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Biomarkers in Alzheimer's disease

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Alzheimer's disease (AD) is the most common form of dementia in the elderly, and it is characterized by progressive impairment in multiple cognitive domains of sufficient severity to interfere with individuals' daily living activities. Historically, the diagnosis of AD has been based on the identification of a clinical syndrome, and accuracy studies of the current clinical criteria conducted in referral clinics have shown high sensitivity for AD. However, the identification of the disease is still not perfect, and there is growing evidence that the use of biomarkers will increase our ability to better indentify the underlying biology of AD, especially in its early stages. These biomarkers will improve the detection of the patients suitable for research studies and drug trials, and they will contribute to a better management of the disease in the clinical practice. In this review, we discuss the most studied biomarkers in AD: cerebrospinal fluid proteins, structural magnetic resonance imaging, functional neuroimaging techniques, and amyloid imaging.

Keywords: Alzheimer's disease, mild cognitive impairment, biomarker, cerebrospinal fluid, magnetic resonance imaging, positron emission tomography

INTRODUCTION

Alzheimer's disease (AD) is the most frequent neurodegenerative disease (Ferri et al., 2005) and is characterized by a progressive dementia that occurs in middle or late life. The neuropathological hallmark of AD is the presence of cortical intracellular neurofibrillary tangles (NFT) and extracellular β-amyloid (Aβ) plaques (Braak and Braak, 1991), which leads to synapse dysfunction, neuronal cell loss and subsequent brain atrophy (Ballard et al., 2011). In the past few decades the knowledge of the key pathogenic mechanisms of the disease has improved, but they are still not completely understood (Querfurth and LaFerla, 2010). The natural history of AD could be divided in three different phases: the pre-clinical phase, where the pathogenic mechanisms of the disease have started but no symptoms can be identified; the prodromal phase, where mild cognitive symptoms appear, but there are not severe enough to meet dementia criteria; and the dementia phase (Dubois et al., 2007). On the other hand, mild cognitive impairment (MCI) is a clinical construct created to capture patients with subtle cognitive symptoms at risk for AD (Petersen et al., 2009). However, some subjects develop other types of dementias, do not progress, or even revert to normal cognition (Ganguli et al., 2004; Brooks and Loewenstein, 2010). Therefore, it is difficult to label MCI patients as having prodromal AD.

Currently, the most frequently used clinical diagnostic criteria for AD are the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; APA, 2000) and the National Institute of Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders (NINCDS–ADRDA; McKhann et al., 1984) working group. These criteria are fulfilled in a two-step diagnostic process. First, the dementia syndrome is established and then, criteria based on the clinical features of the AD type dementia are applied. The DSM-IV-TR criteria require the presence of impairment in multiple cognitive domains of sufficient severity to interfere with the individuals' activities of daily living to diagnose dementia. Hence, the clinical diagnosis of AD is not possible until a patient reach the dementia phase of the disease. On the other hand, these criteria have shown to have good sensitivity and specificity to distinguish between patients with AD type dementia and non-demented subjects, but are less accurate to differentiate AD dementia from other primary dementias (Knopman et al., 2001; Ballard et al., 2011). In fact, up to 20% of patients clinically diagnosed with AD do not have AD pathology at autopsy (Mayeux et al., 1998; Lim et al., 1999).

A more accurate and earlier diagnosis of AD (e.g., in MCI patients that will progress to the AD dementia phase or ideally those subjects in the pre-clinical phase) could enable the administration of potential disease-modifying drugs that would have a great impact on patients' life and profound implications for public health (Brookmeyer et al., 1998). In this context, there is a need of specific biological markers for AD diagnosis in the earliest stages. A biomarker is defined as a measureable feature that can be used to diagnose a physiologic or pathologic condition. The ideal biomarker of AD would be: (1) directed at the fundamental pathophysiology of the disease, (2) a marker of the presence of disease itself, (3) efficacious at prodromal, and even pre-clinical stages of AD, (4) an indicator of disease's severity, (5) a marker of treatment effectiveness, and (6) inexpensive and non-invasive (Klunk, 1998). In the case of AD, different biomarkers have been described using diverse approaches. The development of cerebrospinal fluid (CSF) assays and neuroimaging techniques that can provide information about the presence of AD pathological changes has been a major step forward in the field. Consequently, biomarkers for AD are

called to play a central role in the clinical characterization of the disease.

More recently, the NINCDS–ADRDA criteria have been revised by the National Institute on Aging and the Alzheimer's Association (NIA–AA) workgroup to include the experience in research over the past 25 years (McKhann et al., 2011). The NIA–AA proposed a series of diagnostic classification from pre-clinical AD to MCI to full-blown AD, and introduced CSF and neuroimaging biomarkers as supportive features of the disease (Albert et al., 2011; McKhann et al., 2011; Sperling et al., 2011). However, the authors cautioned about the use of biomarkers, and stated that their use should be limited to research and drug trials. Nevertheless, the core clinical criteria for AD remained relatively intact in the new criteria.

