Heterogeneity of Brain Glucose Metabolism in Mild Cognitive Impairment and Clinical Progression to Alzheimer Disease

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Background: Subjects with amnesic mild cognitive impairment (aMCI) may include patients at high risk for progression to Alzheimer disease (AD) and a population with different underlying pathologic conditions.

Objective: To evaluate the potential roles of positron emission tomography with fluodeoxyglucose F 18 (18FDG-PET) and memory scores in identifying subjects with aMCI and in predicting progression to dementia.

Design, Setting, and Patients: Sixty-seven patients at European centers for neurologic and AD care who were diagnosed as having aMCI each underwent an extensive clinical and neuropsychological examination and an 18FDG-PET study. Forty-eight subjects were followed up periodically for at least 1 year, and progression to dementia was evaluated.

Main Outcome Measures: Brain glucose metabolism and memory scores.

Results: Fourteen subjects with aMCI who converted to AD within 1 year showed bilateral hypometabolism in the inferior parietal, posterior cingulate, and medial temporal cortex. Subjects with “stable” aMCI presented with hypometabolism in the dorsolateral frontal cortex. The severity of memory impairment, as evaluated by the California Verbal Learning Test–Long Delay Free Recall scores, correlated with the following brain metabolic patterns: scores less than 7 were associated with a typical 18FDG-PET AD pattern, and scores of 7 or higher were associated with hypometabolism in the dorsolateral frontal cortex and no progression to AD.

Conclusion: These data provide evidence for clinical and functional heterogeneity among subjects with aMCI and suggest that 18FDG-PET findings combined with memory scores may be useful in predicting short-term conversion to AD.

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Mild cognitive impairment (MCI) is a diagnostic entity used to describe defective memory performances that do not fulfill the criteria for dementia. Mild cognitive impairment includes incipient Alzheimer disease (AD) and other causes of dementia, as well as a form of cognitive impairment that does not progress to dementia and may disappear. This entity has been redefined to include amnesic MCI (aMCI) and nonamnesic MCI, according to the presence of an isolated objective memory deficit or of multiple or isolated extramemory cognitive impairment. This variation in MCI has been evaluated using neuroimaging and biologic markers. Results of clinical studies have suggested that neuropsychological tests, especially those evaluating delayed recall, might play an important role in identifying early or preclinical AD among subjects with MCI. These studies, however, were conducted among small groups of subjects.

Herein, we report data from a clinical and positron emission tomography with fluorodeoxyglucose F 18 (18FDG-PET) assessment within a large multicenter study of subjects with aMCI. The objectives of this study were to evaluate whether 18FDG-PET can differentiate subjects with aMCI from healthy control subjects, to assess functional metabolic patterns in aMCI that might predict different clinical progressions, and to investigate the role of combining
Amnesic MCI was diagnosed using the Mayo Clinic criteria.1

Scale.10

an individual level.18FDG-PET findings and memory scores in predicting conversion to AD at the

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ontary ethics committees, and all participants provided written in-

\(\text{Table. Demographic and Clinical Characteristics of the Study Subjects at Baseline}^*\)

