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Roadmap to Alzheimer's Biomarkers in the Clinic

Clinical validity of presynaptic dopaminergic imaging with ^{123}I-ioflupane and noradrenergic imaging with ^{123}I-MIBG in the differential diagnosis between Alzheimer's disease and dementia with Lewy bodies in the context of a structured 5-phase development framework

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ABSTRACT

The use of biomarkers (BMs) for accurate diagnosis of Alzheimer's disease (AD) has been proposed by recent diagnostic criteria; however, their maturity is not sufficient to grant implementation in the clinical routine. A proper diagnostic process requires not only confirmation of the disease but also the exclusion of similar disorders entering differential diagnosis, like dementia with Lewy bodies (DLB). This review is aimed at evaluating the clinical validity of ^{123}I-ioflupane brain single photon emission tomography and ^{123}I-MIBG cardiac scintigraphy as imaging BMs for DLB. For this purpose, we used an adapted version of the 5-phase oncology framework for BMs development. A review of the literature was conducted using homogenous search criteria with other BMs addressed in parallel reviews. Results of our literature search showed that the rationale for the use of both BMs in the differential diagnosis of DLB and AD is strong (phase 1) and that they allow a good discrimination ability (phase 2), but studies investigating BMs distribution antemortem and postmortem on pathology are lacking. Moreover, thresholds for test positivity have not been defined for ^{123}I-MIBG. The 2 BMs have not been yet assessed in early phases of DLB and AD (phase 3). No phase 4 and phase 5 studies have so far been carried out. This review highlights the priorities to address in future investigations to enable the proper use of ^{123}I-ioflupane and ^{123}I-MIBG for the differential diagnosis of dementia.

1. Introduction

1.1. Background

The early and accurate diagnosis of Alzheimer's disease (AD) is still a challenge for clinicians. Recently proposed diagnostic criteria have suggested the use of biomarkers (BMs) as part of the clinical assessment of patients with cognitive complains (Albert et al., 2011; Dubois et al., 2014; Jack et al., 2011; Morris et al., 2014). Imaging BMs can enhance the accuracy of clinical diagnosis of AD, but to implement their wide use in clinical settings, a previous rigorous procedure for the validation of their state of validity needs to be complied with. A systematic validation procedure, in fact, includes: the demonstration of analytical validity, clinical validity, and clinical utility. Wide evidence of analytical validity is available for BMs for AD and related disorders. However, the limited evidence supporting their clinical validity and utility does not guarantee that BMs would work properly in ordinary clinical contexts.

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To overcome a similar limitation, Pepe et al. (2001) proposed a formal structure in the oncology field, borrowed from drug development, to guide the development of cancer BMs. This is a framework composed of 5 stages that each BM needs to pass through before it can be considered a valid and useful tool in clinical practice. The stages are designed in a manner that earlier phases are generally necessary to the later ones, and each stage comprises primary and secondary aims. The Geneva task force for the roadmap of Alzheimer's BMs has decided to use a similar approach in the field of dementia (Boccardi et al., 2017).

The aim of the roadmap is to assess the clinical validity of BMs for the diagnosis, and differential diagnosis, of AD. The approach of the roadmap is similar to that of oncologists, but each stage has been adapted to the field of dementia. The main goal of this review was to specifically assess the clinical validity of nuclear medicine BMs, namely ^{123}I-ioflupane brain single photon emission tomography (SPECT) and ^{123}I-MIBG cardiac scintigraphy, 2 key BMs for the diagnosis of dementia with Lewy bodies (DLB) and for the differential diagnosis between DLB and AD.

1.2. Differentiating AD and DLB

AD and DLB are respectively the first and second most common causes of neurodegenerative dementia in people aged more than 65 (Zaccai et al., 2005). The 2 clinical conditions can have a complex underlying pathology, with contribution from both AD and Lewy body pathologies. This can be responsible of a similar presentation, with an overlap of clinical symptoms, especially at earliest phases, and overlap on other imaging BMs, such as amyloid and ^{18}F-2-fluoro-deoxy-D-glucose (FDG) positron emission tomography (PET) imaging (Kantarci et al., 2012; Quigley et al., 2011; Siderowf et al., 2014).