This review will focus on the most widely studied and currently accepted sources of biomarkers in AD: CSF, magnetic resonance imaging (MRI), and Nuclear Medicine techniques, including amyloid imaging.

BIOMARKERS IN CSF

Clinical studies employ mainly blood or CSF to search biochemical markers of neurodegenerative diseases. Typically, the CSF better reflects the brain neurochemistry, while biochemical values in plasma or serum may be affected by many non-neurological factors. CSF biomarker research has focused mainly on molecules related to the central neuropathological features of AD, such as Aβ, the main component of the senile neuritic plaques (SNP), and tau proteins that are part of the NFTs. Aβ is a 36–43 amino acid peptide originated from proteolysis of the amyloid protein precursor (Querfurth and LaFerla, 2010). SNPs are mainly composed by Aβ protein with 40 ($A\beta_{40}$) or 42 ($A\beta_{42}$) amino acids, and it seems that Aβ deposition begins with $A\beta_{42}$, and during plaque maturation, they acquire $A\beta_{40}$ (Iwatsubo et al., 1994). By contrast, NFTs are formed by tau proteins, a microtubule-associated stabilizing protein essential for axonal transport. Tau is hyperphosphorylated in AD, which tends to aggregate, leading to synaptic and neuronal dysfunction (Lee, 1996; Blennow et al., 2010; Querfurth and LaFerla, 2010). This process of NFTs formation starts in the entorhinal cortex, spreading to the hippocampus, and then to the rest of the brain. These neuropathological changes begin early, even decades before the onset of clinical symptoms of dementia (Braak and Braak, 1991), but the relative contributions of altered tau and amyloid metabolism to neurodegeneration remain under investigation. Nevertheless, NFTs are more robust associated with measures of synapse loss and cognitive impairment that SNPs (Gomez-Isla et al., 1997).

Typically, AD patients have lower levels of $A\beta_{42}$ in the CSF compared to normal controls, $A\beta_{40}$ tends to remain constant, and tau (t-tau) and phosphorylated tau (p-tau) increase (Arai et al., 1995; Blennow et al., 1995; Motter et al., 1995; Vigo-Pelfrey et al., 1995; Galasko et al., 1998; Kurz et al., 1998; Shoji et al., 1998; Hulstaert et al., 1999; Andreasen et al., 2001; Sunderland et al., 2003; Lewczuk et al., 2004; Schoonenboom et al., 2004; Shaw et al., 2009). The low CSF $A\beta_{42}$ levels in this entity may represent the retention of the peptide into plaques, resulting in reduced availability to diffuse into the CSF. This is supported by the findings that $A\beta_{42}$ in the CSF is inversely correlated with amyloid plaque load at autopsy (Strozyk et al., 2003; Tapiola et al., 2009) and as measured *in vivo* by amyloid imaging (Fagan et al., 2006; Forsberg et al., 2008; Tolboom et al., 2009). The increase in t-tau and p-tau in the CSF of AD patients may stem from release into CSF during neurodegeneration (Blennow et al., 1995), although the exact mechanism is not known. T-tau and p-tau concentrations in the CSF have been associated with NFT load at autopsy (Buerger et al., 2006a; Tapiola et al., 2009), as well as with cognitive decline and brain atrophy (Buerger et al., 2002; Hampel et al., 2005; Fjell et al., 2010; Vemuri et al., 2010b).

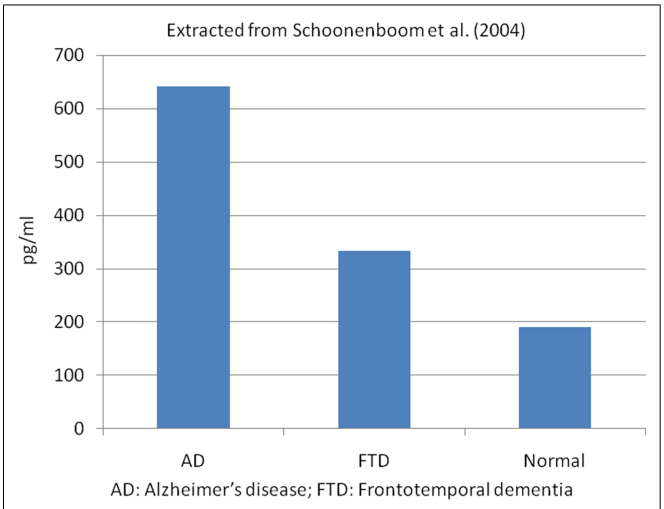

FIGURE 1 | Mean CSF total tau levels in autopsied proven cases. Extracted from Schoonenboom et al. (2004). AD, Alzheimer's disease; FTD, frontotemporal dementia.