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\begin{array}{lcccccc}
\text{Characteristic} & \text{Control Subjects (n = 41)} & \text{Total (n = 67)} & \text{Dropouts (n = 19)} & \text{Nonconverters (n = 34)} & \text{Converters (n = 14)} & \text{P Value}\tabularnewline
\hline
\text{Male-female ratio} & 18/23 & 34/33 & 9/10 & 20/14 & 5/9 & .15\†\tabularnewline
\text{Age, y} & 59.6±5.7 & 67.7±8.3 & 70.1±8.3 & 65.0±9.0 & 71.1±3.9 & .05\tabularnewline
\text{Educational level, y} & 13.8±3.1 & 11.0±4.7 & 12.2±4.8 & 11.2±4.5 & 9.1±5.0 & .17\tabularnewline
\text{Duration of aMCI, mo} & \ldots & 25.5±15.5 & 29.7±19.2 & 24.5±17.0 & 22.7±11.0 & .71\tabularnewline
\text{Mini-Mental State Examination score} & >24 & 27.7±1.7 & 27.2±2.3 & 28.4±1.1 & 26.6±1.7 & .001\tabularnewline
\text{California Verbal Learning Test–Long Delay Free Recall test score} & 12.1±3.2 & 5.6±4.0 & 5.1±3.9 & 6.9±4.0 & 3.0±3.0 & .05\tabularnewline
\hline
\text{Copy} & 32.2±4.0 & 32.3±4.1 & 32.3±4.6 & 33.3±2.6 & 30.0±5.8 & .01\tabularnewline
\text{Delayed recall} & 16.7±11.8 & 11.0±7.5 & 8.4±7.4 & 14.4±6.7 & 6.0±5.7 & .001\tabularnewline
\text{Digit Span Distractibility Test score} & 6.9±1.7 & 6.7±1.7 & 6.7±1.9 & 6.9±1.8 & 6.4±1.5 & .37\tabularnewline
\text{Visual Span} & \ldots & 6.9±1.4 & 6.8±1.7 & 6.9±1.3 & 6.7±1.6 & .49\tabularnewline
\text{Trail-Making Test, s} & A & <93 & 56.5±35.2 & 57.4±32.2 & 53.0±37.5 & 62.9±35.2 & .35\tabularnewline
\text{Stroop Color-Word Test, score} & 21.5±5.5 & 20.1±18.8 & 31.2±24.2 & 24.7±12.2 & 37.1±22.0 & .05\tabularnewline
\text{Mental Control score} & 6.6±1.9 & 5.5±0.8 & 5.4±0.8 & 5.5±0.8 & 5.6±0.6 & .60\tabularnewline
\text{Token Test, No. of errors} & 1.3±1.6 & 2.6±2.6 & 2.9±3.9 & 2.1±1.8 & 3.2±2.4 & .11\tabularnewline
\text{Semantic fluency, score} & \ldots & 16.2±4.9 & 15.6±5.1 & 17.9±4.8 & 13.0±2.5 & .001\tabularnewline
\text{Phonological fluency score} & 29.1±10.9 & 34.2±11.8 & 33.2±13.8 & 35.3±9.9 & 31.1±13.2 & .63\tabularnewline
\text{Boston Naming Test, score} & \ldots & 58.39±3.3 & 58.1±3.5 & 58.6±2.8 & 58.3±4.2 & .77\tabularnewline
\end{array}
\]

Abbreviation: aMCI, amnestic mild cognitive impairment.

*Data are given as mean ± SD unless otherwise indicated.

†Test between aMCI nonconverters and aMCI converters, Pearson product-moment correlation.

‡Test between aMCI dropouts and aMCI nonconverters.

§χ² Test between aMCI nonconverters and aMCI converters unless otherwise indicated.

\(18\text{FDG-PET findings and memory scores in predicting conversion to AD at the individual level.}\)

METHODS

SUBJECTS

Sixty-seven right-handed subjects with aMCI (34 men and 33 women; mean ± SD age, 67.7 ± 8.4 years) and 41 healthy controls (18 men and 23 women; mean ± SD age, 59.6 ± 5.7 years) were enrolled in the study. They were selected at 4 participating centers enrolled in the Network for Efficiency and Standardization of Dementia Diagnosis Fifth European Framework Research Project. The research was approved by the local ethics committees, and all participants provided written informed consent. The controls were interviewed and assessed for cognitive dysfunction.

All subjects underwent a somatic and neurologic examination, routine laboratory tests, a multidimensional neuropsychological assessment, a brain structural imaging study (computed tomography or magnetic resonance imaging), and an 18FDG-PET scan. Amnestic MCI was diagnosed using the Mayo Clinic criteria.1 Behavioral disorders and depression were excluded by the Neuropsychiatric Inventory9 and by the Hamilton Depression Rating Scale.10

Forty-eight subjects with aMCI were followed up every 6 to 7 months for at least 1 year (median follow-up, 12 months; follow-up range, 12-27 months). At follow-up, subjects were diagnosed as having stable aMCI (aMCI nonconverters) or as having converted to AD (aMCI converters) on the basis of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria.11

NEUROPSYCHOLOGICAL ASSESSMENT

The global severity of cognitive impairment was measured by the Mini-Mental State Examination12 and by the Washington University Clinical Dementia Rating scale.13 All patients underwent the extensive neuropsychological Network for Efficiency and Standardization of Dementia Diagnosis battery (Table).14

The California Verbal Learning Test (CVLT)15 was administered at all participating centers, and long-term memory was assessed by different methods at the centers. The test results provided an in-depth evaluation of memory to assess the diagnosis of aMCI.

\(18\text{FDG-PET DATA ACQUISITION AND IMAGE PREPROCESSING}\)

Studies were performed according to previously described methods.16 The software packages SPM99 (Wellcome Department of Cognitive Neurology, University College, London, England) and MATLAB 6.1 (MathWorks Inc, Sherborn, Mass) were used for image preprocessing. Images were spatially normalized to a reference stereotactic template (Montreal Neurological Institute, McGill University, Montreal, Quebec) by a 12-parameter transformation and smoothed by a Gaussian kernel of 12 × 12 × 12-mm voxels full width at half maximum.18,17
Voxel-by-voxel statistical parametric mapping of $^{18}$FDG radioactivity distribution images was performed using SPM99. Global differences in the distribution of the tracer’s uptake and age effect were covaried out for all voxels. Comparisons across the different groups were made using $t$ statistics with appropriate linear contrasts.

