain a comprehensive overview of potential variations in multiple neuropsychological assessment outcomes, a multivariate analysis of variance (MANOVA) was conducted. This approach facilitated a comparison of diverse dependent variables between the two groups.

RESEARCH IN CONTEXT

1. **Systematic review**: The literature was reviewed using traditional sources like PubMed, focusing on studies addressing non-Alzheimer's disease (AD) amnestic mild cognitive impairment (aMCI), fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging, and associated cognitive outcomes. Relevant citations are included to provide a comprehensive background.
2. **Interpretation**: Our findings suggest that non-AD aMCI with medial temporal hypometabolism progresses more slowly than AD-related aMCI. This subgroup also shows a significant likelihood of evolving into frontotemporal dementia.
3. **Future directions**: Future research should aim to identify specific biomarkers for early detection of non-AD aMCI subtypes. Longitudinal studies with larger cohorts and *post mortem* pathological confirmations are necessary to validate these findings and explore underlying mechanisms.

2.3.2 | Baseline FDG-PET

We evaluated the regional differences in hypometabolism between non-AD aMCI cases and AD aMCI controls. Between-group differences in FDG-PET tracer uptake were assessed through voxelwise comparisons of scaled FDG-PET images using two-sample *t*-tests in SPM12. Thresholded maps (voxel level $P_{uncorrected} < 0.001$, family wise error (FWE) corrected cluster level $P_{FWE} < 0.05$) were superimposed on the MNI152 template using the Nilearn package in Python (v3.9.13).

2.3.3 | Rate of cognitive decline

As a primary outcome objective, we evaluated differences in the longitudinal trajectories of MMSE between the two groups. To evaluate group differences in these MMSE trajectories, a Linear Mixed-effects (LME) model included random effects for subject and time and a group × time interaction term as predictor with MMSE score as outcome. Separate models for each group were also constructed, including random effects for subject and time with MMSE score as outcome. In these LME analyses, time was centered around the time of the baseline visit, and all LME models were corrected for age, sex, and baseline MMSE score.

As a sensitivity analysis, all analyses were repeated within a matched subset of 13 controls and cases chosen to ensure one-to-one matching of baseline MMSE scores. For the remaining three cases, there was no control counterpart with the exact same MMSE-score, and they were therefore excluded from the sensitivity analysis.

TABLE 1 Cohort demographics.

Parameter	Cases ($n = 16$)	AD controls ($n = 28$)	p-value
Sex, male/female, n (% male)	12/4 (75%)	20/8 (71%)	1.00
Age (IQR)	67.5 (10)	63.5 (10.5)	0.17
MMSE/30 (IQR)	28 (2.5)	27 (2.25)	0.12
Follow-up time in years (IQR)	4.45 (3.42)	4.52 (3.44)	0.87
AVLT TL (IQR)	35 (13.5)	38 (12)	0.61
AVLT DR (IQR)	0.52 (0.23)	0.56 (0.30)	0.46
TMT Ratio B/A (IQR)	2.17 (0.67)	2.10 (0.92)	0.84
LVF T (IQR)	29 (7.75)	35 (19.5)	0.72
AVF (IQR)	16 (4)	17.5 (8.5)	0.86
BNT (IQR)	54 (4.25)	54 (6)	0.95
ApoE genotype (n)			
Unknown	6	0	
E4/E4	0	6	
E4/E3	1	13	
E4/E2	1	0	
E3/E3	7	9	
E2/E3	1	0	
ApoE contingency table (n)			
E4 carriers	2	19	0.02
Non-E4 carriers	8	9	
E2 carriers	2	0	0.06
Non-E2 carriers	8	28	

Abbreviations: AD, Alzheimer's disease; ApoE, apolipoprotein E; AVF, Animal Verbal Fluency; AVLT, Rey Auditory Verbal Learning Test; BNT, Boston Naming Test; IQR, interquartile range; LVF, Letter Verbal Fluency; MMSE, Mini-Mental State Examination; TMT Ratio A/B, Trail Making Test Ratio B/A.

2.3.4 | Final diagnostic outcome

As the second outcome objective, we reported the final diagnostic outcome in the non-AD aMCI group in a descriptive manner.

3 | RESULTS

3.1 | Neuropsychological evaluation

Baseline characteristics for cases (i.e., amyloid-negative, non-AD, aMCI) and controls (i.e., amyloid-positive, AD in prodromal or mild dementia stage) are shown in Table 1. No significant difference in age, sex nor baseline MMSE (Figure 1) was found between the groups, as they were matched for these variables in this case-control design. AD controls did have a numerically lower baseline MMSE score than non-AD aMCI cases.

Baseline neuropsychological assessments did not significantly differ between non-AD cases and AD controls (Figure 2).