Low CSF $A\beta_{42}$ and high t-tau or p-tau proteins have shown high accuracy for AD diagnosis (Galasko et al., 1998; Andreasen et al., 2001; Schoonenboom et al., 2004). Studies that compared AD patients with normal control subjects have demonstrated that low $A\beta_{42}$ had 78–100% sensitivity and 47–81% specificity for AD diagnosis; high CSF t-tau levels had 70% sensitivity and 92% specificity and p-tau showed 77% sensitivity and 87% specificity. However, p-tau appears to be better than t-tau in the diagnosis of AD, and it has shown a positive predictive value of 90%, especially p-tau phosphorylated at threonine 181 ($p\text{-}tau_{181}$; Hampel et al., 2004a; Mitchell, 2009). **Figure 1** shows the t-tau levels in AD, frontotemporal dementia (FTD), and normal autopsied subjects, and **Figure 2** shows the $A\beta_{42}$ levels in the same population (Schoonenboom et al., 2004).

Because some studies found that $A\beta_{42}$ and tau levels alone were not sufficient to differentiate AD from normal controls or other dementias, the $A\beta_{42}$/tau ratio is used to improve the diagnosis of AD. A meta-analysis showed that the $A\beta_{42}$/tau ratio had a sensitivity of 71% and specificity of 83% for AD (Hampel et al., 2004b); and a recent study showed that the "signature" of AD, based on the CSF $A\beta_{42}/p\text{-}tau_{181}$ ratio cutoffs, was present in 90% of the AD patients compared to 36% in the normal control group (De Meyer et al., 2010). Although, these CSF biomarkers seem to be useful to diagnose AD, they are not sensitive enough to assess disease progression (Sunderland et al., 1999; Vemuri et al., 2010b). Nevertheless, higher CSF t-tau and lower $A\beta_{42}$ values

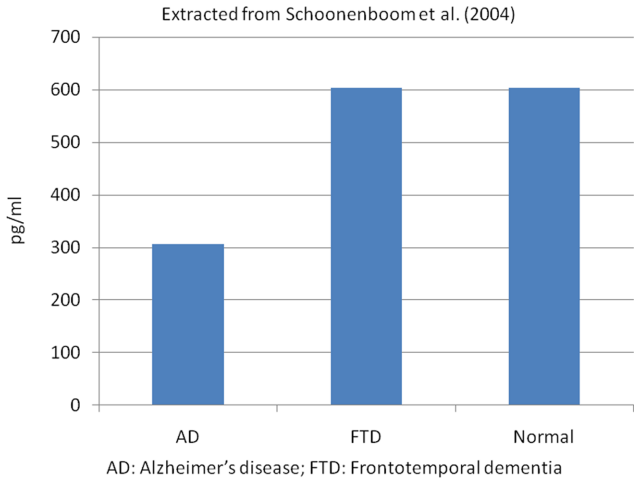

FIGURE 2 | Mean CSF $A\beta_{42}$ levels in autopsied proven cases. Extracted from Schoonenboom et al. (2004). AD, Alzheimer's disease; FTD, frontotemporal dementia.

have been associated with rapid cognitive decline, no response to cholinesterase inhibitor treatment and a higher mortality in patients with AD dementia (Wallin et al., 2010).

Cerebrospinal fluid biomarkers might have a role in the differential diagnosis of AD and other dementias. Patients with dementia with Lewy bodies (DLB), like AD patients, have lower levels of $A\beta_{42}$ in the CSF compared to normal controls, reflecting that most of these subjects also present AD pathology. Nevertheless, shorter amyloid peptides ($A\beta_{37}$, $A\beta_{38}$, and $A\beta_{40}$) appear to be slightly more elevated in AD dementia (Bibl et al., 2006). Consequently, the $A\beta_{42}/A\beta_{37}$ and $A\beta_{42}/A\beta_{38}$ ratios seemed to better discriminate AD from DLB (Bibl et al., 2006; Mulugeta et al., 2010). T-tau and p-tau levels are normal or high in DLB, but most studies have shown that these markers' levels in DLB are definitely lower than those found in AD. Other proposed biomarker for the differentiation of AD from DLB was monomeric soluble α-synuclein, but the available studies in DLB patients showed conflicting results. Elevated, unchanged and decreased total α-synuclein levels have been reported in these patients compared to AD and control subjects (Mukaetova-Ladinska et al., 2010). In addition, there are limited data about oligomeric α-synuclein in CSF, although it could be potential biomarker for synucleinopathies (Tokuda et al., 2010). Possibly, the combination of all these markers will help to distinguish between AD and DLB in the future.

