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Combination Functional and Structural Imaging for the Diagnosis of Neurodegenerative Dementias – A Suggested Imaging Strategy

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Abstract

Early diagnosis of neurodegenerative dementia is challenging due to overlapping clinical and radiological features. With several potential disease-modifying therapies for Alzheimer's disease (AD) currently in the late stages of development, an accurate diagnosis is now more important than ever. Structural and molecular imaging biomarkers including MRI, amyloid PET, 18F-FDG-PET, 123I-FP-CIT SPECT, and 123I-metaiodobenzylguanidine (123I-MIBG) increase diagnostic accuracy and aid clinical decision making but there is confusion as to how or when these biomarkers should be applied. The European association of Nuclear Medicine (EANM) Focus 2 group provides a suggested framework as to how these imaging techniques can be applied and/or combined. They divide patients with cognitive impairment into three distinct groups based on their clinical presentation 1) suspected AD, 2) non-AD pathology suspected, and 3) cognitive decline in combination with Parkinsonian features. A recommended imaging strategy for each of these three groups is provided to increase diagnostic accuracy.

Introduction

Treatment options for AD are currently limited with no effective disease-modifying treatment approved for the past 18 years. However, there are currently several potential targeted disease-modifying therapies in the late stages of development and/or seeking FDA approval [1]. An accurate and early diagnosis of AD is, therefore, crucial but remains challenging. Imaging biomarkers including amyloid PET, 18F-FDG-PET, 123I-FP-CIT SPECT, and 123I-metaiodobenzylguanidine (123I-MIBG) provide valuable information and increase the diagnostic accuracy of neurodegenerative dementias. These imaging biomarkers are recommended in certain settings by several guidelines for the assessment of AD and several non-AD-related dementias. However, there is uncertainty regarding the appropriate application or combination of imaging biomarkers for the differential diagnosis of neurodegenerative dementia. The European Association of Nuclear Medicine (EANM) Focus 2 group has recently suggested a framework on how these imaging biomarkers could be combined to support clinical decision-making (Figure 1). This group proposed three distinct diagnostic pathways based on the clinical presentation with suggested biomarker sequences for each [2]. The three distinct pathways included are; 1) suspected AD, 2) non-AD pathology suspected (such as FTLD) and 3) cognitive decline in combination with Parkinsonian features.

Diagnostic Algorithm

Structural Imaging

Following clinical and neuropsychological assessment structural imaging with MR or CT is recommended as the first step before functional imaging biomarkers are considered. This allows for the detection of other pathologies including tumors, hydrocephalus, or vascular disease. Regional patterns of atrophy are also associated with specific pathologies and can aid the differential diagnosis or track progression of pathology. Structural imaging can however be normal in early disease.

MRI is useful for differentiating AD from FTLD or DLB by comparing characteristic patterns of atrophy best assessed on volumetric T1 weighted sequences. The medial temporal lobe structures are involved to a greater extent in AD. Atrophy of the medial temporal lobe structures is graded by the Medial Temporal Lobe Atrophy (MTA) scoring system, a 5 point scale based on the height of the hippocampus and prominence of the adjacent CSF spaces (Figure 2). A score of 2 or more is abnormal if under the age of 75, or 3 or more if over 75 years of age. High MTA scores are sensitive