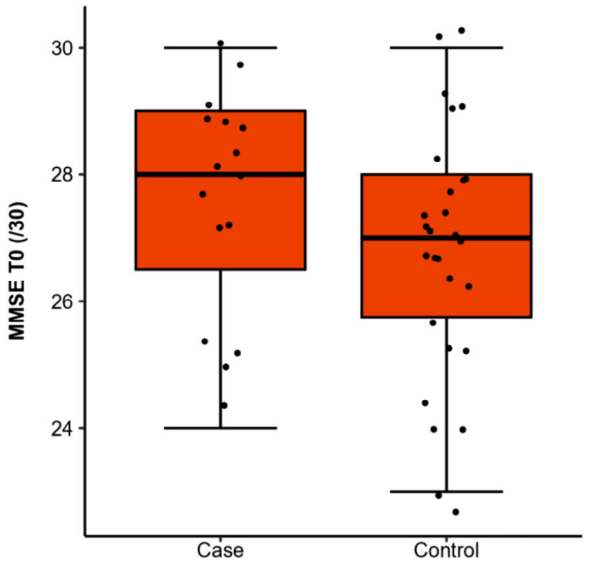

FIGURE 1 Baseline Mini-Mental State Examination (MMSE) of cases and controls.

Moreover, a MANOVA did not reveal a statistically significant global difference ($P > 0.99$) between cases and controls regarding the six cognitive tasks we used as dependent variables.

3.2 | Differences in FDG-PET hypometabolism

Figure 3 shows the areas in which tracer uptake differed between non-AD cases and AD controls. Non-AD cases had lower ^{18}F-FDG tracer uptake in bilateral medial temporal lobes, particularly within the hippocampus and parahippocampal gyrus (Figure S1). However, after FWE correction for multiple comparisons at the cluster level, only the medial temporal cluster within the right hemisphere ($P = 0.04$, $P_{uncorrected} = 0.01$) remained significant (left hemisphere: $P = 0.07$, $P_{uncorrected} = 0.02$). AD controls, on the other hand, demonstrated lower ^{18}F FDG tracer uptake in the inferior parietal lobule, particularly on the right side.

3.3 | Differences in rate of cognitive decline

Decreases in MMSE scores over time, independent of sex, age, and MMSE score at baseline, were observed for both AD ($\beta = -2.00$, 95% CI −2.54 to −1.46, $P < 0.001$) and non-AD ($\beta = -0.51$, 95% CI −0.75 to −0.27, $P = 0.002$) aMCI patients. The rate of MMSE decline was significantly higher in AD aMCI patients ($\beta(Group^{*}time) = -1.58$, 95% CI −2.29 to −0.76, $P < 0.001$) than in the non-AD group, as depicted in Figure 4. This means that the MMSE declined 2.00 points per year in the AD group, whereas it declined 0.5 points per year in the non-AD group.

To further ensure that the observed difference in MMSE progression rates was not biased by the numerically, albeit not significantly,

