Cerebral Metabolic Correlates of the Clinical Dementia Rating Scale in Mild Cognitive Impairment

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ABSTRACT

Mild cognitive impairment (MCI) is often a prodromal state of Alzheimer's disease (AD). Imaging studies have shown that metabolic deficits in cerebral regions known to be affected early by AD pathology are predictive of progression to AD. In the present article, the authors examine associations between clinical impairment (Clinical Dementia Rating scale sum of boxes [CDR-SB]) and regional deficits in glucose utilization in a sample of 41 patients with MCI, who underwent cerebral ^{18}F-FDG PET for the measurement of regional glucose metabolism. A linear regression analysis with CDR-SB score as the independent variable and glucose metabolism as the dependent variable, adjusted for age, gender, and years of school education, was conducted in voxel-by-voxel fashion in SPM2. The regression analysis revealed a significant negative association between CDR-SB score and glucose metabolism in the right posterior cingulate gyrus ($P < .001$, uncorrected for multiple comparisons), which was independent from demographical variables. The authors conclude that clinical severity of impairments is already correlated with deficits in glucose metabolism in the stage of MCI. (*J Geriatr Psychiatry Neurol* 2007;20:84-88)

Keywords: clinical dementia rating; positron emission tomography; cerebral glucose metabolism; mild cognitive impairment; Alzheimer's disease; dementia

The syndrome of mild cognitive impairment (MCI) is defined by the impairment of memory and of other cognitive domains not severe enough to interfere with basic activities of daily living, otherwise intact intellectual ability, and absence of dementia. MCI is clinically heterogeneous and etiologically nonspecific.[1] Prospective studies have consistently demonstrated that the amnestic type of MCI, that is, the type with impairment of memory, frequently but not exclusively represents a predementia stage of Alzheimer's disease (AD).[2] Therefore, patients with amnestic MCI have an increased risk of developing dementia.[3,4] However, in a substantial proportion of cases, MCI is nonprogressive or even reversible.[5,6] Hence, individual prognosis at the stage of MCI is of utmost importance particularly with regard to the development of disease-modifying treatment strategies.

In previous studies using ^{18}F-fluoro-2-deoxy-glucose (^{18}F-FDG) for the measurement of the regional cerebral metabolic rate of glucose utilization (rCMRglc) assessed by positron emission tomography (PET), we have demonstrated that one third of patients with amnestic MCI show areas of metabolic reduction in temporal, parietal, and/or posterior cingulate cortices as compared to controls.[7] This pattern of hypometabolism is typical of AD[8,9] and, if present in MCI, is associated with an increased probability of progression to AD.[10,11]

In the present article, we examine whether the clinical severity of impairments in patients with MCI is associated

with their cerebral glucose utilization. If such an association was present, the use of a clinical staging instrument had considerable diagnostic and prognostic potential in patients at risk of AD. Staging of clinical severity in MCI can be obtained by assessing memory and other cognitive and noncognitive domains. The Clinical Dementia Rating scale (CDR)[12] was particularly designed to stage severity of dementia. It assesses the functional level in daily life in (1) recent and long-term memory; (2) orientation to time, place, and person; (3) judgment and problem solving; (4) community affairs; (5) home and hobby activities; and (6) personal care. The extent of impairment in each of the 6 areas is determined (ranging from 0 for none to 3 for severe impairment), and algorithms are provided for deriving an average level of impairment that ranges from 0 (healthy) to 3 (severe). CDR scores of 0, 0.5, 1, 2, and 3 indicate no, questionable, mild, moderate, and severe dementia, respectively. A more detailed approach to attain a total score of the CDR is to simply add the score of each domain (CDR sum of boxes, CDR-SB). Although, by definition, all MCI patients receive a rating of 0.5 on the CDR,[12] CDR-SB shows a considerable variability and was successfully utilized for stratifying patients with questionable dementia in a previous study.[2]