In FTD, CSF $A\beta_{42}$ levels are lower than in control subjects but higher than in AD, while t-tau and p-tau levels are higher than in controls but lower that in AD patients (Hulstaert et al., 1999; Riemenschneider et al., 2002). Hence, t-tau/$A\beta_{42}$ and p-tau/$A\beta_{42}$ ratios could be a useful tool to distinguish AD from FTD (Bian et al., 2008; Cruz de Souza et al., 2011). Creutzfeldt–Jakob disease (CJD) is characterized by decreased CSF $A\beta_{42}$ concentrations and very high t-tau levels, reflecting intense neuronal damage, while p-tau levels are normal (Kapaki et al., 2001; Riemenschneider et al., 2003; Buerger et al., 2006b). Current data suggest that p-tau levels could be the most relevant marker to differentiate AD from other types of dementias (Hampel et al., 2004b; Kapaki et al., 2007; Koopman et al., 2009).

Cerebrospinal fluid biomarkers may also be useful in predicting progression to AD in subjects with MCI (Andreasen et al., 1999; Hampel et al., 2004c; Ewers et al., 2007; Brys et al., 2009). Low CSF $A\beta_{42}$ levels predicted conversion with 60–80% sensitivity and 65–100% specificity, while t-tau levels had 83–86% sensitivity and 56–90% specificity, and p-tau had 73–84% sensitivity and 47–88% specificity (Hampel et al., 2004b). However, the conversion to AD dementia in MCI subjects has shown significant variability among different CSF studies. Hansson et al. (2006) found high sensitivity (95%) and specificity (87%) for the conversion from MCI to AD dementia using a combination of t-tau and $A\beta_{42}$/p-tau_{181} ratio cutoff values. By contrast, a multicenter CSF study found lower sensitivity (83%) and specificity (72%) for the conversion from MCI to AD than single-site studies, with a considerable inter-site assay variability that highlights a need for standardization of analytical techniques and subject selection (Mattsson et al., 2009). Other large multicenter studies have confirmed the high predictive value of these CSF biomarkers in the identification of cases with prodromal AD in the context of the MCI syndrome (Shaw et al., 2009; Visser et al., 2009).

The CSF biomarkers have been used to identify the pre-clinical stage of AD. Cross-sectional studies in normal control individuals carrying the ApoE4 allele showed lower CSF $A\beta_{42}$ and higher p-tau_{181} levels (Peskind et al., 2006; Kester et al., 2009; Shaw et al., 2009; Vemuri et al., 2010a). Interestingly, CSF levels of $A\beta_{42}$ correlated with brain volume in this group of subjects, while in MCI and AD dementia patients, whole-brain volume correlated with CSF t-tau and p-tau_{181} (Fagan et al., 2009). A longitudinal CSF study in normal controls found increased t-tau levels and no change in $A\beta_{42}$ after a 1-year follow-up (Vemuri et al., 2010b). A few longitudinal studies have assessed which CSF biomarker or combination of biomarkers better predict AD dementia or cognitive decline. Fagan et al. (2007) demonstrated that CSF tau/$A\beta_{42}$ ratios may predict future dementia in cognitively normal older subjects and two other studies showed that low levels of CSF $A\beta_{42}$ predicted cognitive decline, as measured with the mini mental status examination (MMSE; Gustafson et al., 2007; Stomrud et al., 2007). Although there are studies that showed that CSF $A\beta_{42}$ could predict prodromal AD, there was a wide SD in these subjects, which made difficult to determine individually who will progress to AD. Further studies are needed to assess changes in CSF markers over time and to determine the best CSF markers of change.

STRUCTURAL NEUROIMAGING MARKERS

Structural neuroimaging techniques are normally performed during the clinical assessment of patients with dementia, mainly to rule out structural lesions, such as brain tumors, normal pressure hydrocephalus, or vascular lesions. The MRI has shown high sensitivity to detect brain atrophy caused by the neurodegenerative process (Bobinski et al., 2000). Several methods are used to analyze MRI data including visual inspection, volumetry, or region of interest (ROI) analysis (applying manual tracing, automated, or semi-automated techniques) and voxel based morphometry (VBM; Vemuri and Jack, 2010). There are benefits and limitations of these methods. The visual rating of the images and

ROI analysis depend on the *a priori* choice of structures, while VBM is a whole-brain operator-independent analysis (Ashburner and Friston, 2000). However, VBM analysis only allows comparing groups of patients, and it is not useful to classify individual cases. Visual assessment of MRI scans is a fast method to assess brain atrophy but is not the most precise (Raji et al., 2010). Volumetry of the medial temporal lobe structures is the most common quantitative method used in AD. The traditional manual tracing is time-consuming, and consequently, automated or semi-automated methods that require no significant manual intervention have been developed. Other methods to analyze sequential MRIs are boundary shift integral (BSI) and tensor-based morphometry (TBM). BSI has been developed to quantify the global percentage of change in the brain surfaces between two scans, while TBM provides a three-dimension profile of brain atrophy (Vemuri and Jack, 2010).