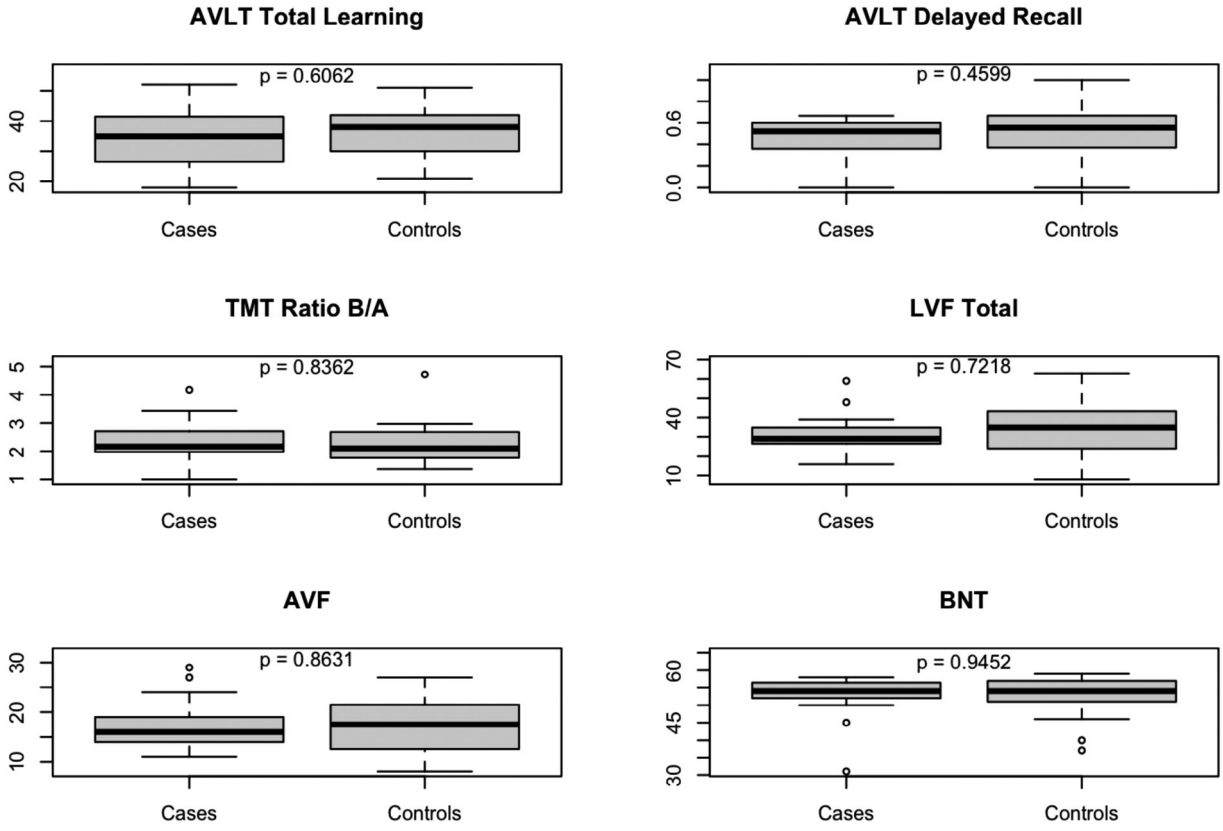

FIGURE 2 Boxplots of cognitive tests in both groups.

lower baseline MMSE score in AD controls compared to non-AD cases, we also conducted a sensitivity analysis in 13 non-AD aMCI cases and 13 AD controls who were matched for baseline MMSE score. Demographics of this subset are shown in the Table S2. No significant differences were found for age and sex, proving they were matched correctly. Baseline neuropsychological assessments did not significantly differ between both groups. So again, we did not find any significant differences between cases and controls in any of the tested cognitive measures, proving the identical baseline phenotype between both groups. This sensitivity analysis similarly showed a significantly faster MMSE-decline in the AD control group ($\beta(Group^{*}time) = -1.53$, 95% CI −2.35 to −0.71, $P = 0.001$) compared to the non-AD aMCI patients (Figure S2).

3.4 | The final diagnostic outcomes in non-AD aMCI patients

We reviewed the final diagnostic outcomes of the 16 cases in a descriptive manner. We were particularly interested in how many cases evolved into a clinical picture corresponding to a non-AD neurodegenerative cognitive disorder. Of the 16 cases, eight cases remained unspecified (i.e., non-AD amnestic deficit). No baseline variable differences were seen between the subgroup with a subsequent diagnosis and those that remained unexplained (Table 2).

Five of the 16 cases were diagnosed with bvFTD during follow-up, including two clinically probable and three definite cases (average follow-up: 6.8 years, range 4.1–10.9 years).

In one probable case, behavioral symptoms appeared 1 year after the memory complaints, fulfilling the criteria of possible bvFTD. Because of further progressive behavioral complaints (disinhibition, apathy, binge eating) over the following years, a new FDG-PET was performed, which confirmed progressive hypometabolism in the right temporal and left frontal cortex, after which the diagnosis of probable bvFTD was made.

The other probable case developed behavioral symptoms 3 years after the amnestic deficit. An FDG-PET confirmed bitemporal hypometabolism, leading to a probable bvFTD diagnosis.

Of the three definite cases, one had a MAPT mutation (p.406 W) diagnosed after behavioral complaints emerged 8 years after the amnestic complaints. This patient had a familial history of dementia with a modified Goldmann score[18] of 1. The second had a C9orf72 mutation with behavioral symptoms 7 years after the initial amnestic syndrome. A new FDG-PET showed striking hypometabolism in the right frontal cortex. There was no familial history (the father died at a young age), and there were no upper or lower motor symptoms at the last consultation. The third developed behavioral symptoms more than 10 years after the amnestic deficit, with an FDG-PET not indicative of a specific neurodegenerative disorder. This patient died 3 years later. An autopsy revealed FTLD-TDP43 type C pathology. In all bvFTD

