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EDITORIAL

A Cochrane review on brain [^{18}F]FDG PET in dementia: limitations and future perspectives

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[^{18}F]FDG PET is a well-established method for the evaluation of patients with suspected Alzheimer's disease (AD) and other neurodegenerative diseases [1]. This tool has the unique ability to estimate the local cerebral metabolic rate of glucose consumption (CMRgl), thus providing information on the distribution of neuronal death and synapse dysfunction in vivo [2]. Clinically, [^{18}F]FDG PET plays a major role in the early and differential diagnosis of dementia due to AD by showing specific disease patterns of hypometabolism, reflecting neuronal dysfunction in affected brain regions even in the earliest stages of the disease [1]. However, the role of [^{18}F]FDG PET in identifying patients affected by AD but who are still at the stage of mild cognitive impairment (MCI) is less established. Although various studies have indicated a high predictive value in this population, appropriate standardization approaches (i.e. semiquantification methods, observer-independent analyses, identification of cut-off values) and the value of [^{18}F]FDG PET in comparison to amyloidosis biomarkers are still a matter of debate.

Recently, a Cochrane review was published with the objective of determining the diagnostic accuracy of [^{18}F]FDG PET for identifying subjects with MCI who will clinically convert to AD or other dementias [3]. The authors concluded that there is no evidence supporting routine clinical use of [^{18}F]FDG PET to identify those patients with MCI who will develop AD. For several reasons, we do not agree with the authors of

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this Cochrane review that existing data on the value of FDG PET in MCI supports such a categorical conclusion. Indeed, clear variability in diagnostic performance of [^{18}F]FDG PET is found in the literature, as correctly reported in the Cochrane review. This variability, however, is not exclusively attributable to the method itself, but rather can be explained by a number of factors concerning study design, definitions of MCI itself and data analysis procedures.

We would like to highlight some of these factors in greater detail, because we believe that knowledge on these issues may be necessary to correctly interpret the available literature and to appreciate the diagnostic value of [^{18}F]FDG PET in MCI.

Methodology

Cochrane reviews are internationally recognized systematic reviews that provide a standard for evidence-based healthcare.

The Cochrane review on brain [^{18}F]FDG PET included longitudinal cohort studies published between 1999 and 2013 in which MCI patients underwent an [^{18}F]FDG PET scan at baseline and were followed-up clinically to assess whether there was conversion to dementia. These studies were selected through an extensive search of electronic databases and by checking the reference lists of relevant studies (for details see Smailagic et al. [3]). Patients included in this review fulfilled specific inclusion criteria. In particular, MCI patients were included (1) according to the clinical criteria defined by Petersen et al. [4] and Winblad et al. [5], (2) if they presented with a Clinical Dementia Rating scale score of 0.5 [6], or (3) if they met one of the other 16 descriptions of MCI discussed by Matthews et al. [7]. This rather 'inclusive' approach reflects the fact that the definition of MCI is quite diverse across the literature of the last 10 years.

Patients with isolated memory impairment, such as those included by Berent et al. [8], are not easily comparable with those who fulfil current MCI criteria. In contrast to dementia based on AD, MCI is not a homogeneous diagnostic entity. This inhomogeneity also applies to the cohorts of MCI patients finally included in the Cochrane review. Therefore, it is questionable whether a meta-analysis of results obtained from a series of highly heterogeneous MCI samples allows any conclusion about the diagnostic method itself. The observed variability in the results obtained with [^{18}F]FDG in MCI may indeed reflect heterogeneity in the patient samples rather than variability in diagnostic performance.