**Volumes of Interest and Receiver Operating Characteristic Curves**

Analysis of volumes of interest (VOIs) and receiver operating characteristic (ROC) curves was aimed at evaluating whether CVLT–Long Delay Free Recall (CVLT-LDFR) scores and $^{18}$FDG-PET findings might be useful in predicting progression to AD at the individual level. The hypometabolic regions of aMCI converters vs controls, obtained by SPM99 analysis at $P<.001$, were used to define VOIs. Considering only clusters exceeding 700 voxels, 3 VOIs in the temporoparietal regions and posterior cingulate cortex were selected. The regional-sensorimotor $^{18}$FDG uptake ratio (regional cerebral glucose metabolism ratio [rCGM-r]) was considered in the analysis. To discriminate among groups, ROC curve analysis was performed on CVLT-LDFR scores (score range, 0-16) and on the rCGM-r.

**Kaplan-Meier Estimates**

We used R software (available at: http://www.r-project.org) to perform Kaplan-Meier analysis of survival to estimate the conversion to AD among the aMCI subgroups in the presence of censored data (aMCI nonconversion and unequal follow-up time to assess conversion). The curves were compared using the log-rank test.

**RESULTS**

**CLINICAL FINDINGS**

Demographic and clinical characteristics of the study group are given in the Table. As expected, subjects with aMCI had impaired performances ($<1.5$ SDs compared with the control data) only on tests of verbal and nonverbal long-term memory.

Forty-eight (71.6%) of 67 subjects with aMCI completed the clinical and neuropsychological follow-up examination. Fourteen (29.2%) of the 48 developed AD and were classified as aMCI converters. Thirty-four (70.8%) of the 48 remained stable and were classified as aMCI nonconverters. Among the 67 subjects, there were 19 dropouts (28.4%) (Table).

Baseline long-term memory scores were significantly lower among aMCI converters compared with aMCI nonconverters, and aMCI converters had CVLT-LDFR scores indicating more severe impairment (score range, 0-6), while aMCI nonconverters had scores that were evenly distributed (Figure 1). Visuospatial abilities and executive functions, even if within normal ranges, were more impaired among aMCI converters than aMCI nonconverters (Table).

**DISCRIMINANT ROC CURVE ANALYSIS**

Discriminant ROC curve analysis was performed among the 48 subjects who completed the follow-up. First, the
ROC curve calculated for CVLT-LDFR scores demonstrated an area under the curve of 0.783. The ROC curve analysis indicated a sensitivity of 96.8%, corresponding to a specificity of 58.8% at a CVLT-LDFR score of 7. At this level, the negative predictive value (the likelihood that the subject is healthy) was 95.2%, while the positive predictive value (the likelihood that the subject will develop AD) was 48.1%. A CVLT-LDFR score of 7 or higher discriminated all the aMCI nonconverters except 1; a CVLT-LDFR score less than 7 had too little power for establishing the risk of progression to AD (Figure 1). Therefore, we defined 2 subgroups, subjects with lower CVLT-LDFR scores, ranging from 0 to 6, and subjects with higher CVLT-LDFR scores, ranging from 7 to 16.

Second, the ROC curve calculated for the rCGM-r, measured in the temporoparietal and posterior cingulate VOIs, demonstrated an area under the curve of 0.863. At an rCGM-r of 1.138, the sensitivity was 92.9%, the specificity was 82.4%, the negative predictive value was 96.5%, and the positive predictive value was 68.4%.

Third, with regard to CVLT-LDFR scores less than 7, the rCGM-r of 1.138 had a positive predictive value of 92.3%, a negative predictive value of 92.8%, a sensitivity of 92.3%, a specificity of 97.1%, a positive predictive value of 92.3%, and a negative predictive value of 94.3%. Results of the Kaplan-Meier analysis showed a risk of conversion to AD that was significantly different among subjects with aMCI based on CVLT-LDFR score (P < .01) or rCGM-r (P < .001) (Figure 2).