Brain MRI studies have shown that AD patients have a widespread cortical volume loss, including the frontal lobes, the temporoparietal regions, precuneus, and mesial temporal lobes, with relative sparing of the sensorimotor, visual, and cerebellar regions (Du et al., 2001; Good et al., 2001; Thompson et al., 2001; Karas et al., 2003; Testa et al., 2004; Ishii et al., 2005; Dickerson et al., 2008; Burton et al., 2009). Longitudinal studies have suggested that atrophy stars in the medial temporal lobes and fusiform gyrus in the prodromal phase of the disease, then spreads out to the posterior temporal and parietal lobes, and by the time of the dementia phase, it involves the medial temporal lobes, temporoparietal cortex, and the frontal lobe (Whitwell et al., 2007). This pattern of atrophy progression on MRI appears to follow the distribution of NFT in the different Braak and Braak (1991) pathological stages (Whitwell et al., 2008). In AD, there is also a greater rate of brain atrophy over time compared with healthy elderly subjects (1.9–2.2% per year versus 0.5–0.7% per year; O'Brien et al., 2001; Sluimer et al., 2008a,b; Henneman et al., 2009). Hippocampal and whole-brain atrophy in AD correlated well with cognitive performance and measures of disease severity (Jack et al., 2008a; Ridha et al., 2008; Schott et al., 2008).

In amnestic MCI subjects as a group, MRI studies show a similar pattern of brain atrophy to that observed in AD (Jack et al., 2000; Chetelat et al., 2002; Karas et al., 2004; Bell-McGinty et al., 2005; Whitwell et al., 2008) and rates of whole-brain atrophy are around 1% per year, between AD and control subjects (Jack et al., 2004). Whole-brain atrophy rate in MCI is associated with impaired cognitive performance (Evans et al., 2010) and predicts progression to AD dementia (Spulber et al., 2008). Whole-brain techniques have also shown that higher rates of atrophy in specific areas such as the hippocampus, posterior cingulated gyrus, and superior parietal cortex were associated with incident AD in MCI cases (Chetelat et al., 2005), and hippocampal and basal forebrain volumes in normal subjects predicted future development of AD (Hall et al., 2008). Interestingly, a recent study showed that normal subjects with the AD CSF profile had increased rates of brain atrophy over time, suggesting they may be in the pre-clinical phase of the neurodegenerative process (Schott et al., 2010). Nevertheless, this observation requires a longer follow-up period to demonstrate that this particular group of subjects has a higher risk to develop AD dementia.

Because the most important clinical manifestation of AD is memory loss, the majority of the researchers have focused on the study of hippocampal atrophy as a marker of the disease. Different neuroimaging studies assessing the mesial temporal lobe structures have consistently shown smaller hippocampal volumes in AD patients compared to controls (Pennanen et al., 2004). Measures of hippocampal atrophy correlate well with the degree of cognitive impairment (Jack et al., 2000; Mortimer et al., 2004) and with AD pathology and hippocampal sclerosis in MRI-post-mortem studies (Jagust et al., 2008). Both normal aging and AD have gradual volume loss overtime, but as with whole-brain volume is greater in AD; the annual rate of hippocampal atrophy is 1.41% for healthy controls and 4.66% for AD patients (Barnes et al., 2009). Several studies have shown that hippocampal atrophy measured by MRI predicts conversion from MCI to AD (Jack et al., 1999; Visser et al., 1999, 2002; Geroldi et al., 2006; Devanand et al., 2007; Teipel et al., 2007). A recent meta-analysis showed that this measure could identify MCI converters with a sensitivity of 73% and a specificity of 81% (Yuan et al., 2009). Although decreased entorhinal cortical thickness has been proposed as a predictor of conversion from MCI to AD, measures of decrease hippocampal volume appeared to be a more robust predictor.

There are several limitations for the use of whole-brain or hippocampal volume as a sole biomarker for AD. One of the most important is that small brain volumes can also be seen in normal aging, and consequently, is difficult to separate cases with early AD from normal controls. On the other hand, the rate of change on whole-brain, entorhinal, and hippocampal volumes seemed to be good markers of neurodegeneration and they can be useful in determining the effects of AD therapies, but these techniques are labor intensive and limited to research studies.

FUNCTIONAL NEUROIMAGING MARKERS

Brain functional neuroimaging techniques – positron emission tomography (PET) and single photon emission computed tomography (SPECT) – allow a broad range of cerebral functions to be assessed in patients currently living with dementia. Actually, brain metabolism, brain perfusion, and different neurotransmitter systems can be measured with a great variety of PET and SPECT tracers. However, brain metabolism with the glucose analog 2-[^{18}F]-fluoro-2-deoxy-d-glucose (^{18}F-FDG) and brain perfusion with technetium-99m hexamethylpropylamine oxime (99mTc-HMPAO) are the two more widely employed techniques in the evaluation of patients with dementia, both in clinical practice and in research. Brain SPECT with 99mTc-HMPAO studies provide information of the regional cerebral blood flow, and ^{18}F-FDG PET estimates the regional brain rate of glucose consumption, therefore providing information about the pattern of neuronal loss or synapse dysfunction in patients with dementia.