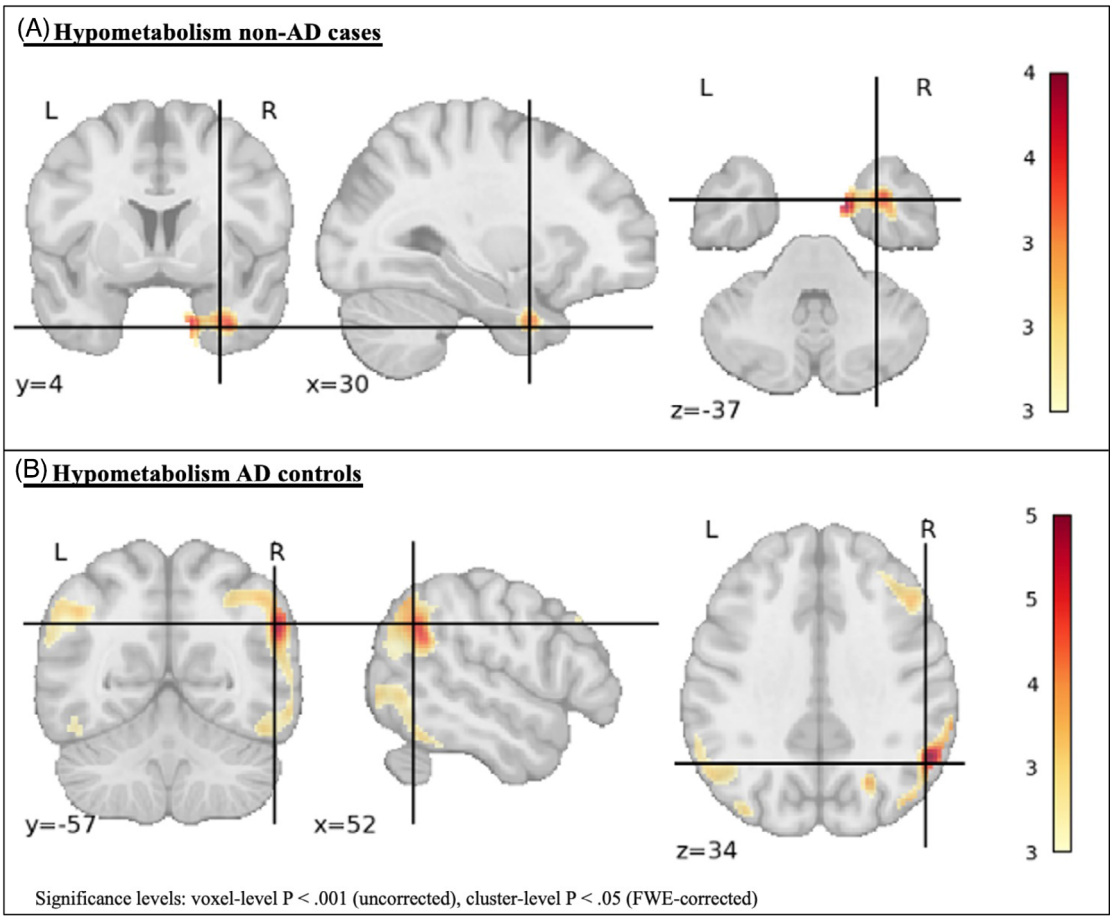

FIGURE 3 FDG-PET analysis, adjusted for covariates age and sex, showing areas with more pronounced hypometabolism compared between both groups. (A) Non-AD cases show more hypometabolism in the medial temporal lobe. (B) AD controls show more hypometabolism in the parietal lobe. AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose-positron emission tomography.

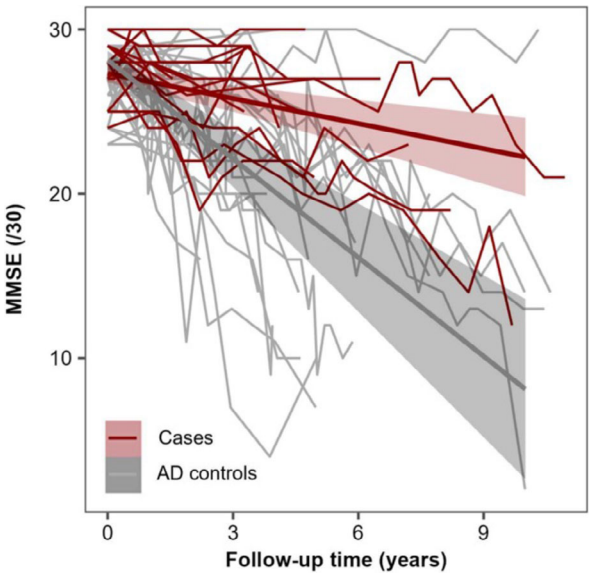

FIGURE 4 MMSE-decline over time in both groups, corrected for baseline MMSE. The rate of MMSE decline was significantly higher in AD aMCI patients ($\beta = -2.00$, $P < 0.001$) than in the non-Alzheimer disease (non-AD) group ($\beta = -0.51$, $P < 0.01$). AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; MMSE, Mini-Mental State Examination.

patients, behavioral symptoms arose several years after the initial presentation.

In one case, extrapyramidal symptoms arose one and a half years after the initial presentation at the memory clinic. This case fulfilled the criteria for (probable) dementia with Lewy bodies (DLB), according to the McKeith 2017 international consensus criteria.[19]

One case was classified as vascular dementia, with Fazekas 3 on the initial MRI scan. None of the other cases had a Fazekas higher than 2 at initial presentation (five cases had Fazekas 0, four cases Fazekas 1, two cases Fazekas 2, four cases did not undergo an MRI due to incompatible devices).

One case turned out to have sleep-/stress-related memory complaints, which were resolved after the patient started an SSRI. On the last consultation, this patient had an MMSE score of 30/30, after which follow-up was discontinued. However, it is important to note that the follow-up period for this case was only 7 months.

4 | DISCUSSION

This study enhances our understanding of non-AD aMCI with medial temporal hypometabolism by comparing its clinical evolution to

TABLE 2 demographics and baseline characteristics of cases with and without final diagnosis.