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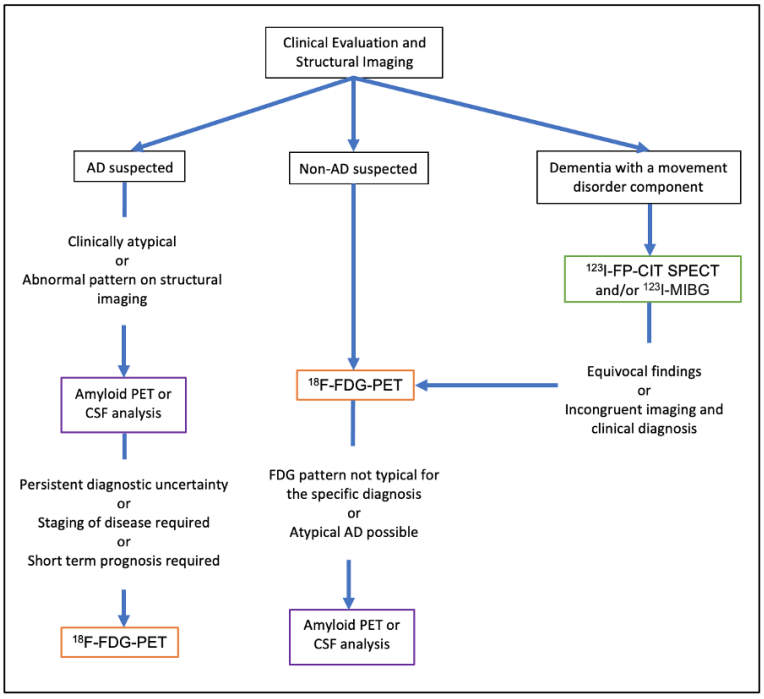

Figure 1: Suggested framework for combining structural and functional imaging to support clinical decision making in neurodegenerative dementia.

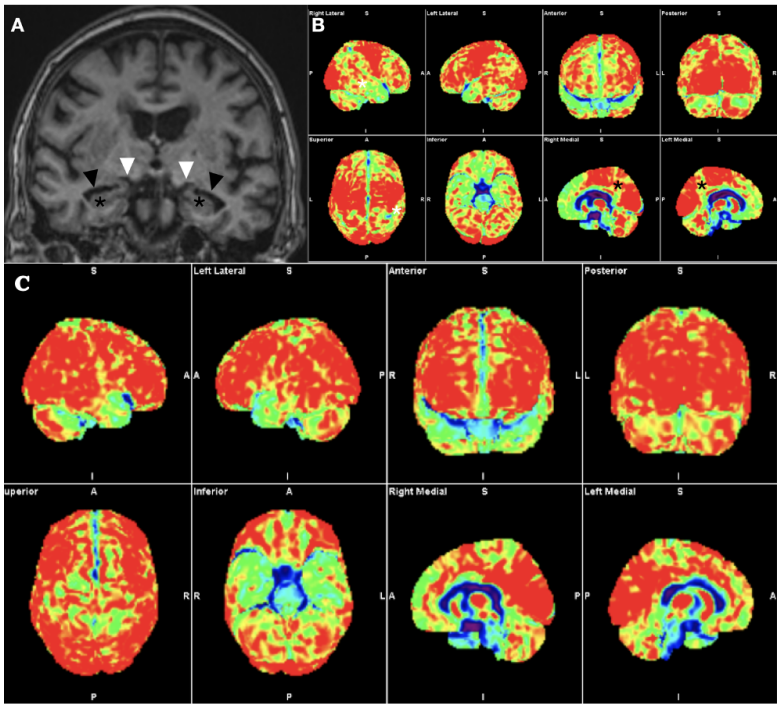

Figure 2: This patient presented with memory difficulties suggestive of mild cognitive impairment or early AD. (A) Coronal volumetric T1-weighted MR imaging through the hippocampi demonstrates widening of the choroidal fissures (white arrows) and temporal horns (black arrows) with minimal reduction in hippocampal size (black asterisks) - MTA 2. (B) 18F-FDG-PET imaging demonstrates subtle hypometabolism in the posterior cingulate gyri (black asterisk) and temporoparietal regions in keeping with early changes of AD. (C) Normal 18F-FDG-PET for comparison purposes.

for the diagnosis of AD [3]. However, they are not specific and can also be seen in vascular disease, hippocampal sclerosis or FTLD for example.