METHODS

Study Sample

The study includes 41 consecutive patients with MCI, who were referred for diagnostic evaluation to a university memory clinic between 1998 and 2003. Diagnostic workup included cognitive testing based on the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery (CERAD-NAB),[13] which incorporates the Mini Mental State Examination (MMSE),[14] an informant interview (in most of the cases, informants were the patients' spouses or relatives, who lived in the same household), laboratory screening, and structural (computed tomography or magnetic resonance imaging), and functional (18F-FDG PET) brain imaging. Patients were excluded who fulfilled diagnostic criteria for dementia in AD, Lewy body disease, frontotemporal lobar degeneration, or cerebrovascular disease. Further exclusion criteria were intracranial tumors, hydrocephalus, epilepsy, alcoholism, and functional psychiatric disorders. The clinical documentation included information on age, gender, and years of school education. The diagnosis of MCI was based on the Mayo Clinic criteria[15] in conjunction with exclusionary criteria commonly used to define probable AD (criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association, NINCDS-ADRDA).[16]

All available information was used to rate patients on the CDR according to the rating procedure described by Morris.[12] Additionally, a total score of the CDR was calculated by adding up the score of each single domain (CDR-SB). All patients included in this study were rated with 0.5 on the CDR (questionable dementia). To exclude the impact of physical disabilities on the rating of clinical impairment, the CDR rating was based only on impairment due to cognitive decline. Informed written consent was obtained from each participant according to the Declaration of Helsinki after the purpose and the procedures of the study had been fully explained to them. The study protocol was approved by the local ethics committee and the radiation protection authorities.

PET-Scan Acquisition and Data Processing

Following exactly the same protocol, all patients underwent PET scanning after being administered with 18F-FDG injection at rest. The detailed PET scanning procedure is described in Drzezga et al.[17] Statistical parametric mapping software (SPM2, http://www.fil.ion.ucl.ac.uk/spm/software/spm2) based on Matlab, v6.5 (The Mathworks Inc, Natick, MA) was used for image realignment, transformation into standard stereotactic space, smoothing, and statistical analyses. Images were smoothed using a Gaussian kernel (12 mm FWHM). Individual global counts were normalized by proportional scaling to a mean value of 50 mg/100 mL/min.

Statistical Analysis

The statistical analysis of imaging data included 2 steps. First, a voxel-based linear regression analysis of rCMRglc as the dependent variable and CDR-SB score as the independent variable was performed to identify brain regions with an association of rCMRglc and CDR-SB score. To control for differences in demographic variables, gender (1 for male, 2 for female), age, and years of school education were included as covariates of no interest in the linear predictor of regression analysis. Statistically significant associations between CDR-SB score and rCMRglc were only expected in brain regions known to be consistently affected in patients with MCI, that is, the posterior cingulate and temporoparietal cortices.[11] Findings meeting a height threshold of $P < .001$ uncorrected for multiple comparisons were considered significant in this predefined cortical network, as reported previously.[18] This analysis was repeated for the subgroup of patients with findings typical of AD in the visual inspection of their 18F-FDG PET scans. Scatterplots between CDR-SB score and rCMRglc were also generated in SPM2 at the cluster with the strongest correlation, and a corresponding regression line was fitted into these plots. A correlation analysis of adjusted rCMRglc and CDR-SB score was performed in

Table 1. Characteristics of the Study Sample

Characteristic	Study Sample (N = 41)
Age, y*	68.85 ± 8.62 (54-81)
Men:Women	17:24
Schooling, y*	10.88 ± 4.11 (8-18)
MMSE score*	27.20 ± 1.08 (26-29)
CDR-SB score*	2.16 ± 0.97 (0.5-4.0)
Duration of cognitive symptoms, y*	2.3 ± 1.7 (1.0-6.5)

Note: MMSE, Mini-Mental-State Examination; CDR-SB, Clinical Dementia Rating scale sum of boxes; y, years.
*mean ± standard deviation (range).

Matlab. Second, a voxel-based linear regression analysis of rCGMglc as dependent and the duration of cognitive symptoms (in years) was also performed to explore if disease duration and glucose metabolism were significantly correlated. Again, findings were only expected in typical regions for patients with MCI as described above and a height threshold of $P < .001$ uncorrected for multiple comparisons was applied. Coordinates in MNI space (Montréal Neurological Institute and Hospital, McGill University; http://www.bic.mni.mcgill.ca) were transformed to Talairach space[19] using the Matlab function mni2tal (http://www.mrc-cbu.cam.ac.uk/Imaging). Anatomical regions were identified using the Talairach Demon Client, version 2.0 (http://ric.uthscsa.edu/recources). Descriptive statistics of patient characteristics and a parametric correlation between CDR-SB score and the duration of cognitive symptoms (in years) were calculated in Matlab. Any P values considered are 2-sided and subject to a significance level of .05.