Parameter	Cases with diagnosis ($n = 8$)	Cases without diagnosis ($n = 8$)	p-value
Sex, male/female, *n* (% male)	7/1 (87.5%)	5/3 (62.5%)	0.56
Age (IQR)	68 (10.75)	67.5 (7.75)	0.83
MMSE/30 (IQR)	28 (2.75)	28 (1.0)	0.79
Follow-up time in years (IQR)	4.67 (1.88)	3.35 (3.51)	0.38
AVLT TL (IQR)	33 (15.75)	35 (8)	0.71
AVLT DR (IQR)	0.5 (0.17)	0.55 (0.27)	0.92
TMT RBA (IQR)	2.35 (0.92)	2.09 (0.34)	0.44
LVF T (IQR)	29 (6.25)	28 (7.75)	0.56
AVF (IQR)	16.5 (11.25)	15.5 (1.5)	0.63
BNT (IQR)	55.5 (6.75)	53.5 (1.5)	0.53

Abbreviations: AD, Alzheimer's disease; ApoE, apolipoprotein E; AVF, Animal Verbal Fluency; AVLT, Rey Auditory Verbal Learning Test; BNT, Boston Naming Test; IQR, interquartile range; LVF, Letter Verbal Fluency; MMSE, Mini-Mental State Examination; TMT Ratio A/B, Trail Making Test Ratio B/A.

amyloid positive aMCI patients with the same clinical phenotype. It is among the first to compare cognitive decline rates and FDG-PET patterns between these groups.

We found a slower MMSE decline in the non-AD aMCI group compared to AD aMCI. Notably, 5 of 16 non-AD cases evolved into a bvFTD phenotype over several years. One case developed DLB, with as initial manifestation non-AD aMCI.

The neuropsychological assessment included the Auditory Verbal Learning Test (AVLT) to detect episodic memory impairment, the earliest and most prominent feature of AD or aMCI.[20] AVLT is a sensitive measure for early AD diagnosis and a valid predictor of conversion from MCI to AD.[21] The assessment also included tests for attention, visuomotor processing, executive function, semantic memory, and language. Previous studies showed Aβ positive aMCI patients score worse on episodic memory,[7,22–24] while Aβ negative aMCI patients perform worse on non-episodic memory domains.[22] We found no baseline differences, indicating proper matching and an indistinguishable cognitive phenotype at baseline. The difference with prior studies can be explained by the medial temporal hypometabolism as an inclusion criterion in our cohort.

In AD, FDG-PET hypometabolism of the bilateral parietotemporal association cortex, has demonstrated a sensitivity of 94% and a specificity of 73% with post-mortem histopathological validation.[25,26] FDG-PET also has been recognized as one of the most accurate biomarkers in MCI, predicting clinical stability or conversion to AD dementia.[15] Limited but important evidence shows that aMCI patients with focal hypometabolism in the medial temporal lobe structures, alongside a negative amyloid load, show a more benign clinical course.[5,15,16,27,28] In AD, the subtype where hypometabolism is limited to the medial temporal cortex has been labeled limbic-predominant AD. As we demonstrate, biomarkers are key to the differentiation between AD and non-AD when isolated medial temporal hypometabolism is seen in aMCI.

In this retrospectively analyzed cohort, it was clearly shown that the amyloid-negative aMCI group with medial temporal hypometabolism has a significantly slower cognitive decline compared to amyloid positive AD-controls. This is a consistent finding with previous studies.[5,6,15,16]

4.1 | Pure amnestic presentation of bvFTD

The cognitive profile of bvFTD typically involves executive deficits with relative sparing of episodic memory.[29] However, some bvFTD patients may present with memory complaints and lower scores in episodic memory tests.[30] The emphasis on preserved episodic memory in the current bvFTD criteria,[29] as it was believed to enable effective differentiation from AD, may need to be revised, given the substantial proportion of amnesic-bvFTD patients.[31]

Current international consensus criteria for bvFTD by Rascovsky et al.[29] state that behavioral symptoms must appear "early", that is, within the first 3 years. This arbitrary cutoff seems suboptimal, as our study shows FTD can present with a pure amnestic deficit, with behavioral symptoms emerging up to 10 years later.

One definite bvFTD patient had a MAPT p.R406W mutation, often linked to an AD-like phenotype.[32] A recent paper[33] showed a duality and heterogeneity in the clinical presentation of p.R406W patients on an FTD-AD spectrum. The second definite bvFTD patient had a C9orf72 mutation. Atypical amnestic presentations of the C9orf72-FTD/ALS spectrum can mimic other neurodegenerative diseases like AD.[34,35] The third definite bvFTD patient developed behavioral symptoms after more than 10 years. An autopsy revealed FTLD-TDP43 type C pathology, defined by a predominance of elongated dystrophic neurites (DNs) in upper cortical layers with few neuronal cytoplasmic inclusions (NCIs).[36] This subtype is associated with severe anterior temporal atrophy and semantic dementia, though bvFTD can also occur.[36–38] We found no literature on FTLD-TDP type C presenting with an amnestic deficit. The uncertainty of clinical diagnosis underscores the need for reliable, sensitive, and more specific in vivo biomarkers for TDP-43 proteinopathies.[39]

