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FDG-PET and CSF biomarker accuracy in prediction of conversion to different dementias in a large multicentre MCI cohort

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ABSTRACT

Background/aims: In this multicentre study in clinical settings, we assessed the accuracy of optimized procedures for FDG-PET brain metabolism and CSF classifications in predicting or excluding the conversion to Alzheimer's disease (AD) dementia and non-AD dementias.

Methods: We included 80 MCI subjects with neurological and neuropsychological assessments, FDG-PET scan and CSF measures at entry, all with clinical follow-up. FDG-PET data were analysed with a validated voxel-based SPM method. Resulting single-subject SPM maps were classified by five imaging experts according to the disease-specific patterns, as "typical-AD", "atypical-AD" (i.e. posterior cortical atrophy, asymmetric logopenic AD variant, frontal-AD variant), "non-AD" (i.e. behavioural variant FTD, corticobasal degeneration, semantic variant FTD; dementia with Lewy bodies) or "negative" patterns. To perform the statistical analyses, the individual patterns were grouped either as "AD dementia vs. non-AD dementia (all diseases)" or as "FTD vs. non-FTD (all diseases)". Aβ42, total and phosphorylated Tau CSF-levels were classified dichotomously, and using the Erlangen Score algorithm. Multivariate logistic models tested the prognostic accuracy of FDG-PET-SPM and CSF dichotomous classifications. Accuracy of Erlangen score and Erlangen Score aided by FDG-PET SPM classification was evaluated.

Results: The multivariate logistic model identified FDG-PET "AD" SPM classification (Expβ = 19.35, 95% C.I. 4.8–77.8, $p < 0.001$) and CSF Aβ42 (Expβ = 6.5, 95% C.I. 1.64–25.43, $p < 0.05$) as the best predictors of conversion from MCI to AD dementia. The "FTD" SPM pattern significantly predicted conversion to FTD dementias at follow-up (Expβ = 14, 95% C.I. 3.1–63, $p < 0.001$). Overall, FDG-PET-SPM classification was the most accurate biomarker, able to correctly differentiate either the MCI subjects who converted to AD or FTD dementias, and those who remained stable or reverted to normal cognition (Expβ = 17.9, 95% C.I. 4.55–70.46, $p < 0.001$).

Conclusions: Our results support the relevant role of FDG-PET-SPM classification in predicting progression to different dementia conditions in prodromal MCI phase, and in the exclusion of progression, outperforming CSF biomarkers.

Abbreviations: aMCI, single-domain amnestic mild cognitive impairment; AD, Alzheimer's disease; AUC, area under curve; bvFTD, behavioral variant of frontotemporal dementia; CBD, corticobasal degeneration; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; DLB, dementia with Lewy bodies; EANM, European Association of Nuclear Medicine; FDG, fluorodeoxyglucose; FTD, frontotemporal dementia; LR+, positive likelihood ratio; LR-, negative likelihood ratio; md aMCI, multi-domain amnestic mild cognitive impairment; md naMCI, multi-domain non-amnestic mild cognitive impairment; MCI, mild cognitive impairment; naMCI, single-domain non-amnestic mild cognitive impairment; p-tau, phosphorylated tau; PET, positron emission tomography; PSP, progressive supranuclear palsy; t-tau, total tau

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1. Introduction

Alzheimer's disease (AD) dementia and other neurodegenerative dementias are preceded by a prodromal phase, namely mild cognitive impairment (MCI), characterized by subtle clinical-neuropsychological changes (Petersen et al., 2009), which are related to synaptic dysfunction and long-lasting pathological deposition of toxic proteins in the brain (Pievani et al., 2014). MCI is characterized by objective neuropsychological deficits in one or more cognitive domains without functional impairment in everyday life activities (Petersen et al., 2009). Clinical longitudinal studies on MCI subjects provided evidence for different clinical outcomes, including conversion to AD or non-AD dementias, to stabilization of cognitive profile, or even reversion to normal cognition (Mitchell and Shiri-Feshki, 2009; Petersen et al., 2009). In the prodromal phase, the clinical-neuropsychological assessment has limited accuracy for the prediction of conversion to AD dementia (Löppönen et al., 2003; Storandt and Morris, 2010). To overcome this limit, diagnostic biomarkers such as neuroimaging (i.e., MRI, FDG-PET and amyloid-PET) and cerebrospinal fluid-CSF (i.e., Aβ42, total (t-Tau) and phosphorylated (p-Tau) Tau measures) have been included in the current research criteria for "MCI due to AD" (Albert et al., 2011). Among these biomarkers, the FDG-PET patterns of hypometabolism seem to be particularly accurate in predicting conversion from MCI to dementia, when compared to other biomarkers (Anchisi et al., 2005; Bloudek et al., 2011; Dukart et al., 2015; Fellgiebel et al., 2007; Landau et al., 2010; Perani et al., 2016; Prestia et al., 2013a; Robb et al., 2017; Shaffer et al., 2013; Yuan et al., 2009). Notably, a recent meta-analysis on a large sample of MCI (N = 97) has shown that adding FDG-PET imaging information to clinical data provides a better prediction of conversion from MCI to dementia in comparison with clinical data alone, with misclassification rate dropping from 41.3% (clinical data alone) to 27.2% (combined clinical and FDG-PET data) (Shaffer et al., 2013). This study also showed that adding CSF and MRI data does not significantly improve clinical diagnosis.

