



REGIONAL CEREBRAL GLUCOSE METABOLISM PREDICTS DECLINE IN MCI SUBJECTS AND PROVIDES A SENSITIVE BIOMARKER OF DISEASE PROGRESSION

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AIM: The heterogeneity of MCI and AD populations regarding clinical decline poses a substantial hurdle to successful clinical trials. The presence of non-decliners in placebo arms can minimize comparative therapeutic response, while their presence in drug arms can lead to misinterpretation of results. For drug trials and diagnosis, it is critical to identify biomarkers that can provide reliable prediction and monitoring of disease progression. The aim of this work was to evaluate the cerebral metabolic rate of glucose (rCMglc) using FDG-PET as an objective predictor and measure of MCI clinical decline and conversion to AD for clinical trials and diagnosis.

METHODS: We defined criteria for three MCI subgroups: Nondecline (MCI-NONDECL), Decline (MCI-DECL), and Convert (MCI-CONV), all having initial diagnosis of MCI and CDRGLOBAL of 0.5, but differentiated by subsequent 18 month changes in cognitive scores and diagnosis. MCI-NONDECL did not increase in CDR subscore total (CDRst) or >1 point in ADAS-11; MCI-DECL increased in CDRst and ADAS-11 totals; MCI-CONV increased in CDRst and ADAS-11 and received a diagnosis of AD within 6-24 months of baseline. We identified 71 subjects from the ADNI database who met these criteria and received longitudinal FDG-PET scans (32 female, 39 male, age 62–88, mean 74.4 years; 20 MCI-NONDECL, 25 MCI-DECL, 26 MCI-CONV). At baseline, there were no significant inter-group differences in age, CDRst, ADAS-11, or MMSE. At 18 months, MCI-NONDECL < MCI-DECL ($p < 0.05$) and < MCI-CONV ($p < 0.01$) in CDRst, and MCI-NONDECL < MCI-DECL and MCI-CONV (p 's < 0.01) in ADAS-11. Using a combination of univariate and multivariate analyses, we measured rCMglc in the FDG PET scans of all subjects at baseline and 18 months, and evaluated the ability to predict subgroup classification and measure longitudinal clinical progression. We implemented a highly sensitive, automated region of interest method (Mosconi et al, 2005; Li et al, 2008) capable of detecting rCMglc in hippocampus and other regions, combined with a multivariate analysis and resampling approach that identifies key differentiating patterns and quantifies reproducibility and predictive power (NPAIRS, Strother et al, 2002).

RESULTS: At baseline, normalized MCI-NONDECL rCMglc levels exceeded those in MCI-DECL and MCI-CONV in regions including hippocampus (HIP), posterior cingulate/precuneus (PCC), medial temporal lobe (MTL), inferior parietal lobe (IPL), and lateral temporal lobe (LTL) (p 's < 0.01; corrected for multiple comparisons). MCI-DECL rCMglc in IPL exceeded that in MCI-CONV ($p < 0.05$). The primary pattern identified by NPAIRS provided nearly complete separation between MCI-NONDECL and MCI-CONV. Within this pattern, including PCC, MTL, IPL, and lingual gyrus, MCI-DECL subjects overlapped with MCI-CONV but showed less decline particularly in lingual gyrus. At 18 months vs. baseline, MCI-NONDECL subjects had no significant changes in HIP, PCC, IPL, MTL, or LTL, while MCI-DECL declined in HIP ($p < 0.05$), and MCI-CONV declined in MTL and IPL (p 's < 0.05). NPAIRS identified a shared pattern of decline in MCI-DECL and MCI-CONV including PCC, temporal and frontal gyri, parahippocampus, and fusiform gyrus; MCI-CONV declines were more pervasive in parietal, occipital, and temporal cortices. Baseline HIP, PCC, IPL, and PFC rCMglc correlated with subsequent change in ADAS-11 and CDRst in the total MCI population (p 's < 0.01).

CONCLUSIONS: The clinical decline of MCI subjects can be predicted and measured using rCMglc. This can help to increase the homogeneity of clinical study populations, provide objective measures of clinical progression, enable longitudinal analysis in the context of predicted decline, and provide improved prognostic information for diagnosis.

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