The pattern of SPECT hypoperfusion and PET hypometabolism usually seen AD involves the anterior medial temporal lobes, the posterior cingulate and posterior temporoparietal cortex (Kogure et al., 2000; Ishii et al., 2001; Alexander et al., 2002; Bradley et al., 2002). Nevertheless, SPECT seems to be less accurate than PET for the diagnosis of AD. One autopsy study found that this technique alone had a sensitivity of 63% and a specificity of 93% to diagnose AD (Jagust et al., 2001). On the other hand,

SPECT seemed to be useful differentiating AD from other dementias. The sensitivity of this procedure discriminating AD from FTD was 71.5% and the specificity was 78.2%, while its sensitivity and specificity to differentiate AD from vascular dementia were 71.3 and 75.9%, respectively (Dougall et al., 2004). In MCI patients, SPECT has shown that can predict conversion to AD with a test accuracy of 82% (Huang et al., 2007).

Positron emission tomography studies in early AD have shown a pattern of reduced metabolism in the posterior cingulate (Minoshima et al., 1997) and mesial temporal cortices. As the disease progresses, there is a greater involvement of the parietotemporal and frontal cortices (Ishii et al., 2001; Silverman et al., 2001; Alexander et al., 2002; Drzezga et al., 2003). This progression of the areas of hypometabolism correlated with cognitive deterioration over time as measured by neuropsychological tests (Engler et al., 2006; Kadir et al., 2010) and dementia severity scales (Foster et al., 1984; Minoshima et al., 1995; Silverman et al., 2001; Mosconi et al., 2005). A meta-analysis showed that pooled ^{18}F-FDG PET sensitivity and specificity to differentiate AD patients from normal subjects were 86% in both cases, but the variability was important between the studies (sensitivity from 61 to 100% and specificity from 54 to 100%; Patwardhan et al., 2004). PET also seems to be a good tool to differentiate AD from other forms of dementia. In an autopsy confirmed study, the presence of occipital hypometabolism was able to distinguish DLB from AD with 90% sensitivity and 80% specificity (Minoshima et al., 2001). This technique also has a high specificity and sensibility to differentiate AD and FTD (Koeppe et al., 2005; Foster et al., 2007; Panegyres et al., 2009).

^{18}F-FDG PET appears to be a promising instrument to discriminate those patients with MCI who will progress to AD dementia. These patients show a medial temporal and posterior cingulate cortices hypometabolism compared with healthy controls (Chetelat et al., 2003; Anchisi et al., 2005; Drzezga et al., 2005). A recent meta-analysis has also shown that ^{18}F-FDG PET performs slightly better than SPECT and structural MRI in identifying the prodromal phase of AD in patients with a clinical diagnosis of MCI (pooled sensitivity of 89% and specificity of 85%; Yuan et al., 2009). Interestingly, similar metabolic reductions in the same regions as those found in MCI and AD patients have been seen in asymptomatic subjects at risk of AD, i.e., in persons with subjective memory complains (Caselli et al., 2008), carriers of an apolipoprotein E ε4 (ApoE4) allele (Reiman et al., 1996, 2001, 2004, 2005), with abnormalities in the CSF markers (Petrie et al., 2009), or with a maternal history of AD (Mosconi et al., 2007, 2009). Furthermore, hippocampal hypometabolism during normal aging predicted cognitive decline years in advance of the clinical diagnosis (de Leon et al., 2001; Jagust et al., 2006; Mosconi et al., 2008). Taken together, these data indicate that ^{18}F-FDG PET has high sensitivity to distinguish AD from controls and from other dementing entities, and also to identify subjects at high AD risk. Consequently, the PET AD pattern has been incorporated into the new clinical criteria for prodromal AD (Dubois et al., 2007), pre-clinical AD (Sperling et al., 2011), and MCI due to AD (Albert et al., 2011).