However, the most recent Cochrane review on the use of FDG-PET for the early diagnosis of AD dementia and other dementias in people with MCI, concluded that there is no enough evidence to support the use of FDG-PET in clinical routine, mainly due to a lack of standardized and validated data analysis procedures (Smailagic et al., 2015). Another paper by the European Association of Nuclear Medicine (EANM) stated that even if a clear variability in diagnostic performance of FDG-PET is reported in the literature, it is not attributable to the method itself, but rather to a number of factors such as study design, definitions of MCI and data analysis procedures (Morbelli et al., 2015). Thus, the lack of validated and standardized methods for semi- or quantitative measures to assess FDG-PET biomarker performance in different clinical settings seems to be the most important factor in producing the discrepancies in the reported accuracy (see (Frisoni et al., 2013, 2017; Garibotto et al., 2017; Perani, 2014; Prestia et al., 2013b)) and a consequent mismatch in the proposed diagnostic algorithms (Albert et al., 2011; Dubois et al., 2014; McKhann et al., 2011a). The use of validated semi-quantitative methods and standardized operating procedures for the correct use of neuroimaging biomarkers in research and clinical settings is indeed strongly recommended by the international scientific societies, with the aim to improve the diagnostic accuracy (Caroli et al., 2012; Frisoni et al., 2013, 2017; Garibotto et al., 2017; Guerra et al., 2015; Mattsson et al., 2017; Perani et al., 2014b).

SPM (Friston et al., 1994) is one of the most widespread methods to statistically analyse voxel-wise FDG-PET data. A recently developed and validated single-subject SPM procedure, takes advantage on a custom FDG-PET dementia-specific template, and of a large normal dataset for comparisons at the individual level, to obtain SPM t-maps with high statistical accuracy (Della Rosa et al., 2014; Perani et al., 2014a). This procedure allows the identification of disease-specific brain hypometabolism patterns at the single-subject level, outperforming both the clinical characterization of patients and the visual qualitative assessment of FDG-PET uptake images (Perani et al., 2014a). This optimized FDG-PET-SPM procedure provides patterns of brain hypometabolism specific for each neurodegenerative condition (Caminiti et al., 2017; Cerami et al., 2017; Perani, 2014; Perani et al., 2016), also in prodromal phases (Cerami et al., 2015; Perani et al., 2014a, 2016).

The same issues apply to CSF biomarkers, with the Alzheimer's Biomarkers Standardization Initiative stating that many factors (e.g., diagnostic procedures, samples processing and testing) challenge the validity and comparability of CSF results among different laboratories (Vanderstichele et al., 2012).

FDG-PET imaging, as well as CSF markers, are considered useful for the early differential diagnosis of AD vs. non-AD dementias (Gaugler et al., 2013). These biomarkers reflect different underlying brain changes, namely neural injury and brain amyloid deposition (Blennow et al., 2015; Perani, 2014). FDG-PET is a highly specific biomarker of neurodegeneration, thus able to detect typical and atypical AD dementia, as well as many non-AD dementia conditions, even in the preclinical and prodromal phase (Arbizu et al., 2013; Bohnen et al., 2012; Caroli et al., 2012; Cerami et al., 2015; Hinrichs et al., 2011; Mosconi et al., 2008; Perani, 2014; Perani et al., 2016; Shaffer et al., 2013; Teipel et al., 2015; Torosyan et al., 2017). On the other hand, CSF Aβ42 can only provide information regarding the presence of brain amyloidosis. Thus, even though low CSF Aβ42 levels well detect AD dementia cases, discriminating them from frontotemporal dementia (FTD) cases (Struyfs et al., 2015), reduced CSF Aβ42 concentrations have been reported in many non-AD conditions (e.g., Parkinson's disease, dementia with Lewy bodies, vascular dementia) (Blennow et al., 2005; Kaerst et al., 2014; Stefani et al., 2012). Concerning CSF Tau, increased concentrations of both t-Tau and p-Tau support the diagnosis of AD dementia. However, especially at the individual level, there is excessive overlap between Tau levels of patients with AD dementia and other dementias and even with controls, thus undermining its potentiality as an accurate biomarker (van Harten et al., 2011). This overlap in CSF levels essentially limits the use of CSF as a unique biomarker for differential diagnosis.

The combined use of biomarkers for neuronal dysfunction (e.g., FDG-PET or CSF Tau levels) and amyloidosis (e.g., CSF Aβ42 levels), assessed with validated and standardized procedures, is expected to improve their diagnostic effectiveness, also providing complementary information. Notwithstanding the increasing use of these biomarkers in research and clinical settings, available works in MCI populations, combining FDG-PET and CSF markers, are limited and strictly focused on conversion to AD dementia (Chen et al., 2016; Choo et al., 2013; Galluzzi et al., 2013; Gomar et al., 2014; Landau et al., 2010; Prestia et al., 2013a; Shaffer et al., 2013; Walhovd et al., 2010; Young et al., 2013). Since AD dementia constitutes only one of the possible clinical outcomes for MCI condition (Mitchell and Shiri-Feshki, 2009), data on validated biomarker accuracy for risk progression to different dementias in a large prodromal MCI sample are necessary, and currently lacking.

Here, we assessed the accuracy of FDG-PET using an optimized voxel-based procedure (Cerami et al., 2015; Della Rosa et al., 2014; Perani et al., 2014a, 2016) and CSF (i.e., Aβ42, t-Tau and p-Tau) biomarkers in the prediction of conversion to AD and non-AD dementias in a large sample of MCI belonging to different clinical centres. The aim of this multicentre study was to evaluate the individual and combined performance of the biomarkers in the risk prediction or, notably, in the exclusion of conversion to AD and non-AD dementia conditions.

2. Materials and methods

2.1. Patients

We retrospectively collected clinical and biomarker information in 80 MCI subjects belonging to a large database resulting from a collaborative multicentre Italian study on neurodegenerative dementias. The