The deposition of β-amyloid (Aβ) plaques in the brain is one of the core hallmarks of AD (Hyman et al., 2012). However, this is also present, along with α-synuclein Lewy bodies deposits, in a majority of patients affected by DLB (McKeith et al., 2005; Schneider et al., 2007). This explains the positivity on amyloid imaging, assessed with ^{11}C-Pittsburgh Compound B, in a high percentage of DLB patients, although lower than in AD (Kantarci et al., 2012). The pattern of glucose hypometabolism detected on ^{18}F-FDG PET in DLB patients involves mostly the occipital and parietal lobes. In particular, both occipital hypometabolism and relative preservation of posterior cingulate metabolism, the so called "cingulate island sign", have been proved to differentiate AD from DLB in both clinically diagnosed and autopsy-confirmed cohorts (Graff-Radford et al., 2014; Kantarci et al., 2012). However, the decline in the occipital glucose metabolism found in advanced phases of AD (Ishii et al., 1997), and associated to atypical AD (Aharon-Peretz et al., 1999), can contribute to an overlap of ^{18}F-FDG PET findings in some cases, and therefore to a decrease in the sensitivity of the exam, when differentiating AD from DLB.

An early and precise diagnosis of DLB is extremely important because it can lead to early initiation of an effective treatment, such as acetyl-cholinesterase inhibitors with a potential benefit on cognitive and psychiatric disturbances, and also avoidance of the use of potentially life-threatening treatments, such as antipsychotics, known to increase the risk of severe adverse reactions in DLB patients (Antonini, 2007).

The diagnosis of DLB relies on a set of consensus criteria that were first described in 1996 and later revised in 2005 (McKeith et al., 1996, 2005). The first version of the clinical diagnostic criteria has shown a limited diagnostic accuracy (high specificity, but low sensitivity) when compared with neuropathologic findings (Litvan et al., 2003; Mckeith et al., 2004). To overcome this limitation, in the revised version of the consensus criteria, new features indicative of Lewy body pathology were included as features of DLB, amongst them: low-dopamine transporter (DAT) uptake in the basal ganglia, measured on ^{123}I-ioflupane SPECT, considered a suggestive feature of DLB, and abnormal (low) uptake of ^{123}I-MIBG in the myocardium, measured on ^{123}I-MIBG scintigraphy, included in the supportive features of DLB. The inclusion of the 2 BMs in the new version of the consensus criteria for DLB highlights their utility as BM for the differential diagnosis between DLB and AD.

1.3. Contribution of ^{123}I-ioflupane and ^{123}I-MIBG to the AD-DLB differential diagnosis

^{123}I-ioflupane (DaTSCAN) is a well-established SPECT radiopharmaceutical, binding in vivo to the DAT and enabling the imaging of the presynaptic dopaminergic terminals. It was first approved for use in the European Union by the European Agency for the Evaluation of Medicinal Products (now European Medicines Agency) in 2000 and then also in Israel, Switzerland, and the United States. Indications include differential diagnosis between essential tremor and parkinsonian syndromes related to Parkinson's disease (PD), and differential diagnosis between probable DLB and AD (Grosset et al., 2014). The DLB consortium, including ^{123}I-ioflupane SPECT among the suggestive features for the diagnosis of DLB (McKeith et al., 2005), gave presynaptic dopaminergic imaging a high level of importance in guiding diagnosis of DLB.

^{123}I-MIBG is a radiolabeled analogue of guanethidine, an adrenergic blocking agent, sharing with norepinephrine the same mechanisms of uptake, storage, and release in noradrenergic neurons (Yamashina and Yamazaki, 2007). ^{123}I-MIBG is used in the clinical practice for several different purposes because it allows in vivo visualization of the sympathetic nerves. Cardiac ^{123}I-MIBG planar scintigraphy allows the estimation of local myocardial sympathetic nerve damage, as it is observed in various heart conditions, as well as in neurological disorders, such as DLB and PD. Cardiac SPECT has been evaluated as well, but the majority of data are collected with planar imaging. The DLB consortium included ^{123}I-MIBG cardiac scintigraphy among the supportive features for the diagnosis of DLB (McKeith et al., 2005), giving noradrenergic imaging a lower level of importance, compared with presynaptic dopaminergic imaging, in the diagnosis of DLB.

The aim of the present review was to evaluate the clinical validity of presynaptic dopaminergic imaging with ^{123}I-ioflupane and of noradrenergic imaging with ^{123}I-MIBG as BMs for the differential diagnosis between DLB and AD. The review of the literature specifically suggested that the use of 2 imaging BMs provides abnormal findings in DLB and normal findings in AD, and therefore they can play a key role in the differential diagnosis between the 2 conditions.

2. Materials and methods

2.1. Target

The review was performed in accordance to the model imported from the oncology field (Pepe et al., 2001) and was adapted to the field of dementia, specifically to the differential diagnosis between DLB and AD (Frisoni et al., 2017). Target population included patients with clinical diagnosis of DLB and AD. Studies conducted on patients with clinical diagnosis of PD or other parkinsonisms, and on healthy volunteers were also included. When available, studies including mild cognitive impairment (MCI) patients were also included.