MOLECULAR NEUROIMAGING MARKERS

The development of PET radiotracers that bind to brain amyloid has revolutionized the use of neuroimaging techniques in patients with dementia. These molecules allow the localization of AD pathology *in vivo*, and have helped to further our understanding of the underlying biology of AD. The most actively tested tracers are *N*-methyl-[^{11}C]2-(4′-methylaminophenyl)-6-hydroxybenzothiazole (^{11}C-PIB; Klunk et al., 2003), (E)-4-(2-(6-(2-(2-(2-(18)F-fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-*N*-methyl benzenamine (^{18}F-AV-45; Choi et al., 2009) and 2-(1-96-(2-^{18}F-fluoroethyl)(methyl)amino)-2-naphthyl)ethyldene) malono nitrile (^{18}F-FDDNP; Small et al., 2006; Shin et al., 2008), but there are multiple ^{11}C and ^{18}F compounds under investigation such as *trans*-4-(*N*-methyl-amino)-4′-2-[2-(2-[18F]fluoroethoxy)-ethoxy]-ethoxy-stilbene (^{18}F-BAY94-9172; Rowe et al., 2008), 4-*N*-[^{11}C-methyl]amino-4′-hydroxystilbene (^{11}C-SB-13; Verhoeff et al., 2004) and 2-(2-[2-dimethylaminothiazol-5-yl]ethenyl)-6-(2-[fluoro]ethoxy)benzoxazole (^{11}C-BF-227; Kudo et al., 2007). While ^{11}C have better affinity for fibrillar amyloid than ^{18}F compounds, the former have a very short life, which limits its use to centers with an available cyclotron that can produce them. Among these tracers, ^{11}C-PIB is the most widely used and best characterized. This thioflavin-T derived binds fibrillar Aβ with high affinity and its brain retention correlates well with levels of amyloid in AD brain tissue (Mathis et al., 2002, 2003; Klunk et al., 2004; Ikonomovic et al., 2008; Leinonen et al., 2008).

Positron emission tomography studies with ^{11}C-PIB have demonstrated an increased retention of this tracer in frontal and parietotemporal cortices, as well as in the striatum of almost all AD patients compared with controls (Klunk et al., 2004; Edison et al., 2006; Rowe et al., 2007). However, it is important to note that a positive ^{11}C-PIB PET scan can also be seen in other entities, often misdiagnosed as AD, such as DLB and cerebral amyloid angiopathy (Edison et al., 2008; Gomperts et al., 2008; Dierksen et al., 2010). ^{11}C-PIB retention in AD correlates with rates of whole-brain atrophy (Archer et al., 2006), parietotemporal hypometabolism on ^{18}F-FDG PET (Klunk et al., 2004; Edison et al., 2006; Engler et al., 2006), and decreased CSF $A\beta_{42}$ levels (Fagan et al., 2006; Grimmer et al., 2009; Jagust et al., 2009). There are few longitudinal studies using amyloid ligands, and the observation time has been relatively short, because these techniques have only been available for research since 2004. Recent longitudinal studies in AD patients assessing amyloid load and progression of neurodegeneration using structural MRI or ^{18}F-FDG PET found that ^{11}C-PIB retention was relatively stable over time, while neurodegenerative markers worsen in parallel with cognitive decline (Engler et al., 2006; Jack et al., 2009; Scheinin et al., 2009; Kadir et al., 2010). These findings are consistent with the hypothesis that there is dissociation between the amyloid deposition and the neurodegenerative process, where amyloid accumulation precedes the clinical symptoms and reaches its maximum detectable level before the cognitive deficits are evident (Jack et al., 2010a). However, another recent study has shown increases of ^{11}C-PIB retention in mild to moderate AD dementia, questioning this hypothesis and suggesting that Aβ deposition might slow down in the later stages of the disease, but it is still present (Villemagne et al., 2011).

In MCI patients, ^{11}C-PIB PET shows a bimodal distribution with some subjects having a pattern of retention similar to AD patients and others similar to control subjects (Pike et al., 2007; Rowe et al., 2007; Jack et al., 2009; Wolk et al., 2009). In these patients, the Aβ burden is related to episodic memory impairment

but not to other cognitive tasks (Pike et al., 2007). The PIB-positive MCI subjects are more likely to carry an ApoE4 allele and to progress to AD (Pike et al., 2007; Forsberg et al., 2008; Okello et al., 2009; Wolk et al., 2009; Jack et al., 2010b). Factors that seem to influence a shorter time to progression in PIB-positive subjects is the presence of hippocampal atrophy, higher ^{11}C-PIB retention values and having an ApoE4 allele (Okello et al., 2009; Jack et al., 2010b; Koivunen et al., 2011). Longitudinal studies assessing changes in ^{11}C-PIB retention in MCI patients are contradictory. Jack et al. (2009) rescanned MCI subjects after a single year, but only a minimal change has seen in this group of persons. However, Villemagne et al. (2011) have shown small but significant increases in ^{11}C-PIB cortical retention in MCI patients from the baseline studies to scans to those performed from 20 months to 3 years later; other studies have reported similar results (Kadir et al., 2010; Koivunen et al., 2011).