RESULTS

Characteristics of the study sample are presented in Table 1. There was no significant correlation between the CDR-SB score and the duration of cognitive symptoms. The visual inspection of the ^{18}F-FDG PET scans demonstrated metabolic patterns typical or suggestive of AD, that is, involvement of the temporal and/or parietal and/or posterior cingulate cortex in approximately 40% of the patients. In nearly all of these patients, the metabolic deficit was bilateral. About 23% of our PET findings showed a pattern that is not typical for AD. In most of these cases, there was an inhomogeneous bilateral cerebral hypometabolism. In one third of the patients, PET images were nearly normal. Again, these findings underline the heterogeneous character of MCI.

Inverse Association of rCMRglc and CDR-SB Score/Duration of Cognitive Symptoms

At the significance level of $P < .001$ uncorrected for multiple comparisons, the voxel-based regression analysis revealed a significant inverse linear association between the CDR-SB score and the adjusted rCMRglc (corrected for demographic variables) in the right posterior cingulate gyrus (cluster of 462 voxels; $Z = 4.63$; maximum at x/y/z in Talairach space: 10/–43/43; see Figure 1). The fitted curve for the linear regression analysis has a negative slope and is also displayed in Figure 1. The additional correlation analysis between the adjusted rCMRglc and the CDR-SB score at the localization of the cluster with the strongest statistical association in the right posterior cingulate gyrus revealed a strong negative association ($r = –.65$). There was no significant positive correlation in any brain region. Furthermore, there was no significant correlation between rCGMglc and duration of cognitive symptoms. The limitation of the analysis to the subgroup of patients with findings typical of AD did not significantly alter the results.

DISCUSSION

The broad ranges of CDR-SB and MMSE scores in our study sample confirm that MCI is a clinically heterogeneous syndrome. Although, by definition, all patients had significant memory impairment relative to their age peers, some showed deterioration in the domains of orientation, community affairs, home and hobbies, judgment and problem solving, and self-care, whereas others did not. We found a statistically significant association between the clinical severity of MCI as assessed by the CDR-SB and the degree of metabolic hypoactivity in the posterior cingulate gyrus, which is known to be affected early in AD.[8] This confirms our assumption that a broader spectrum of cognitive and functional impairment indicates more severe and more widespread AD pathology at the stage of MCI. Furthermore, in an ^{18}F-FDG follow-up study, we found that the hypometabolism of the posterior cingulate cortex was predictive of AD in a cohort of MCI patients.[11] Taking the reduced rCMRglc in the posterior cingulate cortex as a predictor of AD, one could possibly argue in this case that higher scores on the CDR-SB are also predictive of AD in MCI patients. However, follow-up studies will have to prove this assumption.