FTLD shows predominately anterior frontal and temporal lobe atrophy with relative sparing of the medial temporal lobe structures. Gyral atrophy is classified according to the Global cortical Atrophy (GCA) scale ranging from 0 (no atrophy) to 3 (a "knife-edge" appearance) (Figure 3) [4]. Sensitivities and specificities for differentiating FTLD and AD range from 55-94% and 81-97% respectively [5].

MR findings in DLB are non-specific. Occipital lobe atrophy is not described despite the changes evident on 18F-FDG-PET (Figure 4). On

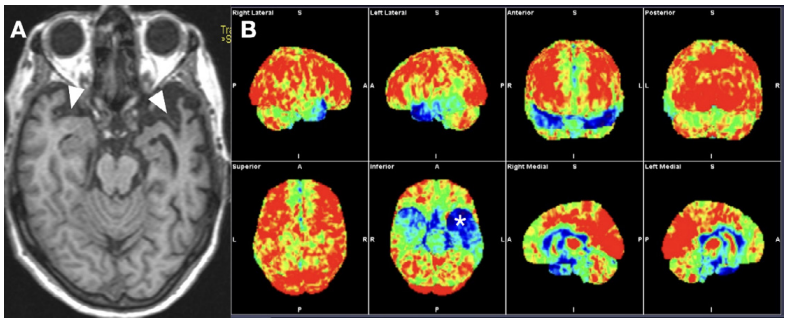

Figure 3: (A) Axial T1-weighted MR imaging in a patient with frontotemporal lobar degeneration (semantic variant) demonstrates asymmetric cerebral volume loss in the temporal lobes (white arrows) with knife-edge atrophy demonstrated on the left side. (B) 18F-FDG-PET demonstrates marked asymmetric hypometabolism affecting the frontal and temporal lobes, most marked on the left (white asterisk). Metabolism within the occipital lobes and posterior cingulate gyri is preserved.

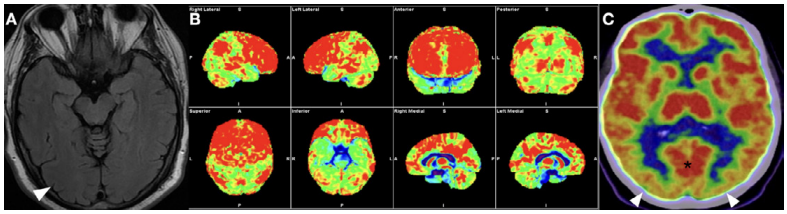

Figure 4: (A) Axial T1-weighted MR imaging in a patient with DLB demonstrates normal cerebral volume, including the occipital lobes. (B) ^{18}F-FDG-PET demonstrates cortical hypometabolism involving both occipital lobes with sparing of the posterior cingulate gyri. (C) Axial 18F-FDG-PET image demonstrates hypometabolism affecting the occipital lobes (white arrows) with relative preservation of the posterior cingulate gyri (black asterisk), producing the "posterior cingulate island" sign.

susceptibility-weighted imaging high signal can normally be seen within nigrosome 1 of the pars compacta known as the swallowtail sign. Loss of the swallowtail appearance occurs in DLB although the accuracy of this sign is <80% [6].

Further diagnostic assessment with functional imaging should take into consideration the treatments available if a particular diagnosis is made. If the treatment options for a given diagnosis are limited and treatable conditions excluded, it may not be necessary to proceed to functional imaging investigations to ascertain the specific underlying etiology of the disease process [2].

Suspected AD

AD is the most common form of dementia accounting for an estimated 60 to 80% of cases. The diagnosis can be particularly difficult early in the disease course or if there is an atypical or ambiguous clinical presentation with a mix of cognitive, behavioral, and motor symptoms. 18F-FDG-PET and amyloid PET neuroimaging and CSF biomarkers are well-established tools for the early diagnosis of AD.