4.2 | Underlying etiology and neuropathology

Several underlying non-AD (Aβ negative) etiologies have been proposed as possible neuropathological causes of aMCI with a more slowly progressive course.[15] The heterogeneous biomarker-based concept called suspected non-AD pathology (SNAP)[40,41] is characterized by neurodegeneration without amyloid deposition. Possible pathological substrates include limbic-predominant age-related TDP-43 encephalopathy (LATE), primary age-related tauopathy (PART), hippocampal sclerosis (HS), and argyrophilic grain disease (AGD). Currently, it is not possible to reliably diagnose LATE, PART, or AGD in vivo.

LATE is an underrecognized disease entity, described in elderly people with episodic memory impairments, and frequently co-occurs with neuropathologically defined AD.[27] Its hallmark is deposits of abnormal, phosphorylated, and mislocalized TDP-43 in limbic brain structures, with or without coexisting HS pathology.[42–44] PART is a tauopathy defined by AD-type neurofibrillary tangles (NFTs) mostly restricted to medial temporal lobe structures, without (or with few) Aβ plaques.[45] AGD is a late-onset, highly frequent sporadic tauopathy, characterized by argyrophilic grains and neuronal pre-tangles, spreading throughout the limbic system.[46,47] AGD usually affects elderly subjects and manifests as very slowly progressive aMCI, often with behavioral abnormalities.[47] HS has been suggested as a main cause of memory loss in patients with aMCI and slow progression. HS refers to severe neuronal loss and astrogliosis of CA1 and/or subiculum. Most elderly people with HS have TDP-43 pathology.[48]

Vascular cognitive impairment (VCI) predominantly involves deficits in executive functioning, due to subcortical vascular pathology interrupting frontostriatal circuits, with less memory impairment than AD.[49] However, cognitive changes in VCI are more variable, and subjects with VCI can present with broader cognitive impairment, including memory deficits.[50] Mild cognitive impairment with Lewy bodies typically starts with a dysexecutive syndrome rather than an amnestic deficit. As our study indicates, a pure amnestic deficit can be the initial presentation of vascular cognitive impairment or Lewy body disease, although FTLD was the leading cause in our series.

4.3 | Strengths and clinical implications

Our study has several strengths. It is one of the first studies to compare the rate of cognitive decline between non-AD aMCI with medial temporal hypometabolism and AD patients, and to compare the FDG-PET patterns between these two groups.

As there is a need to give a more precise prognosis in the aMCI population, the slower rate of cognitive decline in this subgroup of aMCI patients is clinically relevant. The specific neuronal dysfunction involving medial temporal lobes, as shown by ^{18}F-FDG-PET, can be considered a clinically useful biomarker for aMCI due to neurodegenerative disease beyond AD. It is important that AD biomarker negative aMCI patients also receive follow-up, in particular if medial temporal hypometabolism is present on FDG-PET, as a considerable proportion evolves into a bvFTD or DLB phenotype.

4.4 | Limitations

Our study has several limitations. This was a retrospective study with a relatively small sample size. In cases without a genetic or neuropathological definite diagnosis, the study design assumes that the clinical-neurological course illuminates the syndrome's cause at presentation. However, without neuropathological confirmation, one cannot exclude that the original syndrome had a separate cause from symptoms arising over the subsequent years, due to co-pathology. Lastly, the exclusion of AD in non-AD aMCI relies on the sensitivity of the biomarker method used in the clinic, determined by the standardized procedures and specific thresholds balancing sensitivity and specificity. If we adapt the total tau and ^{181}phosphotau CSF cut-offs for maximal sensitivity, two of the cases had total tau and ^{181}phosphotau value above threshold, all with Aβ_{42} or Aβ_{42}/Aβ_{40} well within the normal range. However, maximizing sensitivity comes at the cost of specificity.

5 | CONCLUSION

In conclusion, amyloid-negative or non-AD aMCI patients with medial temporal hypometabolism show a significantly slower cognitive decline compared to their amyloid-positive counterparts. Approximately one-third of these cases were caused by frontotemporal lobar degeneration, while half of the cases remained unexplained during their lifetime. The findings underscore the complexity of aMCI aetiology with medial temporal hypometabolism and the importance of comprehensive diagnostic biomarkers. Future studies with neuropathological verification are needed to confirm our findings and further characterize this subgroup of aMCI.

ACKNOWLEDGMENTS

The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting information.

CONSENT STATEMENT

This study was approved by the Ethics Committee Research UZ/KU Leuven (MP021477).