The studies included, by necessity, employed delayed verification of conversion to dementia and the diagnosis of probable AD was based on NINCDS-ADRDA guidelines [9] and confirmed by exclusion of other causes of dementia through clinical, paraclinical and neuropsychological criteria. The time between [^{18}F]FDG PET and verification of conversion was considered appropriate (low risk of bias) when the duration of follow-up was longer than 1 year. However, as the authors of the Cochrane review state themselves, the duration of follow-up is quite critical, as sufficient time is needed to capture the natural course of progression. A patient who still has "stable" MCI after 1 year may still convert to AD after 2 or 3 years [10]. In this respect, it should be noted that it is hard to say whether positive [^{18}F]FDG PET findings in patients with clinically stable MCI should be considered false-positive if the follow-up time is less than 3 years [11, 12]. In our view, it would be important to define a target conversion time window. This is indeed a relevant topic, partly investigated by Cabral et al. [11]. Their results clearly show that (using a specific machine learning approach) the sensitivity for detection critically increases during the last 12 months prior to conversion. Specific investigations on this topic are thus required in order to specify the time frame in which the [^{18}F]FDG PET results should be considered valid and to define guidelines for repeating the diagnostic test.

Finally, 16 studies were selected, consisting of a total of 697 subjects, and all studies were evaluated for methodological quality. From a methodological point of view, both studies with qualitative and those with semiquantitive analyses of [^{18}F]FDG PET scans were included in the Cochrane review. Sensitivity analysis, however, was performed only in 14 studies (150 subjects) as three studies included patients from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort and only the largest one of these studies was included in the analysis [13]. In contrast, no threshold concerning the number of subjects included in a study was set and actually 6 out of 16 of the studies included had fewer than 30 subjects. The relatively low sample size of some of the studies included may also account for part of the results. In fact, smaller studies are often associated with larger effect sizes, which could be a reflection of 'small study bias' (i.e. the possibility that the available evidence is biased) [14].

Results of the Cochrane review

Sensitivity and specificity values varied widely and ranged from 25 % to 100 % for sensitivity and from 15 % to 100 % for specificity. However, both these values were higher than 80 % in about half of the studies included [15–20], an accuracy that compares better with previous studies in which confirmation of underlying neurodegenerative pathology was obtained at autopsy. In the latter case, [^{18}F]FDG PET identified patients with AD with a sensitivity of 94 % and a specificity of 73 % [21]. In addition, it has to be noted that sensitivity and specificity values at the lower end of the range given above were derived (1) from studies performed using stand-alone PET scanners with poorer sensitivity and lower spatial resolution than available PET/CT scanners, and/or (2) using a very small group of oncological patients without evidence of brain

lesions as controls [22, 23]. All these limitations were clearly discussed by the original authors and these articles represent a proof of past efforts to develop and define the specific pattern of AD at the stage of MCI. Nevertheless, these challenges are now overcome by the availability of both freeware software and officially certified observer-independent analysis tools offered by several vendors allowing comparison with age-matched control databases.

The highly heterogeneous [^{18}F]FDG PET sensitivity and specificity results highlighted in the Cochrane review might also be explained by different criteria and differences in methodological approaches between studies, e.g. regarding criteria for [^{18}F]FDG positivity. In fact, in only ten studies were PET analyses based on a combination of visual qualitative and semiquantitative analyses performed. In addition, different thresholds, different brain regions as well as different scaling procedures were used to assess positivity. Actually, the sensitivity and specificity of [^{18}F]FDG PET (as well as of all AD biomarkers) depend largely on the method of interpretation, resulting in improved diagnostic and prognostic accuracy with software-aided reading [24]. In summary, we do not agree with the view of the authors of the Cochrane review that the variability in diagnostic performance represents the main limitation in the use of [^{18}F]FDG PET in clinical practice. In our opinion, this heterogeneity is rather a reflection of the extensive work that is ongoing to compare and validate analytical tools for guiding interpretation of [^{18}F]FDG PET data within the heterogeneous MCI population.

New data and perspectives

Smailagic et al. searched PubMed and other databases up to January 2013. However, this is a rapidly evolving field and many other studies have been published since then, showing the strong effort of the nuclear medicine community to assess the relevance of cerebral [^{18}F]FDG PET for the early diagnosis of dementia. On 1 March 2015, another 17 papers on this topic, published between January 2013 and February 2015, could be identified [11, 25–40]. In addition, two other papers, published in 2012 and investigating the diagnostic role of [^{18}F]FDG PET in MCI, were not identified by the authors of the Cochrane review [41, 42]. Three of these 19 studies used a normal reference population as the source of normative data, an approach that was not considered in the Cochrane review [38, 39, 41]. The median sensitivity and specificity of these more recent studies were 80 % and 72.5 %, respectively.