CSF Biomarkers

The diagnostic utility of CSF biomarkers is recognized in research guidelines and is used clinically in many countries. They complement or overlap the utility of PET neuroimaging with both techniques offering insights into the presence of neurodegeneration or the presence of tau or amyloid pathology. For the detection of amyloid pathology, both CSF and PET biomarkers are validated although there is some discordance between the two [7]. PET imaging has the additional benefit of staging the disease and assessing the extent and location of amyloid plaques.

18F-FDG-PET

18F-FDG-PET detects regional cortical hypometabolism, a biomarker of neurodegeneration. It can predict progression from mild cognitive impairment to AD and is recommended for this purpose [8]. A normal 18F-FDG-PET can help exclude an underlying diagnosis of AD with a negative predictive value ranging between 77-95% (Figure 2) [9, 10]. An abnormal 18F-FDG-PET study is associated with an increased risk of progressive cognitive deterioration, even in patients without evidence of underlying amyloid pathology [11].

Appearances on 18F-FDG-PET often predate changes on MR as regional hypometabolism may manifest before cortical atrophy (Figure 2). 18F-FDG-PET adds significant diagnostic value over and above that of combination CSF analysis and MR particularly in the setting of predicting MCI progression to AD. In one study the misclassification rate decreased from 27% for CSF analysis and MR combined to 9% when 18F-FDG-PET was also performed [12]. 18F-FDG-PET is particularly useful for short-term prognostication and will play a pivotal role in identifying patients suitable for future disease-modifying therapies, access to which may be limited due to prohibitive costs.

18F-FDG-PET can assess the type, location, and severity of the underlying neurodegenerative process and aid the differential diagnosis. The characteristic appearance of AD is that of temporoparietal hypometabolism with involvement of the posterior cingulate gyri [12]. However atypical variants such as logopaenic variant primary progressive aphasia, frontal executive variant, or posterior cortical atrophy may demonstrate patterns of hypometabolism that overlap with FTLD or DLB.

Amyloid PET Imaging

Amyloid PET imaging allows in-vivo detection of amyloid plaques, a hallmark of AD. It is a well-established imaging technique and is highly

accurate for the detection of amyloid pathology with a sensitivity and specificity of 96% and 100% respectively in patients with an autopsy proven diagnosis of AD [13].

Appropriate use criteria have been proposed and the suggested patient groups that would benefit from amyloid PET include 1). Persistent/ progressive unexplained mild cognitive impairment (MCI). 2). Patients satisfying criteria for possible AD but with an atypical presentation or suspected mixed pathology. 3). Early-onset dementia (less than 65 years of age) [14].

Amyloid PET can also predict progression from MCI to AD with slightly greater sensitivity than 18F-FDG-PET at 93% although specificity is lower than at 56%. It is also not as accurate as 18F-FDG-PET at predicting short-term progression [15]. Amyloid plaques can manifest 30 years before the development of clinical symptoms and positive amyloid PET studies are seen in 10 to 44% of cognitively unimpaired 50 to 90-year-olds [16]. The relevance of this is not known. As a result amyloid PET imaging cannot predict time to clinical conversion from asymptomatic disease and cannot be used to accurately stage disease as it does not correlate well with the clinical picture and plateaus late in the disease process.

Studies of the clinical utility of amyloid PET imaging demonstrate changes to the underlying diagnosis in 30% of cases, a change to patient management in up to 60%, and significant increases in diagnostic confidence [17].

Non-AD Pathology Suspected

Frontotemporal lobar degeneration (FTLD) is one of the most common forms of dementia. Symptoms may resemble AD, particularly its atypical forms. It constitutes a heterogeneous group of neurodegenerative disorders characterized by atrophy of the frontal and temporal lobes. Clinical subtypes include Behavioural variant FTD (bvFTD), Primary Progressive Aphasia (PPA) which can be either Semantic variant PPA (svPPA) or Non-fluent Agrammatic variant PPA (NFA-PPA), and Motor Neuron Disease-associated FTD (FTD-MND).