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REFERENCES

1. Dementia in Europe yearbook. Estimating the prevalence of dementia in Europe. Alzheimer Europe; 2019.
2. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E, Mild cognitive impairment: clinical characterization and outcome [published correction appears in Arch Neurol 1999 Jun;56(6):760]. *Arch Neurol*. 1999;56(3):303-308.
3. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia – meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr Scand*. 2009;119:252-265.
4. Schmidtke K, Hermeneit S. High rate of conversion to Alzheimer's disease in a cohort of amnestic MCI patients. *Int Psychogeriatr*. 2008;20:96-108.
5. Cerami C, Dodich A, Iannaccone S, et al. A biomarker study in long-lasting amnestic mild cognitive impairment. *Alzheimers Res Ther*. 2018;10:42.
6. Cardoso S, Silva D, Alves L, Guerreiro M, de Mendonça A. The outcome of patients with amyloid-negative amnestic mild cognitive impairment. *J Alzheimers Dis*. 2022;86:629-640.
7. Wang Y, Lou F, Li Y, et al. Clinical, neuropsychological, and neuroimaging characteristics of amyloid- positive vs. amyloid-negative patients with clinically diagnosed Alzheimer's disease and amnestic mild cognitive impairment. *Curr Alzheimer Res*. 2021;18:523-532.
8. Boccardi M, Altomare D, Ferrari C, et al. Assessment of the incremental diagnostic value of Florbetapir F 18 imaging in patients with cognitive impairment: the incremental diagnostic value of amyloid PET with [18F]-Florbetapir (INDIA-FBP) study. *JAMA Neurol*. 2016;73:1417-1424.
9. Rabinovici GD, Gatsonis C, Apgar C, et al. Association of amyloid positron emission tomography with subsequent change in clinical management among medicare beneficiaries with mild cognitive impairment or dementia. *JAMA* 2019;321:1286-1294.
10. Olsson B, Lautner R, Andreasson U, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *Lancet Neurology*. 2016;15:673.
11. Leuzy A, Chiotis K, Hasselbalch SG, et al. Pittsburgh compound B imaging and cerebrospinal fluid amyloid-β in a multicentre European memory clinic study. *Brain*. 2016;139:2540-2553.
12. Lim YY, Maruff P, Pietrzak RH, et al. Effect of amyloid on memory and non-memory decline from preclinical to clinical Alzheimer's disease. *Brain*. 2014;137:221-231.
13. Vos SJ, Verhey F, Frölich L, et al. Prevalence and prognosis of Alzheimer's disease at the mild cognitive impairment stage. *Brain*. 2015;138:1327-1338.
14. Silva D, Cardoso S, Guerreiro M, et al. Neuropsychological contribution to predict conversion to dementia in patients with mild cognitive impairment due to Alzheimer's disease. *Journal of Alzheimer's Disease*. 2020;74:785-796.
15. Tondo G, Carli G, Santangelo R, et al. Biomarker-based stability in limbic-predominant amnestic mild cognitive impairment. *Eur J Neurol*. 2021;28:1123-1133.
16. Caminiti SP, De Francesco S, Tondo G, et al. FDG-PET markers of heterogeneity and different risk of progression in amnestic MCI. *Alzheimers Dement*. 2023;20(1):159-172. doi:10.1002/alz.13385
17. Nordberg A, Rinne JO, Kadir A, Långström B. The use of PET in Alzheimer disease. *Nat Rev Neurol*. 2010;6:78-87.
18. Rohrer JD, Guerreiro R, Vandrovcova J, et al. The heritability and genetics of frontotemporal lobar degeneration. *Neurology*. 2009;73:1451-1456.
19. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies. *Neurology*. 2017;89:88-100.
20. Zhao Q, Guo Q, Liang X, et al. Auditory verbal learning test is superior to Rey-Osterrieth complex figure memory for predicting mild cognitive impairment to Alzheimer's disease. *Curr Alzheimer Res*. 2015;12:520-526.
21. Zhao Q, Lv Y, Zhou Y, Hong Z, Guo Q. Short-term delayed recall of auditory verbal learning test is equivalent to long-term delayed recall for identifying amnestic mild cognitive impairment. *PLoS One*. 2012;7:e51157.
22. Tomadesso C, de La Sayette V, de Flores R, et al. Neuropsychology and neuroimaging profiles of amyloid-positive versus amyloid-negative amnestic mild cognitive impairment patients. *Alzheimers Dement (Amst)*. 2018;10:269-277.
23. Landau SM, Horng A, Fero A, Jagust WJ. Amyloid negativity in patients with clinically diagnosed Alzheimer disease and MCI. *Neurology*. 2016;86:1377-1385.
24. Alves L, Cardoso S, Silva D, et al. Neuropsychological profile of amyloid-positive versus amyloid-negative amnestic Mild Cognitive Impairment. *J Neuropsychol* 2021;15(Suppl 1):41-52.
25. Silverman DHS, Small GW, Chang CY, et al. Positron emission tomography in evaluation of dementia: regional brain metabolism and long-term outcome. *JAMA*. 2001;286:2120-2127.
26. Hoffman JM, Welsh-Bohmer KA, Hanson M, et al. FDG PET imaging in patients with pathologically verified dementia. *J Nucl Med*. 2000;41:1920-1928.
27. Nelson PT, Dickson DW, Trojanowski JQ, et al. Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. *Brain*. 2019;142:1503-1527.
28. Marra C, Villa G, Quaranta D, Valenza A, Vita MG, Gainotti G. Probable Alzheimer's disease patients presenting as "focal temporal lobe dysfunction" show a slow rate of cognitive decline. *J Int Neuropsychol Soc*. 2012;18(1):144-150.
29. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134:2456-2477
30. Bussè C, Zorzi G, Pettenuzzo I, Mozzetta S, Cagnin A Episodic memory in amnestic behavioral frontotemporal dementia and Alzheimer's disease. *J Alzheimers Dis Rep*. 2023;7:605-612.
31. Macchitella L, Tosi G, Giaquinto F, et al. Genuine memory deficits as assessed by the free and cued selective reminding test (FCSRT) in the behavioural variant of frontotemporal dementia. a systematic review and meta-analysis study. *Neuropsychol Rev*. 2023. doi:10.1007/s11065-023-09613-3
32. Ygland E, van Westen D, Englund E, et al. Slowly progressive dementia caused by MAPT R406W mutations: longitudinal report on a new kindred and systematic review. *Alzheimers Res Ther* 2018;10:2.
33. Gossye H, Van Mossevelde S, Sieben A, et al. Patients carrying the mutation p.R406W in MAPT present with non-conforming phenotypic spectrum. *Brain* 2023;146:1624-1636.
34. Harms M, Benitez BA, Cairns N, et al. C9orf72 hexanucleotide repeat expansions in clinical alzheimer disease. *JAMA Neurol*. 2013;70:736-741.
35. Gossye H, Engelborghs S, Van Broeckhoven C, van der Zee J. *C9orf72 Frontotemporal Dementia and/or Amyotrophic Lateral Sclerosis*. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. GeneReviews: University of Washington; 2015.
36. Neumann M, Mackenzie IRA. Review: neuropathology of non-tau frontotemporal lobar degeneration. *Neuropathol Appl Neurobiol* 2019;45:19-40.
37. Perry DC, Brown JA, Possin KL, et al. Clinicopathological correlations in behavioural variant frontotemporal dementia. *Brain*. 2017;140:3329-3345.
38. Kawles A, Nishihira Y, Feldman A, et al. Cortical and subcortical pathological burden and neuronal loss in an autopsy series of FTLD-TDP-type C. *Brain*. 2022;145:1069-1078.
39. König T, Wurm R, Parvizi T, et al. C9orf72 repeat length might influence clinical sub-phenotypes in dementia patients. *Neurobiol Dis*. 2022;175:105927.