A systematic review of the results obtained in these studies is beyond the scope of this editorial: we summarize here only some of the more relevant results and trends emerging from this recent literature.

Firstly, the number of subjects included in these more recent studies is much higher than the number incorporated in the Cochrane review with only one study including fewer than 30 subjects [26], suggesting that the use of [^{18}F]FDG PET for early detection of dementia is increasingly being used, and larger series are available for assessing its value. In order to achieve these large sample sizes, a synergistic effort across memory clinics and countries is in place. The vast majority of studies use data from multicentre projects, not only from the ADNI (dataset used in nine of the previously mentioned studies), but also from the Network for Standardisation of Dementia Diagnosis (NEST-DD) and the European Alzheimer's Disease Consortium (EADC) PET project. Indeed, multicentre databases, and in particular the openly available ADNI data, are an ideal testing set for new analytical approaches.

Secondly, all studies published recently used a semiquantitative approach, such as regional uptake or statistical analysis using a reference control group, confirming that the nuclear medicine community is ready for systematic addition of objective approaches to the traditional approach of visual rating. Among these semiquantitative approaches, two main categories can be identified, namely univariate and multivariate tests. Although it can be expected that multivariate approaches may be able to capture the biological complexity better, validation for broad clinical application of tools based on multivariate approaches is still lacking. In contrast, this is available for several univariate methods [43, 44]. Within this context, it is important to note that eight of the studies published during the last 2 years specifically tested "ready to use" tools for single subject analysis, thus providing estimates of performance that can be expected in daily routine [28, 30, 35–38, 40, 41].

Thirdly, four of the recent papers did not just study [^{18}F]FDG PET, but also measured its added value within the overall diagnostic framework when other information (clinical, genetic profile, amyloid positivity) were taken into account, showing that [^{18}F]FDG PET positivity significantly modifies the risk of progression, both in amyloid-positive and in amyloid-negative patients [27, 28, 31, 35]. This is indeed a more natural approach, trying to simulate clinical practice and integrating different AD biomarkers, balancing healthcare costs with diagnostic accuracy. Within this framework, in a recent survey assessing the perceived usefulness of AD biomarkers for the aetiological diagnosis of MCI, neurologists working in EADC centres agreed that only a combination of amyloidosis and neuronal injury biomarkers (such as [^{18}F]FDG PET) is a strong indicator of an AD signature [45]. This position is also in line with published guidelines explicitly requiring the presence of neuronal injury markers to come to a conclusion of "intermediate probability" or "high probability" MCI/AD [46]. Furthermore, recently the validity of this approach has been further confirmed by a large retrospective multicentre study showing that, in the clinical setting, the combined use of both amyloid and neuronal injury markers offers the most accurate prognosis in MCI patients [47].

Conclusions

Based on a large body of evidence on its diagnostic sensitivity for the identification of AD, in 2004 [^{18}F]FDG PET imaging was approved by the Centers for Medicare and Medicaid Services (CMS, USA) as a routine examination tool for early and differential diagnosis of AD. Since then, large amounts of additional [^{18}F]FDG PET data have become available showing that the addition of [^{18}F]FDG PET to clinical examinations increases diagnostic accuracy in identifying AD patients even in the predementia stage. Of course, new opportunities and new challenges are coming up, which require the definition of the specific role of [^{18}F]FDG PET in the era of AD biomarkers (i.e. relationship with other biomarkers and role as a marker of progression in AD [46, 48]). Meanwhile, in daily clinical practice, nuclear medicine experts should continue to perform high-quality [^{18}F]FDG PET scans, constantly improving the standard through continuous education and the use of appropriate tools, knowing that it is one of the most informative biomarkers currently available for the prediction of dementia at the MCI stage.

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