Some limitations of our study have to be taken into account as well. No definite conclusions for individual patients can be drawn from a group analysis because of the significant inter-individual differences in ^{18}F-FDG PET scans. Furthermore, in the SPM analyses of ^{18}F-FDG PET data, only brain clusters with statistically significant differences in rCMRglc are identified. In other words, regions with equally poor or equally good glucose utilization in relation to CDR-SB score would have not been detected in our study. Moreover, the evaluation of follow-up data may have helped to explore if patients
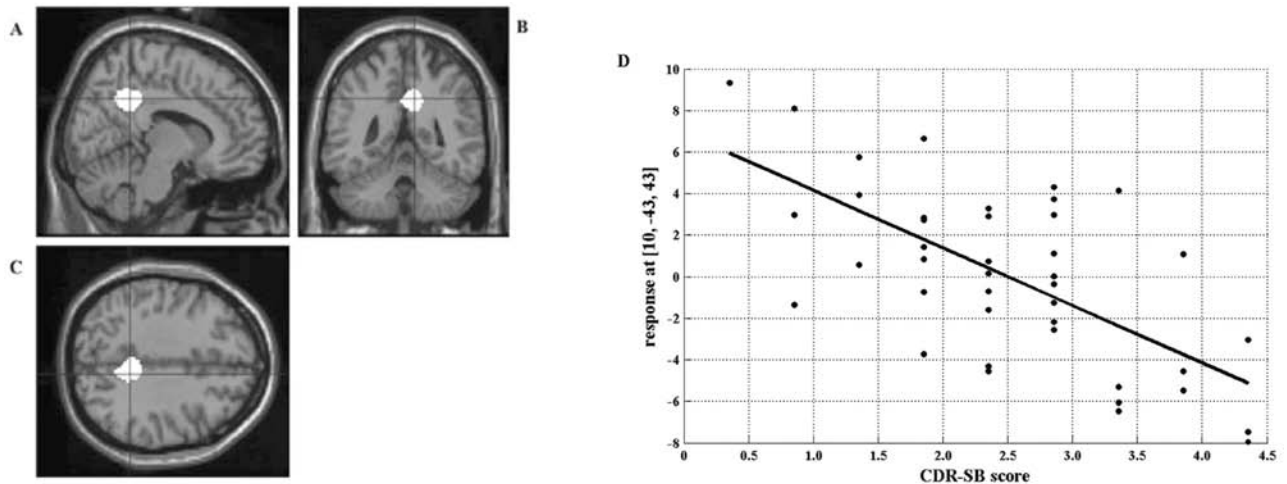
Figure 1.   Inverse association between rCGMglc (regional cerebral metabolic rate of glucose utilization) and CDR-SB (Clinical Dementia Rating scale sum of boxes) score in the mild cognitive impairment group (N = 41). Anatomical localization of the significant cluster (maximum at Talairach coordinates x/y/z 10/–43/43, right posterior cingulate gyrus, $P < .005$ for display purposes), as projected on (A) saggital, (B) coronal, and (C) axial sections of a normal magnetic resonance imaging, spatially normalized into MNI's template (Montréal Neurological Institute and Hospital, McGill University; http://www.bic.mni.mcgill.ca), and (D) regression analysis of fitted and adjusted rCMRglc response in arbitrary units as dependent variable and CDR-SB scores as independent variable at the position of the most significant cluster.

with more pronounced metabolic deficits in the posterior cingulate cortex are more likely to progress rapidly to AD. However, no such data were available.

It is unlikely that our finding of reduced rCMRglc can be attributed to the inclusion of patients who had already progressed to dementia. Patients were excluded from the study who met diagnostic criteria for probable AD or were rated 1 or higher on the CDR. Furthermore, the MMSE scores of our MCI patients were suggestive of MCI.[20] Our sample was also entirely comparable to patient populations enrolled in other MCI studies. In a recent study evaluating donepezil and vitamin E in patients with the amnestic subtype of MCI,[21] patients were of similar age (mean value 72.9, standard deviation 7.3), had a comparable cognitive level as assessed by the MMSE (mean value 27.27, standard deviation 1.8), and had similar scores on the CDR-SB (mean value 1.82, standard deviation 0.8). Additionally, in a recent publication by Geslani et al,[22] which used an operational definition of the Mayo-Clinic criteria to explore the conversion rate of MCI to AD, the patients also showed similar demographics (age: mean value 73.07, standard deviation 7.72; education: mean value 12.67, standard deviation 3.24) and test characteristics (MMSE: mean value 26.58, standard deviation 2.20).

To sum up, the CDR-SB, which provides a readily available and easily applicable global assessment of cognitive and functional ability, is significantly associated with the severity of metabolic deficits in patients with MCI in a particular brain region, the posterior cingulate cortex, which is typically affected in individuals at a high risk for

AD. Therefore, if hypometabolism of the posterior cingulate cortex in a group of MCI patients is significantly correlated with the CDR-SB scores and metabolic reductions in that particular brain region are regarded as predictors of future AD in patients with MCI, one could argue that MCI patients with higher scores on the CDR-SB are more likely to develop dementia in the future. Supporting our findings, Galvin and colleagues[23] recently found in a clinico-pathological study that even minimal cognitive impairment, as determined clinically by the CDR-SB, identifies older individuals without dementia who will develop AD in the future. Therefore, we conclude that the CDR-SB has not only considerable diagnostic, but also prognostic, potential in individuals at risk for developing dementia. Hence, the CDR-SB can facilitate prognostic conclusions in individual patients, either alone or in conjunction with other sensitive diagnostic techniques.

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