18F-FDG-PET has a well-established role in the diagnosis of FTLD and increases the diagnostic accuracy for the differentiation of FTLD from AD compared to clinical criteria alone [18]. Patterns of hypometabolism correspond well with the associated clinical syndrome and may predate atrophy visible on MRI. Hypometabolism within the frontal and temporal lobes is most associated with bvFTD. Left anterior temporal lobe hypometabolism is associated with svPPA and nfaPPA with hypometabolism in the frontal and temporal lobes and the angular gyri. Combination MRI and 18F-FDG-PET have a sensitivity of 96% and specificity of 73% for the diagnosis of FTLD (Figure 3) [5]. Amyloid PET is useful to rule out underlying amyloid pathology as a normal study essentially excludes AD as a possibility [19].

Cognitive Decline with Parkinsonian Features

Dementia syndromes are often associated with Parkinsonian features. Specific diagnostic considerations in this setting include Parkinson's disease dementia (PDD), dementia with Lewy bodies (DLB), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD).

DLB and PDD are synucleinopathies characterized neuropathologically by Lewy Body intracellular inclusions, rich in alpha-synuclein. They have overlapping clinical features with the dominant features determined by the anatomical distribution of Lewy Body pathology. Both conditions are characterized by nigrostriatal degeneration and therefore demonstrate abnormal appearances at 123I-FP-CIT SPECT. Nigrostriatal degeneration does not typically occur in AD and 123I-FP-CIT SPECT can therefore be used to distinguish PPD or DLB from AD with the caveat that 123I-FP-CIT SPECT can be normal in early DLB.

In normality, 123I-FP-CIT SPECT demonstrates symmetric, comma-shaped radiotracer uptake within the caudate nuclei and putamina with normal background uptake (Figure 5). Nigrostriatal degeneration manifests with reduced putaminal uptake resulting in loss of the normal comma shape formed by the caudate and putamen (Figure 5). Regional uptake within the caudate and putamen should be directly compared – a caudate to putamen ratio of <1.3 is considered normal. The striatal binding ratio (SBR) can also be calculated to reduce inter and intra-observer variability. Regions of interest are drawn over the caudate or putamen and the occipital lobes and the SBR calculated as follows: (Caudate or Putamen count density – Occipital lobe count density) / (Occipital lobe count density). An abnormal SBR is less than 1. Greater than 2 is normal. Between 1 and 2 is indeterminate. Abnormal studies are divided into three separate categories; Grade 1; reduced radiotracer uptake within the putamen with normal

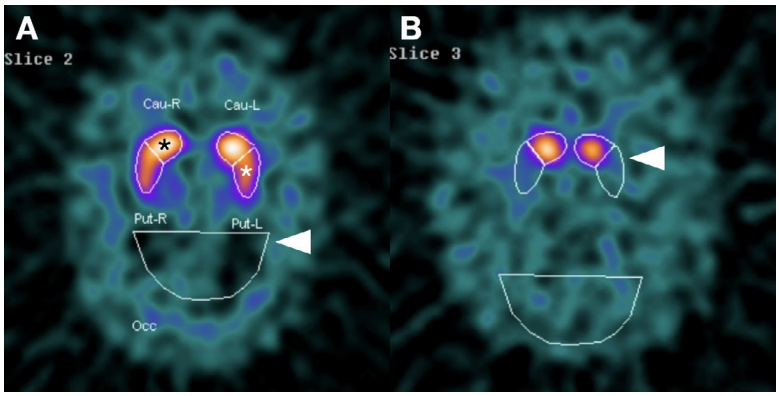

Figure 5: (A) Normal 123I-Ioflupane-SPECT demonstrates a comma shaped appearance of radiotracer uptake in the caudate (black asterisk) and putamen (white asterisk). All readings are relative to uptake within quantitative regions of interest over the occipital lobes (white arrow). (B) Abnormal 123I-Ioflupane-SPECT with reduced uptake in the putamina bilaterally. There is also slightly reduced uptake in both caudate nuclei, in keeping with a grade 3 abnormal study.

uptake in the contralateral putamen, Grade 2; symmetrically reduced uptake in the putamina. Uptake is confined to the caudate nuclei, and Grade 3; absent uptake within the corpus striatum bilaterally [5].