40. Jack CR Jr, Knopman DS, Chételat G, et al. Suspected non-Alzheimer disease pathophysiology – concept and controversy. *Nat Rev Neurol* 2016;12:117-124.
41. Vos SJB, Delvenne A, Jack CR, Thal DR, Visser PJ The clinical importance of suspected non-Alzheimer disease pathophysiology. *Nat Rev Neurol*. 2024;20:337-346. doi:10.1038/s41582-024-00962-y
42. Grothe MJ, Moscoso A, Silva-Rodríguez J, et al. Differential diagnosis of amnestic dementia patients based on an FDG-PET signature of autopsy-confirmed LATE-NC. *Alzheimers Dement*. 2023;19:1234-1244.
43. Grothe MJ, Silva-Rodríguez J, Moscoso A, Schöll M Clinical and biomarker characteristics of amnestic MCI patients exhibiting a temporo-limbic FDG-PET pattern suggestive of LATE. *Alzheimers Dement*. 2023;19.
44. Corriveau-Lecavalier N, Botha H, Graff-Radford J, et al. A limbic-predominant amnestic neurodegenerative syndrome associated with TDP-43 pathology. *medRxiv*. 2023.
45. Crary JF, Trojanowski JQ, Schneider JA, et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. *Acta Neuropathol* 2014;128:755-766.
46. Ferrer I, Santpere G, Van Leeuwen FW. Argyrophilic grain disease. *Brain*. 2008;131:1416-1432.
47. Rodriguez RD, Grinberg LT. Argyrophilic grain disease: an underestimated tauopathy. *Dement Neuropsychol*. 2015;9:2-8.
48. Nag S, Yu L, Wilson RS, Chen EY, Bennett DA, Schneider JA. TDP-43 pathology and memory impairment in elders without pathologic diagnoses of AD or FTLD. *Neurology*. 2017;88:653-660.
49. O'Brien JT, Thomas A. Vascular dementia. *Lancet* 2015;386(10004):1698-1706.
50. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia. *Stroke* 2011;42:2672-2713.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: De Keersmaecker S, De Meyer S, Vandenberghe R. Non-Alzheimer's amnestic mild cognitive impairment with medial temporal hypometabolism. *Alzheimer's Dement*. 2024;16:1–10. https://doi.org/10.1002/dad2.70018