SPM FINDINGS

aMCI Converters vs aMCI Nonconverters

Among aMCI converters compared with controls, 18FDG-PET showed significant bilateral hypometabolism in the inferior parietal cortex (x, y, z Montreal Neurological Institute [MNI] Talairach coordinates −32, −72, 38; −46, −62, 30; 44, −62, 28; and 40, −56, 42), posterior cingulate cortex (coordinates −2, −56, 26), and left inferior dorsolateral frontal cortex (coordinates −54, 38, 2) (Figure 3A). The right hippocampal structures (coordinates 26, −16, −2) and left parahippocampal gyrus (coordinates −40, −24, −22) were also hypometabolic. Among aMCI nonconverters compared with controls, regions in the right and left dorsolateral frontal cortex (coordinates 56, 18, 0 and −46, 40, 12) showed significant hypometabolism (Figure 3B). A direct comparison between groups confirmed the typical AD temporoparietal metabolic pattern among aMCI converters.
Among subjects with CVLT-LDFR scores less than 7, we found a significant bilateral reduction of tracer uptake in the inferior parietal cortex (x, y, z MNI coordinates −46, 64, 26 and 30, −56, 16), posterior cingulate cortex (coordinates 8, −60, 24 and 4, −58, 20), and precuneus (coordinates 0, −42, 44) (Figure 4). Among subjects with CVLT-LDFR scores of 7 or higher, we found a predominant reduction of tracer uptake in the right dorsolateral frontal cortex (coordinates 58, 18, 2 and 54, 30, 18). A direct comparison between subgroups confirmed bilateral involvement of the posterior parietal cortex (MNI coordinates −36, −76, 46 and 42, −60, 26), posterior cingulate cortex (MNI coordinates 2, −44, 36), and precuneus (MNI coordinates 4, −74, 40) in the group with more severe memory deficits. No pixels exceeding the threshold were detected by the opposite comparison that is between the group with CVLT-LDFR scores 7 or higher and the group with scores 6 or lower.

**Figure 4. Pattern of reduced positron emission tomography with fluorodeoxyglucose F 18 uptake in subjects with amnestic mild cognitive impairment with low California Verbal Learning Test–Long Delay Free Recall scores (score range, 0-6), superimposed on a standardized magnetic resonance imaging brain template. On the image are reported the z Montreal Neurological Institute coordinates (in millimeters) of the sections displayed. R indicates right.**

**aMCI Subgroup Comparison According to CVLT-LDFR Scores**

Improved characterization of MCI features may aid in identifying subjects with incipient but asymptomatic AD. Among a large group of subjects with aMCI, our study differentiated these subjects from controls, and we demonstrated 18FDG-PET metabolic heterogeneity among the subjects with aMCI. One year before the onset of AD, aMCI converters showed the typical AD functional pattern, with hypometabolism in the parietal and posterior cingulate cortex. Among aMCI nonconverters, hypometabolism was confined to the dorsolateral frontal cortex.

In addition, 18FDG-PET metabolic heterogeneity was associated with different severities of memory impairment, as assessed by CVLT-LDFR scores. Severe memory impairment with an AD metabolic pattern is associated with a high risk of short-term conversion to dementia. In contrast, subjects with less memory impairment without conversion to AD show a frontal metabolic pattern. Memory impairment in aMCI nonconverters might be ascribed to the dorsolateral frontal hypometabolism. Prefrontal structures are known to be involved in episodic memory processes such as encoding and retrieval. The combined use of CVLT-LDFR scores and 18FDG uptake in selected VOIs, as shown by the ROC curve analysis, seems to be a promising tool for predicting outcomes among individual subjects with aMCI. When considering only CVLT-LDFR scores, we demonstrated a low probability of converting to AD (4.8%) among patients with milder long-term memory deficit, and we found high probabilities of converting to AD (48.1%) or of maintaining aMCI (51.9%) among subjects with more severe memory impairment. Therefore, among subjects with severe memory impairment, 18FDG-PET findings were crucial in predicting which subjects would rapidly develop dementia. Indeed, the mean levels of 18FDG uptake measured in selected VOIs correctly classified 92.3% of aMCI converters and 92.8% of aMCI nonconverters. Although conversion to AD is time dependent and subjects with aMCI were followed up for variable intervals (follow-up range, 12-27 months), the Kaplan-Meier analysis showed that the differences observed in this study are not due to censored data.

Our findings have implications for clinical practice. This study supports the view that the present criteria for aMCI define a heterogeneous population whose degree of memory impairment correlates with different patterns of brain functional involvement and possibly with different pathologic substrates. Therefore, proposed criteria for aMCI may apply to a heterogeneous population in which reports of memory loss could be due to somatic diseases, drug-induced states, affective disorders, or other neurologic conditions, rather than an ongoing AD-related process. Longer follow-up is needed to estimate the clinical outcome of subjects with a frontal hypometabolic pattern of aMCI.

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