An abnormal 123I-FP-CIT SPECT study has a sensitivity of 78% and a specificity of 90% for the differentiation of probable DLB from AD. This exceeds the sensitivity of consensus clinical criteria [20]. An abnormal study does not differentiate DLB from other causes of nigrostriatal degeneration (Figure 6).

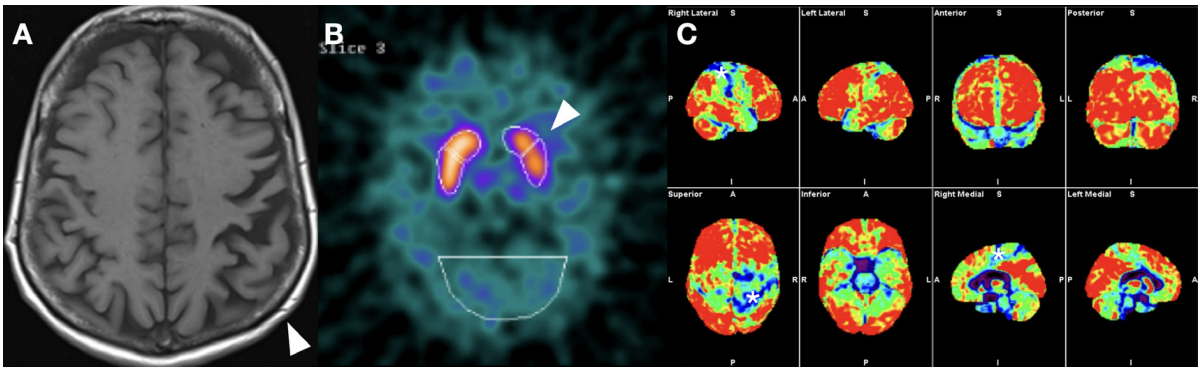

Figure 6: (A) Axial T1-weighted MR imaging of a patient initially reported as normal age related involutional change, demonstrates asymmetric frontoparietal atrophy on the left side (white arrow), subsequently diagnosed with CBD. (B) 123I-Ioflupane-SPECT in the same patient, demonstrates unilateral balanced loss of radiotracer uptake within the left caudate and putamen (white arrow). (C) 18F-FDG-PET imaging in a different patient demonstrates asymmetric hypometabolism in the superior parietal and posterior frontal areas bilaterally, more pronounced on the right side (white asterisk).

123I-MIBG cardiac scintigraphy is widely utilized in PD and DLB and can accurately differentiate these entities from AD. MIBG is an analog of norepinephrine and binds to postganglionic autonomic cardiac receptors. Cardiac radiotracer uptake is then compared to nonspecific mediastinal binding and the H (heart) to M (mediastinum) ratio is calculated. A H:M ratio of less than 2 is considered abnormal.

PD and DLB are both associated with degeneration of the pre and postganglionic autonomic neurons resulting in reduced cardiac sympathetic binding. These neurons are preserved in AD and therefore a normal study is expected [5].

Conclusion

With several disease-modifying therapies in the late stages of approval, an accurate and timely diagnosis of neurodegenerative dementia is more important than ever. The EANM Focus meeting 2 groups offer a useful diagnostic algorithm that serves as a framework for the workup of neurodegenerative dementia. The optimal combination of biomarkers is separated into three distinct pathways with the choice of biomarker dependent on the clinical scenario and specific diagnostic question. This algorithm will help with diagnostic decision-making and aims to increase diagnostic accuracy and efficiency.

Declaration

RP Killeen has previously provided paid educational content for Biogen on the use of molecular imaging in Alzheimer's disease.

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