In agreement with autopsy data (Price and Morris, 1999), approximately 20–30% of elderly cognitively normal subjects show some degree of ^{11}C-PIB retention, mainly in the prefrontal cortex, posterior cingulate and precuneus regions (Mintun et al., 2006; Pike et al., 2007; Rowe et al., 2007; Aizenstein et al., 2008). In fact, the proportion of ^{11}C-PIB-positive healthy control subjects increases with age (Morris et al., 2010). In these subjects, some studies have reported a strong relationship between impaired episodic memory performance and ^{11}C-PIB binding that could be modified by cognitive reserve (Pike et al., 2007; Mormino et al., 2009; Rentz et al., 2010), but some others have not found this association (Mintun et al., 2006; Jack et al., 2008b; Stornadt et al., 2009). Studies directly relating structural MRI data to Aβ burden in control subjects has yield contradictory results. Some authors have reported reduced hippocampal volume (Mormino et al., 2009; Stornadt et al., 2009), a cortical thinning pattern consistent with early AD (Dickerson et al., 2008; Becker et al., 2010) and an increased rate of brain atrophy (Scheinin et al., 2009), while others have found brain atrophy only in ^{11}C-PIB-positive subjects or in normal individuals with subjective cognitive impairment (Chetelat et al., 2010). There are only two longitudinal studies reporting progression of cognitively normal subjects scanned with ^{11}C-PIB PET to symptomatic AD. In one study, Morris et al. (2009) reported that the relative risk of conversion from cognitive normal to AD was increased almost five-fold with a ^{11}C-PIB-positive PET scan. Villemagne et al. (2011) performed serial ^{11}C-PIB PET scans in a group of normal subjects and found that 25% of individuals with a positive scan developed MCI or AD dementia by 3 years. In addition, the authors also reported an increase in ^{11}C-PIB brain retention in those control subjects with a positive baseline scan, suggesting a slow process of Aβ accumulation in the brain over time (Villemagne et al., 2011). These data are consistent with the hypothesis that amyloid imaging can detect Aβ accumulation in advance of the onset of dementia (Jack et al., 2010a), although more longitudinal studies are required to determinate the sequence of pathological events in the process from normalcy to AD. **Figure 3** shows the spectrum of amyloid deposition in normal controls, MCI and AD cases, as measured with ^{11}C-PIB PET (Mathis et al., 2007).

Although amyloid imaging is a relatively new technique, we can state that it accurately detects Aβ accumulation in the brain.

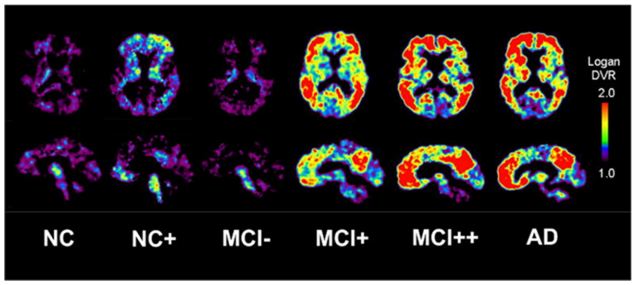

FIGURE 3 | Transaxial and sagittal planes of ^{11}C-PIB PET scans in a normal control (NC), a ^{11}C-PIB-positive NC (NC+), ^{11}C-PIB-negative MCI subject (MCI−), a ^{11}C-PIB-positive MCI subject (MCI+), a highly ^{11}C-PIB-positive MCI subject (MCI++), and a ^{11}C-PIB-positive AD patient (AD). Reprinted from Mathis et al. (2007).

However, it has been reported the case of a patient clinically diagnosed of mild AD with a negative ^{11}C-PIB PET scan, where low levels of amyloid pathology at autopsy were found (Cairns et al., 2009). On the other hand, there are not reported cases of subjects with a positive amyloid PET without presence of Aβ at autopsy. These data suggests that ^{11}C-PIB PET is a technique with high specificity and positive predictive value for early AD diagnosis. Nevertheless, having an ^{11}C-PIB-positive scan does not mean to be at a pre-dementia stage of AD, and the prognostic value of increased Aβ load on PET has to be established with more extensive longitudinal studies. In this scenario, adding techniques that assess functional brain changes suggesting early AD could be of special interest. Definitely, the information obtained with current amyloid tracers will bring to light important issues in the biology of amyloid deposition in the transition from normal to AD.

CONCLUSION

In this review, several potential AD biomarkers in different modalities have been highlighted. Current data suggest that diagnosis of AD can be enhanced by use of these promising biomarkers to increase accuracy and identify early stages of the disease. Each of these biomarkers seems to indicate a specific process in AD, so that amyloid imaging and decreased CSF $A\beta_{42}$ are indicators of brain amyloid burden, while CSF tau, brain atrophy and brain metabolism are biomarkers of the neurodegenerative process. Some authors have proposed a model of disease in which there is timing for the use of different biomarkers (Jack et al., 2010a). The AD pathologic cascade appears to have a sequential two stage process initiated by amyloid accumulation and followed by neuronal pathology. To validate this hypothesis and the right use of biomarkers in the clinical practice, it is necessary to determine the dynamics of the amyloid process with other biomarkers at the different stages of the disease. An early AD diagnosis could enable to administer treatments with potential disease-modifying effect before neurodegeneration becomes severe.

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